Clinical Study Protocol

Full Title:	**Managing Repetitive Behaviours: A clinical and cost effectiveness trial of a parent group intervention to manage restricted and repetitive behaviours in young children with Autism Spectrum Disorder.**
Short Title/Acronym:	**Managing Repetitive Behaviours Parent Group Study / MRB Study**
Protocol Version Number & Date:	**02, 25th July 2018**
Previous Versions:	**01, 20th June 2018**

Statement:

This protocol has regard for the HRA guidance.

This study is funded by the NIHR Health Technology Assessment Programme (ref 16/111/95). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

RESEARCH REFERENCE NUMBERS

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RESEARCH SPONSOR

Sponsor Name:	Northumberland, Tyne and Wear NHS Foundation Trust
Sponsor Reference:	RES-17-032

RESEARCH FUNDER(S)

Funder Name:	National Institute Health Research (NIHR) Health Technology Assessment
Funder Reference:	16/111/95

PROTOCOL APPROVAL SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted. The Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the UK Policy for Health and Social Care Research, Good Clinical Practice (GCP) guidelines, the relevant Standard Operating Procedures and other regulatory requirements as applicable.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

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PROTOCOL ACCEPTANCE SIGNATURE PAGE

Short Trial Title: MRB Study

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I have carefully read and understood protocol version 01, dated 20th June 2018. I agree to conduct the trial in compliance with Good Clinical Practice and all required regulatory requirements.

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TRIAL SUMMARY

Trial Title	Managing Repetitive Behaviours: A clinical and cost effectiveness trial of a parent group intervention to manage restricted repetitive behaviours in young children with Autism Spectrum Disorder	
Acronym	MRB Study	
Summary of Trial Design	A multicenter randomized controlled trial of the MRB Intervention versus a Psychoeducation Parent Group (Learning About Autism; attentional control) in the management of restricted repetitive behaviours in young children with Autism Spectrum Disorder.	
Summary of Participant Population	Parents/carers of young children (aged 3-7yrs11months) with Autism Spectrum Disorder (ASD) across a range of functioning levels and abilities (verbal and non-verbal).	
Planned Sample Size	250 families	
Planned Number of Sites	3 (Tees, Esk and Wear Valley (Teesside), Northumberland, Tyne and Wear (Tyneside), Edinburgh and the Lothians)	
Intervention Duration	8 weeks	
Follow Up Duration	52 weeks	
Planned Trial Period	40 months	
	Objectives	**Outcome Measures**
Primary	Compare the clinical effectiveness of the MRB intervention for NHS community clinical practice with psychoeducation for the management of challenging RRB in children with ASD at 24 weeks follow-up Incremental costs to achieve a positive difference in the CGI-I at 24 weeks	Clinical Global Impression - Improvement scale (CGI-I) The improvement scores from the CGI-I will be taken from each randomised arm of the trial to inform the efficiency of the intervention. A cost per additional child achieving at least the target improvement in CGI-I scale will be calculated in each pathway.

Secondary	Compare frequency and intensity/severity of RRB of the MRB intervention for NHS community clinical practice with psychoeducation for the management of challenging RRB in children with ASD at 10, 24 and 52 weeks follow-up.	Measurement of RRB: Measurement of the target behaviour vignette.
	Compare child's adaptive functioning of the MRB intervention for NHS community clinical practice with psychoeducation for the management of challenging RRB in children with ASD at 24 weeks follow-up	Repetitive Behaviour Questionnaire - 2 (RBQ-2). Teacher Repetitive Behaviour Questionnaire 2 (Teacher RBQ-2)
	Compare parents knowledge and confidence in managing behaviours typically exhibited by children with ASD including RRB at 10, 24 and 52 weeks follow-up	Vineland Adaptive Behaviour Scales II (VABS II)
	Compare parenting stress specific to core and co-morbid symptoms of ASD of the MRB intervention for NHS community clinical practice with psychoeducation for the management of challenging RRB in children with ASD at 10, 24 and 52 weeks follow-up	Parent self-efficacy
	Compare parent mental wellbeing of the MRB intervention for NHS community clinical practice with psychoeducation for the management of challenging RRB in children with ASD at 24 and 52 weeks follow-up	Autism Parenting Stress Index (APSI)

	Compare impact of an intervention on young children with ASD and on their family (everyday activities) of the MRB intervention for NHS community clinical practice with psychoeducation for the management of challenging RRB in children with ASD at 24 and 52 weeks follow-up	Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS). Autism Family Experience Questionnaire (AFEQ)
	Cost-consequences	A number of primary and secondary clinical outcomes and quality of life effects for the child will be used as outcomes for the cost-consequences analysis. In addition quality of life effects for the caregivers also will be included in the cost-consequences outcomes.
	Compare Incremental cost per QALY gained for the child of the MRB intervention for NHS community clinical practice with psychoeducation for the management of challenging RRB in children with ASD at 24 and 52 weeks follow-up	Cost to the family related to RRB will be estimated. A resource questionnaire and time and travel questionnaires will be used to aid the estimation of these costs
	Compare QALYs for the caregiver of the MRB intervention for NHS community clinical practice with psychoeducation for the management of challenging RRB in children with ASD at 24 and 52 weeks follow-up.	The CHU9D will be used to measure quality of life in relation to the child. The scores from this instrument will be used to create utility values, which will be incorporated in QALY outcomes

	Costs to the family will be measured at baseline, 24 and 52 weeks in both groups. Compare use of health care resources of the MRB intervention for NHS community clinical practice with psychoeducation for the management of challenging RRB in children with ASD at 24 and 52 weeks follow-up. Compare Health related quality of life of caregivers reported per child of the MRB intervention for NHS community clinical practice with psychoeducation for the management of challenging RRB in children with ASD at 24 and 52 weeks follow-up. Compare Health related quality of life of the child with RRB of the MRB intervention for NHS community clinical practice with psychoeducation for the management of challenging RRB in children with ASD at 24 and 52 weeks follow-up.	A bespoke questionnaire A bespoke questionnaire which ask the caregivers to report the amount of times that the patient accessed certain services (e.g. GP or outpatient appointments) will be completed. The EQ-5D-5L will be used to measure quality of life in the caregivers. This instrument will be used to create utility values, which will be incorporated in QALY outcomes. The CHU9D proxy version will be used. The CHU9D is a paediatric generic preference based measure of health related quality of life that is suitable for use in this particular patient group.
Intervention	Managing Repetitive Behaviours (MRB) is an eight session parent mediated group intervention for parent if young children (aged 3-7 years and 11 months) with a diagnosis of ASD. MRB aims to support parent to develop an understanding of the form and potential function of their child's challenging RRB. It also aims to support parents to develop effective strategies to improve the management of their child's challenging RRB in order to reduce the deleterious impact of these behaviours on child, parent and family functioning. Functional analysis principles will help parents to understand where and how to intervene and to develop alternative strategies and techniques to manage their child's negative experiences across a range of everyday contexts. The programme is delivered in eight, two hour sessions using a manualised programme which builds systematically on prior learning.	

Contents

GLOSSARY OF ABREVIATIONS

ABBREVIATION	DEFINITION
AE	Adverse Event
AR	Adverse Reaction
ASD	Autism Spectrum Disorder
CI	Chief Investigator
eCRF	Electronic Case Report Form
EoI	Expression of Interest
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
GP	GP General Practice
MRB	Managing Repetitive Behaviours
NCTU	Newcastle Clinical Trials Unit
NIHR-HTA	National Institute for Health Research – Health Technology Assessment
NHS	National Health Service
PI	Principal Investigator
R&D	Research & Development
RA	Research Associate
RCT	Randomised Control Trial
REC	Research Ethics Committee
RfPB	Research for Patient Benefit
RRB	Restrictive and repetitive behaviours
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
USAR	Unexpected Serious Adverse Reaction
TSC	Trial Steering Committee

1. BACKGROUND

Autism spectrum disorder (ASD) is a lifelong neurodevelopmental disorder affecting 1-2% of the population, with profound impact on individuals, families and society [1,2]. Restricted and Repetitive Behaviours (RRB) are one of two key symptom domains required for a diagnosis of ASD [3]. The presence of challenging RRB in ASD is frequently identified by parents as the most difficult aspect of their child's ASD to manage [4]. A recent meta-analysis indicates that parents of children with ASD experience higher levels of stress than parents of children with other disabilities and that stress is highly correlated with a child's challenging RRB [5]. RRB typically include repetitive motor mannerisms, rigid adherence to specific routines, highly circumscribed interests, and extreme responses to everyday sensory experiences. RRB can take up large amounts of time, interfere with the child's ability to engage in everyday living activities, reduce opportunities to take part in social play, social interactions and prevent learning [6]. RRB can be stigmatizing, and are associated with self-injurious behaviours and aggression to others, which further isolate the child and family [7,8]. The disruptive impact of RRB can in turn provoke coercive parenting styles, a further risk for the child, especially when parents are not able to access appropriate support [9]. Parents report they do not receive specific professional advice on how to recognise or understand their child's challenging RRB. There is an urgent need for evidence based, effective and efficient, early interventions to meet this unmet clinical need. Such interventions would improve the well-being of children and their families, reduce parental stress, greatly enhance potential for learning, improve longer-term outcomes and be an efficient use of society's scarce resources.

2. RATIONALE

The National Service Framework for Disabled Children and Young People and those with Complex Health Needs highlights the burden of care on parents of children with ASD, and the need for effective and efficient, evidence based parent training interventions [10]. An evidence base for the effectiveness of parent-mediated interventions for young children with ASD is emerging [11]. However, most ASD specific early intervention programmes focus on social communication [12,13]. The recent systematic literature review undertaken by NICE [14] confirmed that there is little published evidence on the treatment of RRB in children with ASD, despite RRB being a priority for parents [15,16]. Furthermore, a recent systematic review on effectiveness of treatments for RRB in ASD [17] has established that strategies based on functional analysis of specific behaviours (the core of the MRB manualised approach) were promising but lacked sufficient evidence, as the majority of studies were single case studies and focused solely on stereotypy (only one type of RRB). A review (May 2017) of trial databases (USNIH and UKCTG) indicates only one current behavioural trial registered for treatment of RRB. This trial aims to use mobile technology to reduce stereotypy in a narrow subset of children with ASD and is thus not relevant to the current trial. A pilot feasibility and acceptability randomised controlled trial of the MRB intervention to manage challenging RRB in young children with ASD has been completed and published, providing a basis for the current study [18]. This intervention has the potential to extend the range of early interventions available to meet the needs of young children with ASD and their families, ensuring best use of therapeutic resources and reducing the risk that challenging RRB become entrenched. However, before recommending that this parent

group intervention is included within local community early intervention services, an appropriately powered multi-site trial is required.

2.1 Risk Assessment

The MRB study is a non-ctIMP, interventional, multicentre trial to assess the effectiveness and cost-effectiveness of the MRB intervention.

The MRB intervention is a novel parent-level intervention for the management of children diagnosed with autism or autism spectrum disorder. A pilot trial has been carried out previously where no significant risks to the research participants were identified. The attentional control arm employs a psychoeducation intervention which is provided by the National Autistic Society and represents no higher risk than standard care.

3. OBJECTIVES AND OUTCOME MEASURES

3.1 Primary Objective

- To evaluate the clinical and cost effectiveness of the Managing Repetitive Behaviours (MRB) parent group intervention compared with Learning About Autism (a psychoeducation parent group, equivalent to current best practice), for the management of challenging RRB in children with ASD as measured by the Clinical Global Impression – Improvement Scale at 24 weeks.

3.2 Secondary Objective(s)

- Treatment effectiveness will be assessed using secondary (child and parent) measures to ensure we capture both independent (researcher) ratings of overall clinical improvement, teacher reported change in RRB and parent reported changes in RRB.

- Families will be assessed at baseline, at the end of treatment (week 10), and at the primary endpoint (week 24) to assess effectiveness of the intervention and impact on child RRB, child's adaptive functioning, parent self-efficacy, parent stress and wellbeing and family social participation.

- We will assess maintenance of effect and potential longer term (downstream) impact on child and family functioning (e.g. social participation) at 52 weeks from baseline.
- An embedded economic evaluation will be conducted involving the estimation of costs to the NHS, personal social services and to families, as well as impacts on health related quality of life and the aforesaid outcomes.

3.3 Outcome Measures

3.3.1 Primary Outcome Measure

- Clinical Global Impression - Improvement scale (CGI-I) at 24 weeks.

3.3.2 Primary Economic Outcome Measure

- Cost per additional child achieving at least the target improvement in CGI-I scale will be calculated in each pathway.

3.3.3 Secondary Child Outcome Measures

- Measurement of RRB: Target Behaviour Vignette at baseline, Week 10, Week 24 and Week 52

- Measurement of RRB: Repetitive Behaviour Questionnaire - 2 (RBQ-2) at baseline, Week 10, Week 24 and Week 52

- Measurement of RRB: Teacher Repetitive Behaviour Questionnaire 2 (Teacher RBQ-2) at baseline, Week 10, Week 24 and Week 52

- Vineland Adaptive Behaviour Scales II (VABS II) at baseline and Week 24

3.3.4 Parent Outcome Measures

- Parent self-efficacy questionnaire at baseline, Week 10, Week 24 and Week 52

- Autism Parenting Stress Index (APSI) at baseline, Week 10, Week 24 and Week 52

- Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS) at baseline, Week 24 and Week 52

3.3.5 Secondary Family Outcome Measures

- Autism Family Experience Questionnaire (AFEQ) at baseline, Week 24 and Week 52

3.3.6 Secondary Economic Measures

- Costs to the NHS, personal social services (PSS) and the family (see economic analysis section below for details).

- Health related quality of life of the child with RRB. This will be elicited using the CHU9D proxy version. Following recommended practice parents/caregivers will be asked to complete the CHU9D by saying how he/she rates the health of the child. The CHU9D is a paediatric generic preference based measure of health related quality of life that can be used to generate utility values. The utility values generated will be used in the cost utility analysis.

- Health related quality of life of parents/carers will be measured using the EQ-5D-5L health questionnaire. This provides a simple descriptive profile and a single index value for health status. These results will be used to generate utility values which will be used in the cost utility analysis.

- Cost-utility analysis with results presented as incremental cost per QALY gained with QALYs taken from the perspective of the child and the caregiver. Costs from the perspective of NHS and PSS with a sensitivity analysis widening the cost perspective to include the costs borne by the family.

- Cost-consequences of adopting the MRB intervention compared with psychoeducation (see economic evaluation section below for details).

3.3.5 Baseline Characterisation Measures

- Autism Diagnostic Observation Schedule-2 (ADOS-2) will be collected at baseline.

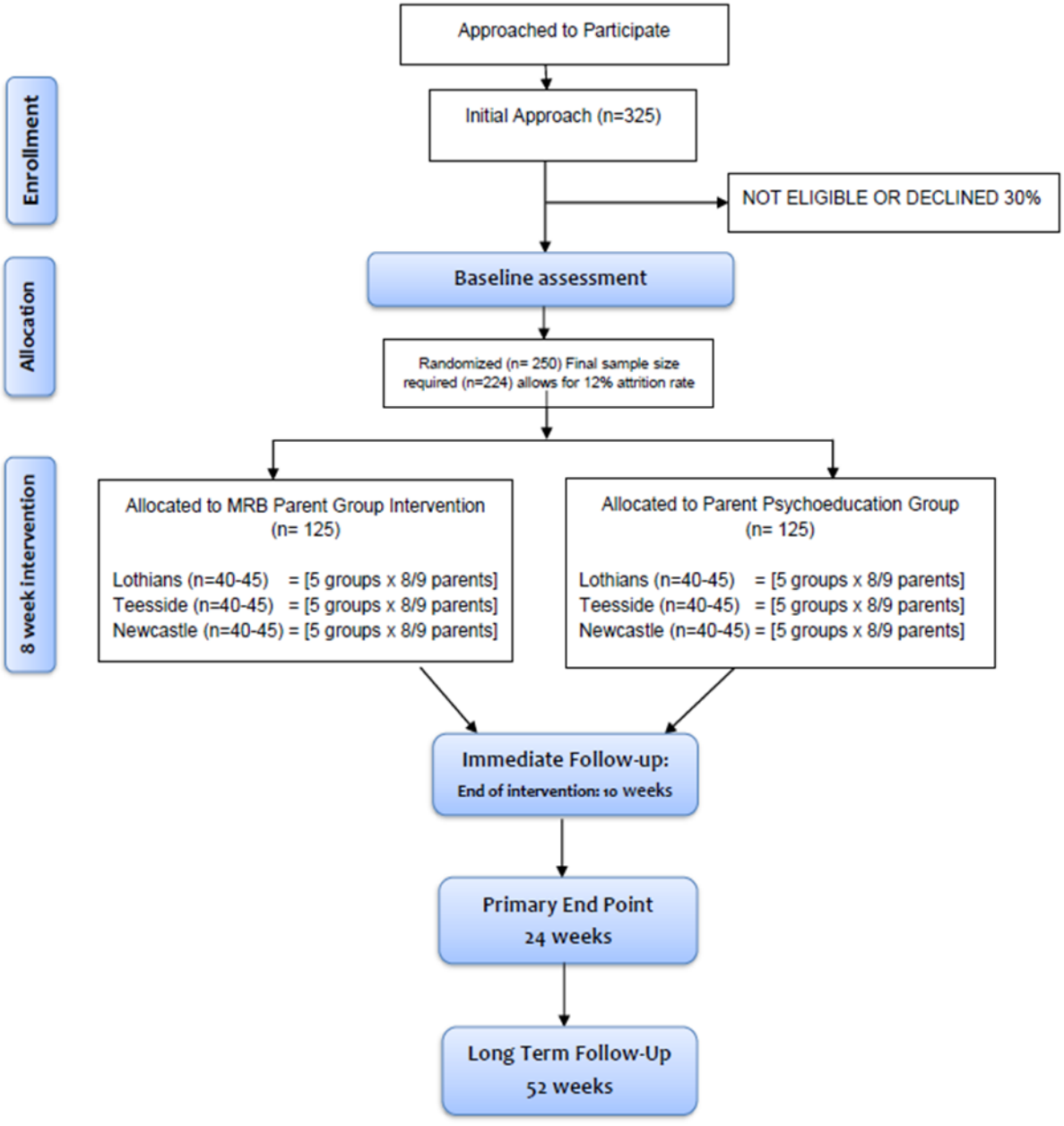
- Social Responsiveness Scale – Second Edition (SRS-2) to be collected at baseline.

- Demographic data, to be collected at first appointment and updated at 24 and 52 weeks, including child's age, gender, type of nursery/school provision, diagnosis and ethnicity, previous interventions, current medication and additional diagnoses. Information will also be obtained on parents' level of education, employment status, family structure, and if they have attended any previous course or intervention for children with a diagnosis of ASD.

4. TRIAL DESIGN

This is a randomised controlled trial of a parent group intervention to address challenging RRB in children with ASD, randomised to treatment Managing Repetitive Behaviours Parent Group (MRB) or Learning About Autism, a psychoeducation parent group (equivalent to current best practice). The Learning About Autism group will also comprise eight parent group sessions (attentional control) focusing on understanding ASD and general advice on managing behaviour.

Patients will be randomised 1:1 to receive either the MRB intervention (N=125) or the Learning About Autism attentional control arm (N=125). Recruitment will be conducted through three research sites (Teesside, Tyneside, Edinburgh and the Lothians).



4.1 Initial Phase

The MRB study includes an initial phase with robust progression criteria to be assessed following 9 months of recruitment. The progression criteria to the main phase are classified using a Red/Amber/Green system according to-

Stop criteria (red): If the mean recruitment rate shows that there are only 1-2 families per site per month meeting eligibility criteria (study overall total 3-6 per month), and that there is between 20-45% of the target recruitment rate of families/centre/month, we would reach 25-57 families by 9 months (recruitment half way point). We propose that if there are less than 36 families after 9 months of recruitment then the first wave of parent groups cannot commence and it is very unlikely that the target can be reached. In such a circumstance the likely recommendation of the TSC to NIHR would be that trial is futile and should be stopped. If there are enough families to run the first wave of groups at each site, but the overall recruitment rate is still slow, we would implement the remedial action plan immediately.

Remedial action (amber): If the mean recruitment rate shows that there are between 2-4 families per site per month meeting eligibility criteria (study overall total 6-12 per month), and that there is between 45-90% of the target recruitment rate of families/centre/month, we would reach 57-108 families by 9 months (recruitment half way point). At this rate of recruitment we estimate we would develop a full recovery plan. In terms of a recovery plan, we would consider the feasibility of increasing the number of centres recruiting, and other recruitment initiatives such as study newsletters or meetings with clinicians to remind them about the study eligibility criteria. We would also consider approaching ASD-UK (based at Newcastle University) a UK research family database of children with an autism spectrum disorder (ASD) which includes over 1700 families interested in participating in research and covers all three sites. Consideration will also be given to whether recruitment rates have seasonal fluctuations e.g. during summer school holidays and Christmas. In this circumstance we would implement the recovery plan and the likely recommendation of the TSC to NIHR would be that the trial proceeds with additional monitoring.

Continue (green): If the mean recruitment rate shows that there are between 4-5 families per site per month (across actively recruiting centres) meeting eligibility criteria (study overall total 12-14 per month), and that there is between 90- 100% of target recruitment rate, we would reach 108-126 families by 9 months (recruitment halfway point). In this circumstance we would consider whether we need to increase the number of centres recruiting but the likely recommendation of the TSC to NIHR would be that the final sample size is likely to be reached and the trial proceeds.

4.2 Main Phase

Upon review and confirmation of acceptance by the Trial Steering Committee and Funder, the MRB study may progress to the main phase.

5. STUDY SETTING

The intervention has been developed to be delivered in local community settings by early years professionals experienced in working with young children with ASD and their families. The Managing Repetitive Behaviours intervention and the Learning About Autism parent groups will take place in community settings in different geographical locations across the three sites. This is in line with the National CAMHS Review (2008) [19], which indicated young people and families want accessible services in convenient places. We have carefully considered the level of professional expertise necessary to deliver the MRB intervention effectively and safely. The MRB group will be delivered by two group leaders with experience in working with young children with ASD and their families, with appropriate additional specialist MRB training and supervision.

6. ELIGIBILITY CRITERIA

6.1 Inclusion Criteria

Parents/carers aged 18 years and over who:

- Have a child aged between 3 years and 7 years and 11 months at the time of consent with a clinical diagnosis of Autism or Autism Spectrum Disorder

- Have sufficient spoken and written English to-
    - provide written informed consent
    - complete the assessments including being able to identify one or more challenging RRB
    - participate in the group-based intervention

- Are willing to be randomised and attend all the group sessions for the allocated arm of the study

- Agree to maintain their child's current medication regime

- Agree not to participate in any other trials while involved in the trial up to 24 weeks

6.2 Exclusion Criteria

- Parent and child currently taking part in another parent group-based intervention

- Parent with a current severe learning disability or a severe disabling mental illness that interferes with ability to take part in group-based intervention

- Sibling is taking part in this study

NB: Enrolling a patient onto the trial who does not meet the inclusion/exclusion criteria is considered a protocol waiver. PROTOCOL WAIVERS ARE NOT PERMITTED

7. TRIAL PROCEDURES

7.1 Recruitment

7.1.1 Patient Identification

Clinicians will be provided with information on the MRB study, and asked to introduce the study to families. Clinicians will give potential families copies of the information sheets, and an Expression of Interest (EoI) form to be returned by the clinician or the family to the research team using the stamped address envelope provided. We will request ethical permission to collect data from families who do not opt in, exploring reasons for declining to participate or for dropping out. The local Clinical Research Network at each site will assist with recruitment.

7.1.2 Screening

Eligibility Procedure

- Where there is any doubt, after first home visit or after all assessments, eligibility will be discussed by research associate (RA), principal investigator (PI) and other members of the team.
- If the participant meets eligibility criteria, the RA sends a letter thanking the parents for participating in all the assessments, and to confirm eligibility and say that the family will be put forward for randomisation. A separate letter will be sent to GP/referrer to notify them of this.
- If the child doesn't meet eligibility criteria the RA or PI will contact the family to discuss.
- The RA or PI will also inform the referrer if the child doesn't meet eligibility criteria.

7.2 Consent

At each recruiting site once the EoI has been received by the research team, parents will be 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 will be given the opportunity to discuss any questions or concerns they may have to ensure they are fully informed about the study, they will then be asked to give informed consent at this initial contact appointment. A minimum of 24 hours will be afforded for consent.

Informed Consent Process

- Refer to the study information sheet (providing parents with a copy if they have misplaced theirs) and discuss any queries that may arise

- Discuss with parents the randomisation process making sure to explain:

that as MRB is a new intervention, it is necessary to undertake a RCT to test the clinical and cost effectiveness compared to current best practice

As the family may interact with other families with a child with ASD we ask that families keep the materials to themselves.

Families may come across another family who is experiencing difficulty regarding RRB, but we ask them not to give advice, but to direct families to local clinical lead or relevant health professional.

Travel expenses will be refunded for any assessment visits that participants attend in relation to the study.

7.3 Randomisation

Randomisation will be done at child level using equal allocation ratio. Each parent/caregiver will automatically be considered in their child's randomisation group. We opted for child level randomisation instead of parent level randomisation, because the primary outcome is at child level and it is important to account for children level characteristics that can affect the primary outcome.

Age (3-5 years vs 6-7 years 11 months), gender (male vs female) and ethnicity (white vs non-white) will be accounted for in allocating children to either MRB group or Learning About Autism comparison group. Due to the nature of the study and the few factors (site, age, gender and ethnicity) that needs to be accounted for in the randomisation, a minimisation scheme instead of stratified randomisation will be used to minimise sample fragmentation because of the too many strata and to avoid accidental imbalance between the MRB group and the Learning About Autism comparison group. Unlike stratified randomisation, minimisation works toward minimizing the total imbalance for all factors together instead of considering mutually exclusive subgroups. For the minimisation scheme, the first 25 children (10%) will be allocated to either MRB group or Learning About Autism group using simple randomisation with 50% equal probability. The remaining 225 children will be allocated to either MRB group or the Learning About Autism group by minimising marginal imbalance between the two groups based on sites, age, gender and ethnicity. For example, if the 26th child to be randomised is a male, 3-5 years, white and from site 1. Suppose 8 male, 5 children aged 3-5 years and 5 white children from site 1 were already allocated to the MRB group. And suppose 6 male, 4 children aged 3-5 years and 4 white children from site 1 were allocated to the psychoeducation comparison group. Allocating the 26th child to the Learning About Autism group would result in an imbalance score of 1, whereas allocating the child to the MRB group will result in an imbalance score of 7. The 26th child will be assigned to the Learning About Autism group, because that would lead to less overall imbalance.

7.4 Blinding

The research associates (RA) at each of the three recruiting sites will be based in a separate location (usually university premises) to the clinical therapists and will remain throughout the study 'blind' to

the therapy status of all the recruited children and families in the MRB trial. The RAs will be trained to high levels of reliability in all baseline characterisation and outcome measures. For each recruited child and parent(s), once informed consent and all the baseline measures have been completed and scored and eligibility confirmed by an investigator, the participants will be randomised. The site clinical lead will be informed (in writing via email) of the outcome of the randomisation. The parent participant will then receive a letter from the clinical lead at each site confirming the randomisation outcome. The RA will not be informed of the randomisation outcome. Then prior to and at each subsequent follow up visit parents/carers will be reminded not to disclose to the RA the child/family randomisation status. This means that throughout the trial the RAs should remain blind to the randomisation status of all study participants.

7.5 Unblinding

Patients and therapists will be unblinded to the intervention. Only assessors of the study outcomes (research associates and research leads at each site) will be blinded. As such, there is no anticipation for the need of unblinding while the study is in progress.

If the RA is inadvertently unblinded to the treatment status of an individual child, the site clinical and research leads will be informed.

7.6 Trial Assessments & Data

Baseline characterisation measures

Autism Diagnostic Observation Schedule-2 (ADOS-2; [20]); This is an observational assessment undertaken by a trained research associate. It is a semi-structured set of play and social communication activities that involves both specific activities and spontaneous social interaction between the examiner and the child; children will be 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 Restricted and Repetitive Behaviour (RRB). The scores for the domains are combined into a total score. Severity scores are calculated ranging from 1 to 10, with scores of 1–2, 3-4, 5-7, 8-10 indicating minimal to no evidence, low, moderate and high degree of autistic impairment respectively.

Social Responsiveness Scale – Second Edition (SRS-2; [21]): The SRS-2 (preschool form or school form according to child's age) is a 65-item questionnaire measure of the severity and type of social impairments that are characteristic of ASD, completed by the parent/caregiver. Higher total scores on the SRS-2 indicate greater severity of social impairment.

Demographics: Parents will be asked about their child's age, gender, type of nursery/school provision, diagnosis and ethnicity, previous interventions, current medication and additional diagnoses. Information will also be obtained on parents' level of education, employment status, family structure, and if they have attended any previous course or intervention for children with a diagnosis of ASD.

Primary Outcome Measure

Clinical Global Impression - Improvement scale (CGI-I; [22]): 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). A research associate, blind to group allocation, will be trained to reliably and independently rate global improvement in how much the child's challenging RRB had changed over the 24 weeks (from baseline to primary endpoint), using all available child information from baseline, week 10 and week 24 (parent and teacher RBQ-2, Warwick-Edinburgh Mental Wellbeing Scale, Autism Family Experience Questionnaire, parent self-efficacy and Autism Parent Stress Index), SRS-2, VABS-II, ADOS-2 videos, target behaviour vignettes before reaching a rating about change for each child. The training manual and procedures were successfully designed and tested during the RfPB funded pilot study [18]. Ratings of 1 (very much improved) and 2 (much improved) are regarded as clinically significant 'improvement' and are used to define the binary outcome of improvement or no improvement after MRB intervention.

Economic Outcome Measures

Costs to the family: Cost to the family related to MRB will be estimated. Resources questionnaires and time and travel cost questionnaires will be used to aid the estimation of these costs. Measured at baseline 24 and 52 weeks.

Incremental costs to achieve target difference in the CGI-I at 24 weeks: The improvement scores from the CGI-I will be taken from each randomised arm of the trial to inform the efficiency of the intervention. A cost per incremental improvement of CGI-I scale will be calculated in each pathway.

Incremental cost per QALY gained for the child: The CHU9D [23] will be measured in both arms of the trial to measure quality of life in relation to the child. This will be measured at baseline, 24 and 52 weeks. The scores from this instrument will be used to create utility values, which will be incorporated in QALY outcomes. This will be expressed an in an average incremental costs per QALY ratio for the children in each arm.

QALYs for the caregiver: The EQ-5D-5L [24] will be completed at baseline, 24 and 52 weeks by the caregiver for the child. The scores from this instrument will be used to create utility values, which will used to create QALYs for the caregivers. This outcome will be included as part of the cost consequence analysis.

Cost-consequences: A number of primary and secondary clinical outcomes, quality of life effects for the child and quality of life effects for the caregivers will be used as outcomes for the cost-consequences analysis.

Secondary child outcome measures

Measurement of RRB: Target Behaviour Vignette [25]: As part of the baseline characterisation, parents will be asked to identify two challenging restrictive repetitive behaviours (RRB). Parents will be asked questions about the duration, impact and possible triggers and functions of this challenging RRB. The protocol for measuring change in the parent defined Target behaviour was developed by The Research Units on Paediatric Psychopharmacology and Psychosocial Interventions (RUPP Autism Network). At each outcome assessment point, the parent will be asked "At the beginning of the study

you said you were concerned about (parent defined target behaviour at baseline). How has it been in the last couple of weeks?" The parent responses at each time point will contribute to a vignette written by the researcher (blind to group intervention status). In keeping with the procedure developed by RUPP, after all data are collected, a panel of blinded ASD experts will independently rate change in each target behaviour. Three pairs of vignettes (comparing each time point to baseline) will be rated for each child on a 9 point scale of improvement/deterioration (1 – normalised behaviour; 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 is defined as a rating of 3 or less.

Measurement of RRB: Repetitive Behaviour Questionnaire - 2 (RBQ-2; [26]): 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 ASD and typical development. The RBQ-2 was developed using items from the RBQ 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 [27]

The Teacher Repetitive Behaviour Questionnaire - 2 (Teacher RBQ-2) [28] is the corresponding version of the parent RBQ-2 for completion by teachers/teaching assistants. It measures the frequency, intensity and severity of RRB in a classroom setting.

Vineland Adaptive Behaviour Scales II (VABS II; [29]): The VABS II measures aspects of the child's level of adaptive functioning. The parent/caregiver rating form will be used. This focuses on four domains of everyday functioning: communication, daily living skills, socialisation and motor skills. The assessment will be undertaken with parents by a trained researcher. The domain composite scores provide an adaptive behaviour composite.

Secondary parent outcome measures
Secondary Parent Measures will be completed by the parent/carer who will attend group sessions in both conditions or if both parents plan to attend sessions the nominated main carer will be asked to complete all parent report measures.

Parent self-efficacy [30]: This 15-item questionnaire completed by parents/carers measures behaviours typically exhibited by children with ASD including RRB. Parents 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.

Autism Parenting Stress Index (APSI) [31]. This is a measure of parenting stress specific to core and co-morbid symptoms of ASD. It was designed to be used to identify areas where parents need support with parenting skills, and to assess the effect of intervention on parenting stress. Exploratory factor analysis suggested three factors impacting parenting stress: relating to core deficits, to co-morbid behavioural symptoms, and to co-morbid physical symptoms. Psychometric properties are good (e.g. Cronbach's alpha 0.83).

Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS) [32] is a psychometrically robust parent rated 14 item wellbeing questionnaire with good internal consistency (Cronbach's alpha 0.89) and test-retest reliability (ICC 0.83). It is recommended by Department of Health as the preferred measure of mental wellbeing and important to incorporate in parent mediated studies where parental wellbeing may impact on child outcomes.

Secondary family outcome measures

Autism Family Experience Questionnaire (AFEQ) [33]. This questionnaire was developed to measure broader impact of an intervention on young children with ASD and on their family in terms of participation in everyday activities. It was commissioned by the Medical Research Council as part of the Preschool Autism Communication Trial [8] and based on focus groups and piloting with parents of young children with ASD to reflect what changes in their lives would 'make a difference'.

Secondary economic outcome measures

Measurement of the health care resources. Resources which are used by the children will be measured. This will be measured by a bespoke questionnaire which ask the caregivers to report the amount of times that the patient accessed certain services (e.g. GP or outpatient appointments) will be completed at 24 weeks and 52 weeks. This will be calculated to result in an average cost of services per pathway.

Time and travel costs. Costs and time lost to travel will be measured via a questionnaire which has utilised in a number of previous studies to measure costs and time spent travelling. The travel costs will be valued according to the type activity that the travel is displacing (work or leisure time) and valued appropriately based on a review of the literature in the UK.

Health related quality of life of caregivers reported per child. This will be elicited by using the EQ-5D-5L [24]. This is a standardised instrument for use as a measure of health outcome. It is applicable to a wide range of health conditions and treatments. The EQ-5D-5L health questionnaire provides a simple descriptive profile and a single index value for health status.

Health related quality of life of the child with RRB. This will be elicited using the CHU9D proxy version [23]. The CHU9D is a paediatric generic preference based measure of health related quality of life that is suitable for use in this particular patient group. Following recommended practice parents/caregivers will be asked to complete the CHU9D with the child at baseline, 24 and 52 weeks.

Quality Adjusted Life Years (QALY) for the gained from the perspective of the NHS and Personal Social Services will be produced as part of a cost utility analysis examining the two interventions. QALYs will be estimated from responses to the EQ-5D-5L and the CHU9D of the caregivers and the child respectively.

Cost and Benefits which may not be captured in the metric of a QALY, such as costs borne by the family will be described as part of a Cost-consequence analysis.

Resource use questionnaire: A bespoke questionnaire will be given to parents to complete detailing the use of health care resources. This will details the use of health and personal social services (PSS) for the child and the time that this diverts away from usual activities.

7.7 Trial Assessments

<u>Screening</u>

- Informed Consent
- Child and Parent demographics
- Eligibility

Baseline

- ADOS-2
- VABS II
- SRS-2
- RBQ-2
- Teacher RBQ-2
- Measurement of the target behaviour vignette
- Parent self-efficacy questionnaire
- Autism Parenting Stress Index
- WEMWBS
- Autism Family Experience Questionnaire
- CHU9D
- EQ-5D-5L
- Resource Use Questionnaire
- Time and Travel Questionnaire
- Randomisation

Treatment Phase – Weeks 1-8

- Weekly parent group intervention sessions (MRB or Learning About Autism)

Follow-up – Week 10

- RBQ-2
- Teacher RBQ-2
- Measurement of Target Behaviour Vignette
- Parent self-efficacy questionnaire
- Autism Parenting Stress Index

Follow-up – Week 24

- Child and Parent demographics
- CGI-I
- VABS II
- RBQ-2
- Teacher RBQ-2
- Measurement of Target Behaviour Vignette
- Parent self-efficacy questionnaire
- Autism Parenting Stress Index
- WEMWBS
- CHU9D
- EQ-5D-5L
- Resource Use Questionnaire

Follow-up – Week 52

- Child and Parent demographics
- RBQ-2
- Teacher RBQ-2
- Measurement of Target Behaviour Vignette
- Parent self-efficacy questionnaire
- Autism Parenting Stress Index
- WEMWBS
- Autism Family Experience Questionnaire
- CHU9D
- EQ-5D-5L
- Resource Use Questionnaire

7.7.1 Schedule of Events

Procedure	Screening	Baseline	Treatment Phase	Follow-up		
			Weeks 1-8	Week 10#	Week 24#	Week 52#
Informed consent	X					
Child and Parent Demographics*	X				X	X
Eligibility	X					
ADOS-2		X				
SRS-2		X				
CGI-I					X	
RBQ-2		X		X	X	X
Teacher RBQ-2		X		X	X	X
Measurement of the target behaviour vignette		X		X	X	X
VABS II		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
CHU9D		X			X	X

EQ-5D-5L		X			X	X
Resource use questionnaire		X			X	X
Time and travel questionnaire		X				
Randomisation**		X				
Weekly intervention (MRB or Learning About Autism)			X			

*Child demographics to include – child age, gender, type of nursery/school, diagnosis, current medications, additional diagnoses, ethnicity, previous intervention exposure,

*Parent demographics to include – level of education, employment status, family structure, attendance at previous courses or interventions relating to children with a diagnosis of ASD.

**Randomisation to take place following completion of baseline assessment

Timing of follow-up assessments will be relative to Week 1 of the treatment Phase. A +/- 2 week window is allowable per protocol, but it is accepted that there may be some variability in the timing of assessments.

7.8 Withdrawal Criteria

Participants have the right to withdraw from the trial at any time without having to give a reason. Investigator sites should try to ascertain the reason for withdrawal and document this reason within the Case Report Form and participant's medical notes. For patients who withdraw consent, data captured up until the point of withdrawal will be retained, unless parents withdraw consent.

The clinical lead at each site may discontinue a participant from the trial at any time if they consider it necessary for any reason including. This decision will initially be made at each site, but discussed with the wider research team if necessary. The CI and CTU will then be informed.

- Symptomatic deterioration
- Parent withdrawal of consent
- Significant protocol deviation or non-compliance
- Investigator's discretion that it is in the best interest of the child and/or parent/carer to withdraw
- An adverse event that requires discontinuation of the trial intervention or renders the child or parent unable to continue in the trial
- Termination of the clinical trial by the sponsor

Participants who withdraw from the trial will not be replaced.

7.9 End of Trial

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

8 TRIAL INTERVENTION

8.1 Name and Description of Interventions

Managing Repetitive Behaviour (MRB) Intervention

MRB is a manualised intervention designed to help parents of young children with ASD to recognise, understand and learn how to manage their child's challenging RRB. It is an eight week manualised intervention designed to be delivered by community based professionals with knowledge and experience of working with young children with ASD and their families who have been trained to deliver the MRB intervention. Full details of the MRB intervention are included in the MRB manual.

Learning About Autism Parent Group

The Learning About Autism parent group sessions will act as an attentional control and comprise and eight week programme focussed on understanding the social communication and social interaction

difficulties children with ASD may have, and signposting to local resources. These sessions will be delivered by the National Autistic Society.

8.2 Schedule

Eight weekly sessions with an anticipated duration of 2 hours per session, giving a total duration of approximately 16 hours.

8.3 Known Risks

The risks of parent mediated group based interventions are low as there is extensive experience of successful implementation [11]. It is appreciated that attendance can be complicated by life-pressures and demands on families who have a child with ASD such as logistical challenges including distance involved in traveling to treatment services. We will try to alleviate this by being flexible in scheduling assessment appointments and delivering the intervention (our RfPB feasibility and acceptability pilot demonstrated successful attendance at parent groups (90%) and high retention from baseline to primary endpoint, 24 weeks (89%).

MRB parent groups will be run across a range of geographical locations in all three sites. Parental motivation and advocacy are generally very high in ASD research. We have included a relatively broad eligibility criteria, that is flexible enough to apply to children with a range of abilities, functioning levels and different types of challenging RRB and reflects a typical NHS early years ASD patient group. This means that the majority of families' first experience of research is likely to be positive, rather than narrow recruitment criteria being another barrier.

8.4 Assessment of Compliance

Fidelity

We will assess fidelity of delivery of intervention. Four independent raters will be trained to use the MRB fidelity coding checklist. This measure was developed and used successfully in our previous feasibility and acceptability study to ensure consistent training of and delivery by group leaders across sites. The independent raters will then be randomly allocated 20% of the recorded parent group intervention sessions and asked to rate both fidelity to the treatment manual and the therapeutic compliance of the group leaders to ensure maintenance of best practice.

9 SAFETY REPORTING

9.1 Definitions

For the purposes of this trial, Adverse Events will be captured for the parent/carer and child participants. Adverse Events will be captured from the start date of intervention until the final follow-up assessment at Week 24.

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant, including occurrences which are not necessarily caused by or related to the intervention under study.
Adverse Reaction (AR)	An untoward or unintended response in a participant to which is related to the intervention under study i.e. that a causal relationship between the trial intervention and an AE is at least a reasonable possibility and the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial intervention qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • Results in death • Is life-threatening* • Requires inpatient hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability/incapacity • Consists of a congenital anomaly or birth defect • Other important medical events that jeopardise the participant or require intervention to prevent one of the above consequences * - life-threatening refers to an event in which the participant was at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to the trial intervention, based upon the information provided.
Unexpected Serious Adverse Reaction (USAR)	A serious adverse reaction, the nature and severity of which is not consistent with the known information about the intervention under study.

9.2 Recording and Reporting AEs and SAEs

For each SAE the following information will be collected:

- Full details in medical terms and case description
- Event duration (start and end dates, if applicable)
- Action taken
- Outcome
- Seriousness criteria
- Causality in the opinion of the investigator
- Whether the event is considered expected or unexpected.

Any change of condition or other follow-up information should be faxed to the NCTU as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

9.3 Recording and Reporting USARs

All USARs occurring from the intervention until Week 24 must be reported to the NHS REC. The NCTU will perform this reporting.

The assessment of expectedness will be performed by the CI against the known information for the trial.

USARs must be reported no later than 15 calendar days after the NCTUhas first knowledge of the event. Any relevant follow-up information should be sought and reported as soon as possible after the initial report.

As soon as a site suspects that a SAR may be a USAR they must contact the CI, sponsor representative and the trial manager immediately. The reporting timeframe starts at day 0 when the NCTU is in receipt of a minimum set of information:

- Sponsor trial reference and trial name (sponsor reference)
- Patient trial number and date of birth
- 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., Principal Investigator)

This information must be provided on [name of form or media of notification]. The site is expected to fully cooperate with the NCTU in order that a full and detailed report can be submitted to the NHS REC within the required timelines.

PIs will be informed of all USARs by the NCTU.

9.4 Responsibilities

Principal Investigator

- *Checking for AEs and ARs when participants attend for treatment or follow-up*
- *Using clinical judgement in assigning seriousness and causality and providing an opinion on expectedness of events.*

- *Ensuring that all SAEs and SARs, including USARs, are recorded and reported to the Sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available.*
- *Ensuring that AEs and ARs are recorded and reported to the Sponsor in line with the requirements of the protocol.*

Chief Investigator

- *Clinical oversight of the safety of trial participants, including an ongoing review of the risk/benefit.*
- *Using clinical judgement in assigning seriousness, causality and expectedness of SAEs where it has not been possible to obtain local medical assessment.*
- *Using clinical judgement in assigning expectedness to SARs.*
- *Immediate review of all USARs.*
- *Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol.*

Sponsor

- *Assessment of expectedness of any USARs*
- *Expedited reporting of USARs to the REC within required timelines*
- *Notification of all investigator sites of any USAR that occurs*

TSC/DMC/TOC

- *Review of safety data collected to date to identify any trends*

9.5 Reporting Urgent Safety Measures

An Urgent Safety Measure (USM) is an action that the Sponsor or an Investigator may take in order to protect the subjects of a trial against any immediate hazard to their health or safety. Upon implementation of an USM by an Investigator, the NCTU must be notified immediately and details of the USM given. The NCTU must inform the NHS REC within 3 days of the USM taking place in accordance with the NCTU's standard operating procedures.

10 STATISTICAL CONSIDERATIONS

10.1 Analysis Population

All analyses will be done in accordance with intention-to-treat principle where all children and parent outcome are analysed as randomised. This means that those that were randomised into the intervention group but did not receive the intervention would be analysed as the intervention group. Sensitivity analysis based on per protocol and as treated will be considered to further understand the impact of the intervention. Demographic data and baseline characterisation will be analysed using descriptive statistics to describe participants' compositions. Descriptive statistics will also be used to analyse the minimisation factors to investigate whether there is accidental imbalance between MRB intervention group and the Learning About Autism group. Mean and standard deviation as well as median and range (min-max) will be used for continuous data. Percentages and frequencies will be reported for categorical data. Baseline ordinal data will be described using frequency table.

10.2 Statistical Analyses

10.2.1 Analysis of the Primary Outcome Measure

The analysis of the primary outcome data at 24 weeks will use generalised linear model with binomial distribution and logit link to account for the binary nature of the primary outcome. Sandwich estimator via Generalised Estimating Equation (GEE) with exchangeable working correlation will be used to account for the clustering of children by parent groups. The primary analysis will be sensitised for the impact of number of clusters using restricted pseudo-likelihood approach with and without small sample adjustment.

Similar approach will be used for analysis of outcome data at 52 weeks. Longer term impact of MRB intervention will be assessed by the interaction between the time points and intervention's indicator (1- MRB and 0- psychoeducation group) accounting for the paired data per child and clustering of children by parent group. Furthermore, sensitivity analyses for the primary outcome data will be performed by analysing it on its original ordinal scale of 'very much improved', 'much improved', 'minimally improved', 'no change', 'minimally worse', 'much worse' or 'very much worse' using cumulative proportional odd model and adjacent category model.

10.2.2 Analysis of Secondary Outcome Measures

All secondary outcomes, except the health economic outcomes will be described using mean and standard deviation for continuous data, percentages and frequency for categorical data. The secondary outcomes will first be analysed at 24 weeks using linear mixed effect model accounting for paired data (at baseline and at 24 weeks) per child and clustering of children by parent groups. Same model will be applied to the data at week 52, which will be analysed as longitudinal data incorporating data at baseline and 24 weeks. The dropout rate in MRB intervention group and psychoeducation support group will be assessed using cross tabulation. If the attrition rate is more than 15%, missing data analysis will include dropout model to identify baseline factors that are predictive of drop out. The impact of missing data will be investigated under the missingness mechanism of missing completely at random (MCAR) and missing at random (MAR). MAR analysis will use 10 imputed datasets generated by multiple imputation. Weighted GEE will also be performed for the primary outcome. All analysis will be done in R (using most recent version) and SAS 9.4.

10.2.3 Subgroup Analyses

Subgroup analyses will be performed for the minimisation factors to explore whether there is a differential impact of the intervention between their respective categories.

10.2.4 Interim Analyses and Criteria for the Premature Termination of the Trial

There is no planned interim analysis. The proposed internal pilot phase would end approximately 9 months after the commencement of recruitment and is just under half way through the recruitment period. The primary purpose of the initial phase is to evaluate recruitment and retention. Progression criteria are presented in Section 4.1.

10.3 Sample Size Calculations

We plan to approach approximately 325 families and expect 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 group) are required to detect 20% improvement rate between the MRB intervention and Learning About Autism group at 24 weeks. Allowing for an attrition rate of 12%, 250 families will be randomised. The 10% intra-cluster correlation was based on review of group interventions in education trials [34]. Sample size was calculated in R using n4pros in CRTSize package.

10.4 Statistical Analysis Plan

The detail of planned analyses will be written and submitted for approval to IDMEC and TSC by December 2019.

11 HEALTH ECONOMICS

11.1 Economic Evaluation

The economic evaluation will be carried out from the perspective from the NHS and personal social services. A cost effectiveness analysis within trial which will compare the costs to achieve the target mean difference in the CGI-I in both the MRB and Learning About Autism groups at 24 weeks. A cost utility approach will also be undertaken using the data from the CHU9D questionnaire to synthesise QALYs for the children and compare the interventions using an incremental costs per QALY approach. To measure the benefits which would not be captured in the metric of a QALY, a costs consequence will be used to compare costs and benefits from a wider perspective (for example the broader costs to families).

11.2 Measurement of Costs

A bespoke questionnaire will be used to collect information in relation to the use of health and personal social services (PSS) for the child and the time that this diverts away from usual activities. It will also measure the amount of time the caregivers must spend to provide care. The questionnaire will be administered at baseline, 24 weeks and 52 weeks follow up periods. The costs for NHS and PSS use will estimated by combining the information on the amount of resources which the child has used with nationally available unit costs for these services. Study specific estimates will be used in the absence of any nationally published costs. These costs will be used to produce a mean cost of services utilised for each child.

Travel costs will be measured using a separate questionnaire which has been used in other large trials to estimate the average cost of attending specific kinds of health services (e.g. GP or outpatient appointments). The travel costs will be valued according to the type activity that the travel is displacing (work or leisure time) and valued appropriately based on a review of the literature in the UK. From these two estimates a mean costs per child in each arm of the trial will be calculated.

11.3 Measurement of Effects

For the costs effectiveness analysis the effectiveness measure will be based on the results from the primary trial outcome; the target mean difference in the CGI-I.

The costs utility analysis will use the responses from the CHU9D based on the proxy responses from child's caregiver. The CHU9D will be administered at baseline, 24 weeks and 52 weeks. This will measure the quality of life of the child which will be converted into QALYs for each child using the under the curve approach and an average incremental cost per QALY in each randomised arm will be calculated.

The caregiver will complete ED-5D-5L at baseline, 24 and 52 weeks. These responses will measure quality of life in relation to the caregiver and will be scored using the values sets for England. This data will also be converted into QALYs using the under the curve approach. The QALYs which are calculated for the carers will be included as part of the cost consequence analysis. Further consequences will be examined as part of the cost consequences analysis including primary and secondary clinical outcomes, particularly the health related quality of life of the child and their care-giver. These will include benefits which cannot be included with the scope of the QALY outcome.

11.4 Analysis

For the costs effectiveness analysis an incremental cost per unit change in the CGI-I scale will be calculated, with the aim of calculating the cost for achieving a minimally important difference in the CGI-I. Point estimates of costs and effects, cost effect plots and acceptability curves will be produced. Statistical imprecision and uncertainty will be examined using a stochastic sensitivity analysis. The cost utility analysis will be analysed in a similar way, to the cost effectiveness analysis. A formal decision analytic model is not currently predicted but may be used if the cost of the intervention is not offset by a reduction in resource use or gain in QALYs for the child. If the results are conclusive (i.e. the intervention more effective and less costly or less effective and more costly) then a model will not be required.

The cost consequence analysis will present the costs and consequences as a difference between randomised groups with appropriate measures of variance.

12 DATA HANDLING

12.1 Data Collection Tools and Source Document Identification

Data relating to health service resource use will be collected using a questionnaire administered at baseline, 24 weeks and 52 weeks. The data collection tool will be informed from instruments used in previous studies and from other research teams (www.dirum.org). The questionnaire will collect information on the kind of services which were accessed and how frequently they were utilised.

A questionnaire will be administered to assess time and travel costs at 52 weeks (which has been used successfully in a large number of previous studies) which will be used to estimate the mean time and travel for costs for accessing each specific types of care.

Data including the number of patients screened, approached and interested in taking part will be collected via a log completed by staff conducting screening.

The Clinical Data Management System (Elsevier's MACRO) used for this trial is fully compliant with all regulatory frameworks for research of this nature. It uses a secure web-based interface for data entry; no data are stored on computers at site. MACRO users are assigned role based permissions specific to their site and role. The system has an inbuilt back-up facility, through Elsevier's hosting partner Rackspace's secure premises in London, and is managed and supported by the Rackspace team.
Trial data for an individual patient will be collected by each PI or their delegated person and recorded in the electronic case report form (eCRF) for the trial. Patient identification on the eCRF will be through a unique trial identifier number. A record linking the patient's name to the unique trial identifier number will be held only in a locked room at the trial site, and is the responsibility of the PI. As such, patients cannot be identified from eCRFs. The CI or delegated person will monitor completeness and quality of data recording in eCRFs and will correspond regularly with site PIs (or their delegated team member) with the aim of capturing any missing data where possible, and ensuring continuous high quality of data.

Participants will complete the paper assessment tools as required. The tools will also only be identified using the unique patient identifier number. Data will be entered at sites onto a secure online system, with the paper originals remaining at site.

12.2 Data Handling and Record Keeping

Overall responsibility for data collection lies with the CI. Data collected on paper assessment tools will be entered onto a secure validated clinical data management system at sites. A unique trial number is allocate at randomisation and will be used to identify participants on all paper data collection forms throughout the duration of the trial. No participant identifiable data will leave the study site. The quality and retention of study data will be the responsibility of the CI. All study data will be retained in accordance with the latest Directive on GCP (2005/28/EC) and local policy.

12.3 Access to Data

Staff involved in the conduct of the trial, including the PIs, Trial Management Group and therapist staff involved in screening and intervention will have access to the site files.

Clinical information shall not be released without the written permission of the participant, except as necessary for monitoring and auditing by the Sponsor, its designee, Regulatory Authorities, the DMC or the REC. Secure anonymised electronic data may however be released to the trial statistician for analysis. The PI and trial site staff involved with this trial may not disclose or use for any purpose other than performance of the trial, any data, record, or other unpublished, confidential information

disclosed to those individuals for the purpose of the trial. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

12.4 Archiving

All trial data will be archived until 3 years after the youngest subject reaches 18 years old in accordance with GCP and the Sponsor and Newcastle CTU SOPs.

13 MONITORING, AUDIT & INSPECTION

The trial may be subject to audit by representatives of the Sponsor or inspection by the HTA. Each investigator site will permit trial-related monitoring, audits and regulatory inspection including access to all essential and source data relating to the trial.

14 ETHICAL AND REGULATORY CONSIDERATIONS

14.1 Research Ethics Committee Review and Reports

The CI will obtain a favourable ethical opinion from an NHS Research Ethics Committee (REC) prior to the start of the trial. All parties will conduct the trial in accordance with this ethical opinion.

The NCTU will notify the REC of all required substantial amendments to the trial and those non-substantial amendments that result in a change to trial documentation (e.g. protocol or patient information sheet). Substantial amendments that require a REC favourable opinion will not be implemented until this REC favourable opinion is obtained. The NCTU will notify the REC of any serious breaches of GCP or the protocol, urgent safety measures or USARs that occur during the trial.

An annual progress report will be submitted each year to the REC by NCTU until the end of the trial. This report will be submitted within 30 days of the anniversary date on which the original favourable ethical opinion was granted.

The NCTU will notify the REC of the early termination or end of trial in accordance with the required timelines.

14.2 Peer Review

The trial has undergone peer review as arranged by the NIHR HTA as part of the funding process. The protocol has been reviewed and authorised by the sponsor, funder, Chief Investigator, co-applicants, Senior Trial Manager and Senior Statistician.

14.3 Public and Patient Involvement

From the outset, parents have been involved in development groups and have contributed to the design of the intervention, such as proposing the use of video feedback as a strategy for working on child RRB. They also informed the content of the parent information sheets, including how to explain the need for randomisation, keeping researchers 'blind' and recommended the best ways to sustain contact between families and the research team. This active collaboration has improved the intervention and research design. The trial will include a parent advisory group and parents as steering group members. Parents will oversee recruitment/retention strategies, implementation of study procedures and co-lead dissemination plans. The parents involved in this research will receive appropriate training, support and payment for their contributions following INVOLVE guidelines. In our RfPB study parents facilitated the end of study focus groups following training and supervision in quantitative research methods. The parent experts (including a National Autistic Society specialist advisor and co-applicant) have contributed to and agreed this full application, will co-author reports and present the findings.

14.4 Regulatory Compliance

The trial will be conducted in accordance with the UK Policy on Health and Social Care Research. Before any site can enrol patients into the trial, that site must be in receipt of Health Research Authority (HRA) approval, have issued capacity and capability confirmation and been issued the green light to recruitment by NCTU.

14.5 Notification of Serious Breaches to GCP and/or the Protocol

A serious breach is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or
(b) the scientific value of the trial

The sponsor must be notified immediately of any incident that may be classified as a serious breach. The NCTU will notify the NHS REC within the required timelines in accordance with the NCTU SOP.

14.6 Data Protection and Patient Confidentiality

Data will be handled, computerised and stored in accordance with the General Data Protection Regulation.

14.7 Indemnity

The sponsor will provide indemnity in the event that trial participants suffer negligent harm due to the management of the trial. This indemnity will be provided under the NHS indemnity arrangements for clinical negligence claims in the NHS.

The substantial employers of the protocol authors will provide indemnity in the event that trial participants suffer negligent harm due to the design of the trial.

The trial sites will provide indemnity in the event that trial participants suffer negligent harm due to the conduct of the trial at their site under the NHS indemnity arrangements for clinical negligence claims in the NHS. NHS Organisations must ensure that site staff without substantive NHS contracts hold honorary contracts to ensure they can access patients and are covered under the NHS indemnity arrangements. Trial staff without NHS contracts e.g. General Practitioners or Dentists will provide their own professional indemnity.

This is a non-commercial trial and there are no arrangements for non-negligent compensation.

14.9 Amendments

It is the responsibility of the Research Sponsor to determine if an amendment is substantial or not and study procedures must not be changed without the mutual agreement of the CI, Sponsor and the Trial Management Group & Trial Steering Committee.

Substantial amendments will be submitted to the REC and will not be implemented until this approval is in place. It is the responsibility of the NCTU to submit substantial amendments.

Non-substantial amendments may be made at any time with a record of the amendment held in the Trial Master File. Any non-substantial amendment that requires an update to the trial documentation will be submitted to the NHS REC for acknowledgement of the revised version of the document.

Substantial amendments and those minor amendments which may impact sites will be submitted to the relevant NHS R&D Departments for notification to determine if the amendment affects the NHS permission for that site. Amendment documentation will provide to sites by the NCTU.

14.10 Post-Trial Care

If participants have health related care needs that arise following participation in the intervention but are not identified until the final follow-up assessment; we will signpost families to their primary care physician (General Practitioner), or for those who are already within secondary care we will advise them to contact their clinicians.

14.11 Access to the Final Trial Dataset

The data will be the property of the Chief Investigator and Co-Investigators. Any requests to access the final trial dataset may be considered under the NCTU data sharing policy.

15 DISSEMINATION POLICY

The dissemination strategy for this research will include several complementary strands of activity:

Local dissemination at each site:

- Newsletters summarising the progress and findings of the study will be designed by the research team and parent advisors. These will be sent to families and local professionals who have taken part in recruitment and supported the study, both during the trial to support retention, and at the end of the study to share findings.

- A celebration event to be held at the end of the study at each site, where the findings of the study will be presented to an audience of participating families, local professionals, the study steering group and stakeholders who supported the study (including if possible a presentation by a parent participant).

Wider national and international dissemination:

- The parent representatives on the steering group, with support from the research team, will submit an article to the INVOLVE newsletter and present the study findings at appropriate parent/third sector/professional conferences e.g. National Autistic Society Annual Conference.

- Reports in accessible newsletters such as Your Autism and Your Impact (NAS), Asperger United.

- Dissemination via websites (Autistica, Centre for Developmental Disorders and Childhood Autism Research Group Online) and social media (including Twitter and Facebook) to access a wider audience.

- The study protocol will be published, and findings will be written up for academic peer reviewed journals (including open access) and presented at relevant national and other conferences including the International Meeting for Autism Research.

NHS Clinicians and Commissioners:

- The conclusions will be presented to interested members of the public and for commissioners of services within official websites such as networkautism.org.uk.

- Workshops will be held across the three sites for families of children with ASD, clinicians, service managers and commissioners to discuss the implications of the research. The aim will be to raise awareness of behavioural interventions to target challenging RRB in young children with ASD.

- We will ensure clinicians can access the findings, if found to be effective, the manualised intervention will be available through NTW NHS Trust and disseminated through targeted training workshops in conjunction with professional bodies to stimulate discussion on both the research findings and clinical applications.

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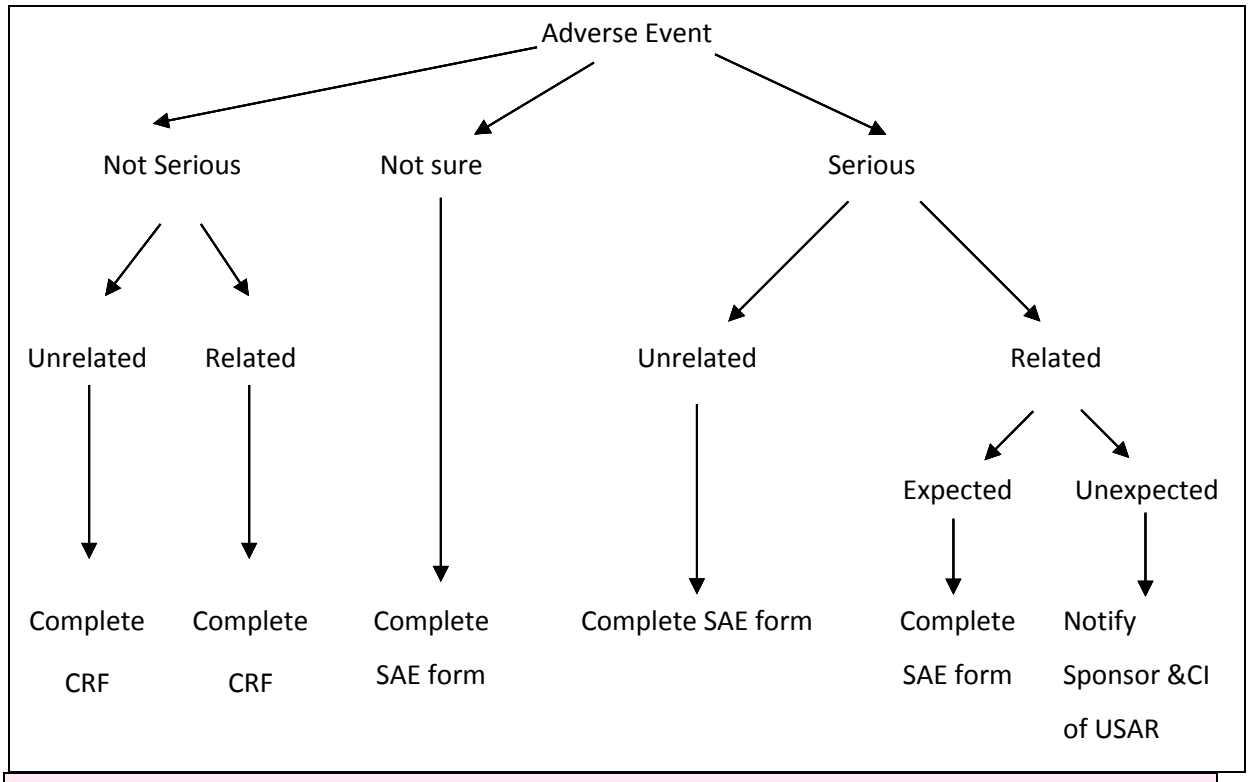
17 APPENDICES

17.1 Appendix 1 - Safety Reporting Diagram



Contact details for reporting SAEs and USARs

Please see SAE reporting guidelines document for sending SAE forms to NCTU

17.2 Appendix 2 – Amendment History

Amendment Number	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
N/A	02	25 July 2018	Trial Manager/ Statistician	Clarity on archiving period and minimisation factors
N/A	01	20 June 2018	N/A	Original version