FULL/LONG TITLE OF THE TRIAL

A randomised controlled trial comparing the effectiveness of a therapist-led intervention (SAFE: Systemic Autism-related Family Enabling) plus treatment as usual versus treatment as usual only on global family functioning and mental health in three dimensions (strengths and adaptability, coping with difficulties and problem solving, communication and understanding) in families of autistic children: a multicentre assessor-blinded trial with parallel process evaluation and economic evaluation.

SHORT TRIAL TITLE

The SAFE Trial: A randomised controlled trial and economic evaluation of SAFE (Systemic Autism-related Family Enabling) plus treatment as usual versus treatment as usual for family functioning and mental health in families of autistic children.

PROTOCOL

Version 1.0 20th Feb 2026

IRAS ID:	343024
ISRCTN:	ISRCTN89355835
Funder's reference number:	NIHR167788
Sponsor:	Devon Partnership NHS Trust

This protocol has regard for the HRA guidance and order of content.

i. SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and in accordance with the UK Policy Framework for Health and Social Care Research, the Data Protection Act 2018), the principles of Good Clinical Practice (GCP) and the Sponsor's (and any other relevant) SOPs.

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 clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly 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.

For and on behalf of the Trial Sponsor:

Name: Dr Tobit Emmens
Position: Associate Director of Research and Development, Devon Partnership NHS Trust

Signature: 

Date: 2nd March 2026

Lead Applicant & Chief Investigator:

Name: Dr Rebecca Stancer

Signature: 

Date: 2nd March 2026

Interim Co-Chief Investigator:

Name: Dr Tom Thompson

Signature: 

Date: 2nd March 2026

Senior Trial Statistician:

Name: Professor Victoria Allgar

Signature: 

Date: 2nd March 2026

ii. PROTOCOL MODIFICATION HISTORY

Modification No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
NA	1.0	20Feb2026	NA – First version	NA – First version.

iii. KEY TRIAL CONTACTS

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Mrs Jessica Lane, Glendinning Academy Devon, PPIE Representative
Data Monitoring Committee
Chair: Dr Mike Blows, Clinical Psychiatrist (Freelance), mikeblows@hotmail.com Independent members: Prof Judi Kidger, Professor of Public Mental Health, University of Bristol, Judi.Kidger@bristol.ac.uk Dr Saskia Eddy, Assistant Professor in Medical Statistics, University of Sussex, s.eddy@bsms.ac.uk

iv. LIST OF CONTENTS

TABLE OF CONTENTS

v. LIST OF ABBREVIATIONS

AC	Autistic child (the family index case)
ADHD	Attention Deficit Hyperactivity Disorder
AE	Adverse Event
ALCOA	Attributable, Legible, Contemporaneous, Original, Accurate
ASD	Autism Spectrum Disorder
CAMHS	Child and Adolescent Mental Health Services
CARP-A	Coding of Attachment Related Parenting for use in children with Autism
CEA	Cost Economic Analysis
CFIR	Consolidated Framework for Implementation Research
CHU-9D	Child Health Utility 9 Dimensions
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CPD	Continuing Professional Development
CTCAE	Common Terminology Criteria for Adverse Events
CTU	Clinical Trials Unit
DBS	Disclosure and Barring Service
DMEC	Data Monitoring and Ethics Committee
DMP	Data Management Plan
DSM	Diagnostic and Statistical Manual of Mental Disorders
DPT	Devon Partnership NHS Trust
(e)CRF	Case Report Form
ED	Eating disorders
EDI	Equality, Diversity and Inclusion
EHCP	Education Health and Care Plan
EOI	Expression of Interest
ERIC	Expert Recommendations for Implementing Change
EQ-5D-5L	EuroQoL 5 Dimensions 5 Levels
FT	Family Therapist
GAD-7	Generalised Anxiety Disorder-7 Questionnaire
GDPR	General Data Protection Regulations
GP	General Practitioner
HAT	Helpful Aspects of Therapy questionnaire
HEAP	Health Economics Plan
HTA	Health Technology Assessment
HRA	Health Research Authority
IAPT	Improving Access to Psychological Therapies
ICEPOP-A	ICEpop CAPability measure for Adults
(ICH) GCP	(International Council for Harmonisation) Good Clinical Practice
ID	Identification
IDPPI	Inclusion and Diversity Patient and Public Involvement
IMD	Index of Multiple Deprivation
IP	Intellectual Property
IRAS	Integrated Research Application System

ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention to Treat
LA	Local Authority
MRC	Medical Research Council
NCI	National Cancer Institute
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
OCD	Obsessive-Compulsive Disorder
PC	Primary Caregiver
PDI	Parent Development Interview
PenCTU	Peninsula Clinical Trials Unit
PI	Principal Investigator
PIC	Participant Identification Centre
PID	Participant Information Document
PIS	Participant Information Sheet
PHQ-9	Patient Health Questionnaire – 9
PPI(E)	Patient and Public Involvement (and Engagement)
PRO	Patient Reported Outcome
QALY	Quality Adjusted Life Year
RA	Research Assistant
RAG	Red, Amber, Green (Progression Criteria)
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RUQ	Resource Use Questionnaire
SAE	Serious Adverse Event
SAFE	Systemic Autism-related Family Enabling
SAFE+TAU	SAFE plus Treatment as Usual
SAM	Self Autism Mapping
SAP	Statistical Analysis Plan
SCORE-15	Systemic CORE 15
SD	Standard Deviation
SEND	Special Educational Needs and Disabilities
SES	Socio-economic Status
SOC	Service Organisation Control
SOP	Standard Operating Procedure
TAU	Treatment as Usual
TCQ	Training and Checklist Questionnaire
TMF	Trial Master File
TMG	Trial Management Group
TMP	Trial Monitoring Plan
TSC	Trial Steering Committee
UKATT PRS	UK Alcohol Treatment Trial Process Rating Scale
USM	Urgent Safety Measure
WHO	World Health Organisation
YFC	Years of Full Capability

vi. DEFINITIONS

Autism Spectrum Disorder (ASD)

For the purposes of the SAFE trial, Autism Spectrum Disorder (ASD) will be defined as a diagnosis according to the Diagnostic and Statistical Manual of mental disorders, 5th edition: DSM-5 (edited by American Psychiatric Association, 2013)[1].

Family

The SCORE-15 family assessment instrument defines a family as any group of people who care about each other and define themselves as such. For the purposes of this study, all references to 'family' mean those family members who are willing to participate in the study assessments and who would be willing to consent to take part in family therapy sessions (if randomised to the intervention group). The SAFE study will orient people towards thinking of household members, but invite them at baseline (prior to randomisation) to choose who they want to invite to consent to be included in study assessments and therapy sessions (if applicable). This will typically include the parent(s) of the autistic child (henceforth autistic child, AC), the AC, the sibling(s) and additional family members that have a significant level of involvement with the AC. The minimum number of family members that will be required to be present for a family therapy session (if the family is allocated to the intervention) is the primary caregiver and the AC.

vii. TRIAL SUMMARY

HTA programme title	A randomised controlled trial to evaluate the effectiveness and cost-effectiveness of SAFE (Systemic Autism-related Family Enabling), an intervention for families of autistic children.
Full title	A randomised controlled trial comparing the effectiveness of a therapist-led intervention (SAFE: Systemic Autism-related Family Enabling) plus treatment as usual versus treatment as usual on family functioning and mental health in three dimensions (strengths and adaptability, coping with difficulties and problem solving, communication and understanding) in families of autistic children: a multicentre assessor-blinded trial with parallel process evaluation and economic evaluation.
Short title	The SAFE Trial: A randomised controlled trial and economic evaluation of SAFE (Systemic Autism-related Family Enabling) plus treatment as usual versus treatment as usual for family functioning and mental health in families of autistic children.
Trial acronym	SAFE
Trial design	Multicentre, two-arm, randomised controlled assessor-blinded trial of SAFE (intervention) plus Treatment as Usual (TAU) versus TAU (control) with parallel process evaluation and economic evaluation and an internal pilot.
Trial setting	6 NHS locations across UK
Trial participants	Families including a child aged 3-16 years with a diagnosis of autism severity level 1 or 2, and a Primary Caregiver. If co-morbid conditions are present in addition to autism (e.g. ADHD, OCD, ED, epilepsy), autism is the primary diagnosis.
Planned sample size	494 families of autistic children (2:1 randomisation to SAFE+TAU or TAU).
Trial arms	Intervention: Systemic Autism-related Family Enabling (SAFE) plus TAU. Control: TAU for 20 weeks.
Treatment duration	20 weeks (7 sessions: 2 x 3 hour and 5 x 2 hour)
Follow-up duration	22 weeks and 52 weeks post-randomisation
Planned trial period	48 months total study duration: set-up 9 months, recruitment, intervention and follow-up 32 months, analysis & write-up 7 months.
End of study	Date that last family has completed the 52-week follow-up visit (Last Patient Last Visit) and all data collection activities are complete.
Aim	To conduct a randomised controlled trial (RCT) to compare the effectiveness and assess the cost-effectiveness of SAFE plus TAU with TAU alone.
Primary objective	Test effectiveness of SAFE plus TAU (intervention) with TAU alone (control) on family functioning and mental health of the primary caregiver as measured by the SCORE-15.
Primary outcome	Systemic Clinical Outcome and Routine Evaluation-15 (SCORE-15) total score at 22 weeks post-randomisation.

Secondary objectives	Test effectiveness of SAFE plus TAU (intervention) with TAU alone (control) with respect to: 1) Family functioning, 2) Child-parent attachment, 3) Anxiety and depression, 4) Frequency and severity of extreme behavioural outbursts (meltdowns) experienced by the autistic child (AC) participant.
Secondary outcomes	1) SCORE-15 total score (52 weeks post-randomisation) and dimension scores; Child SCORE-15 total score and dimension scores, 2) Coding of Attachment Related Parenting for use with AC (CARP-A) score, 3) Patient Health Questionnaire – 9 (PHQ-9) and Generalised Anxiety Disorder – 7 Questionnaire (GAD-7) scores, 4) Frequency and severity of behavioural outbursts by the AC participant.
Economic evaluation objectives	Assess the cost, cost-effectiveness and cost-utility of SAFE plus TAU compared to TAU alone
Process evaluation objectives	1) Produce an implementation guide/toolkit. 2) Monitor intervention delivery fidelity. 3) Refine the theory of change/logic model.

viii. FUNDING AND SUPPORT IN KIND

FUNDER(S)	FINANCIAL SUPPORT GIVEN
National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme	Total research costs: £2,820,056.90

ix. ROLE OF TRIAL SPONSOR AND FUNDER

The Sponsor for this study, Devon Partnership NHS Trust, assumes overall responsibility for the initiation and management of the trial in accordance with the current UK policy for conduct of health and social care research.

The Sponsor and funder will not have direct involvement in trial design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results.

The trial was designed by the Chief Investigator, co-lead applicant and co-applicants (including patient representatives) with support from the NIHR Research Support Service Hub (Southampton and Partners) and the Peninsula Clinical Trials Unit (CTU).

x. ROLE OF THE COORDINATING CLINICAL TRIALS UNIT (CTU)

The Sponsor of the study has allocated tasks associated with overall trial management and data management to the Peninsula CTU (PenCTU) at the University of Plymouth (UoP). A detailed breakdown of tasks undertaken by PenCTU on behalf of the CI and trial Sponsor is described in a formal written Sponsor agreement and task allocation matrix.

xi. ROLES OF TRIAL OVERSIGHT COMMITEES AND GROUPS

The Trial Steering Committee (TSC) is an executive oversight body operating on behalf of the Sponsor and will make decisions as to the future continuation (or otherwise) of the trial. The TSC has an independent chair (Dr Ben Grey), independent clinicians (Dr Chip Chimera, Dr Mark Hudson, Dr Rebecca Kandiyali, Dr Hannah Wilson), independent statistician (Dr Christopher Newby) and PPIE representatives (Dr Sarah Williams, Mrs Jessica Lane).

The Data Monitoring and Ethics Committee (DMEC) is an independent committee that takes a particular interest in participant safety, data quality and ethical conduct of the study. The DMEC also reviews any interim analyses and may view unblinded data on request. DMEC recommendations in relation to continuing or halting the trial are made directly to the chair of the TSC. The DMEC has an independent chair (Dr Mike Blows) and independent experts Prof Judi Kidler and Dr Saskia Eddy.

The TSC and DMEC will meet at every 6 months in accordance with an agreed set of terms of reference to review the progress of the trial and will report to the Sponsor.

The Trial Management Group (TMG) is chaired by the CI and includes representation from the Sponsor, process evaluation team, health economics team, statistics team, Patient Advisory Group/public/advocates and PenCTU. The TMG and will meet monthly to review trial progress and to ensure appropriate management of the trial, in accordance with the terms of reference for the Group.

xii. KEY WORDS

Randomised Controlled Trial, economic evaluation, process evaluation, Autism, Family Therapy, mental health**.**

xiii. Protocol contributors

Several contributors have been involved in the development of this protocol; these include the CI's (Dr Rebecca Stancer and Dr Tom Thompson), trial statisticians (Prof Victoria Allgar, Dr Jade Chynoweth), Co-Applicants (Prof Rudi Dallos, Dr Elizabeth Goodwin, Prof Annie Hawton, Dr Tara Vassallo, Dr Janet Georgeson), as well as members of the PenCTU trial management (Dr Wendy Ingram, Miss Kayle-Anne Sands, Miss Emma O'Shaughnessy, Miss Rebecca Petty) and data management team (Dr Paigan Aspinall, Dr Helen Hambly).

xiv. TRIAL FLOW CHARTS

Figure 1. Simplified participant flow chart

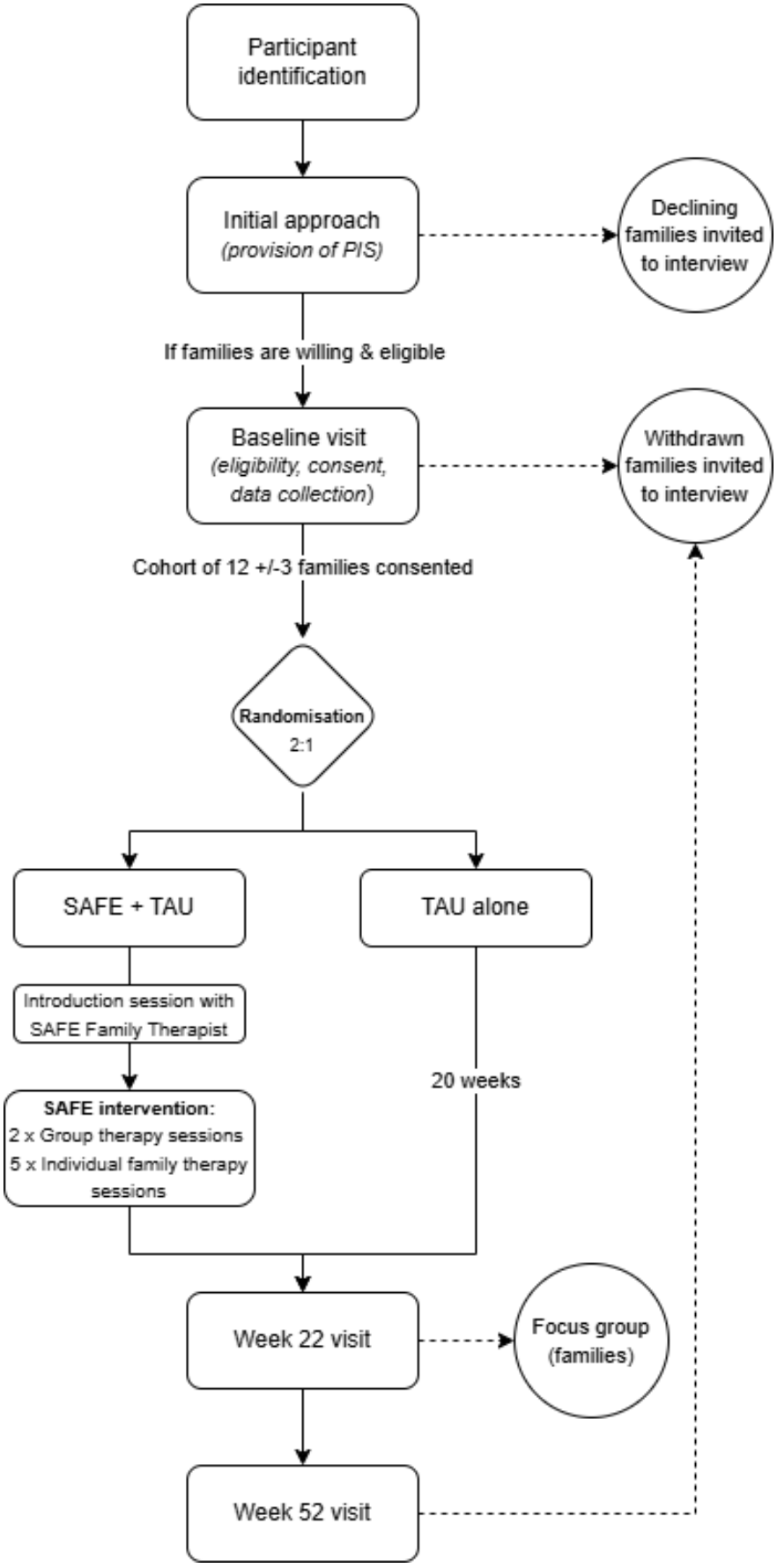
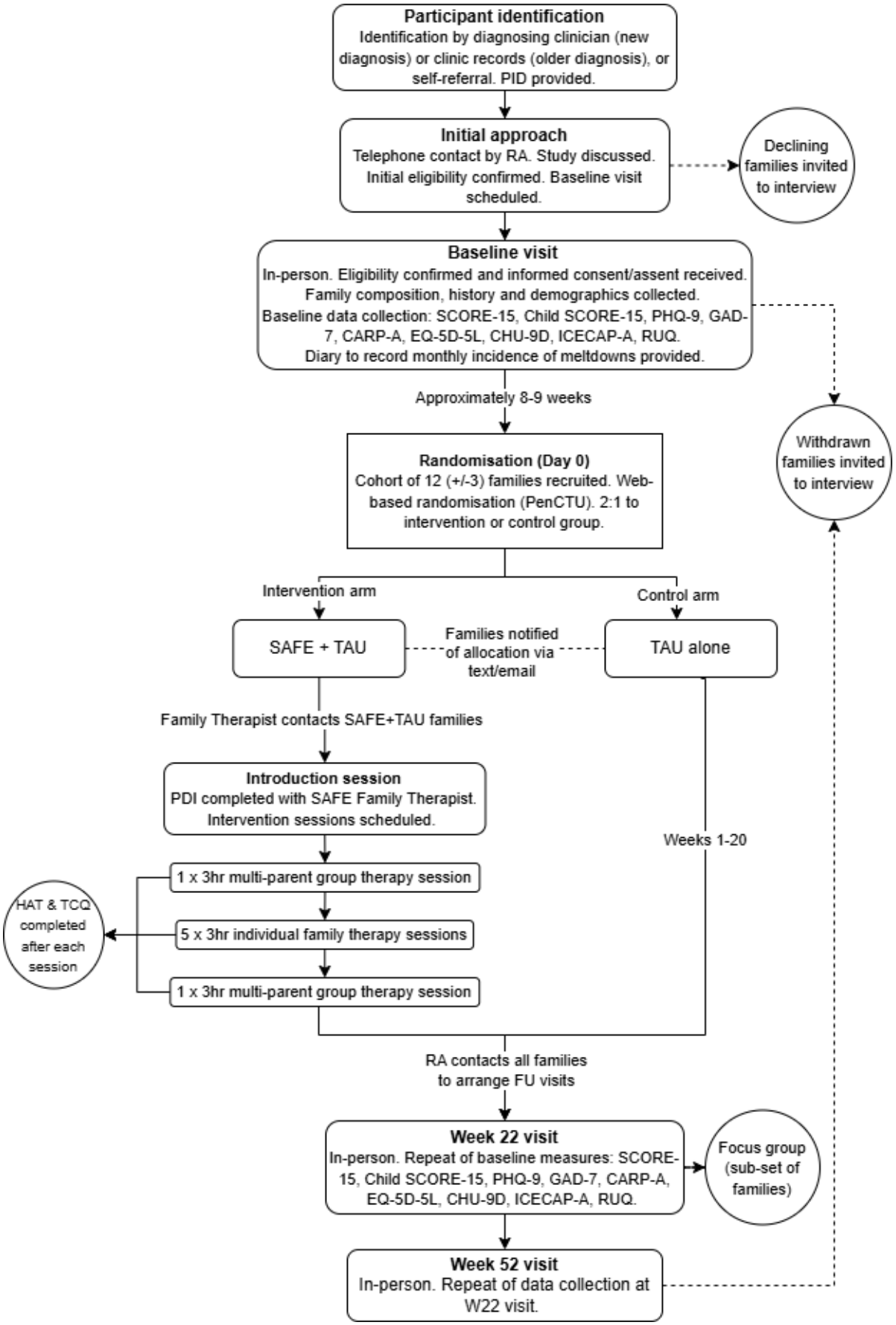


Figure 2. Detailed participant flow-chart



1 BACKGROUND AND RATIONALE

1.1 Problem addressed

UK autism prevalence is around 2% [1, 2] and 2.44% of school children have a diagnosis [3]. Autistic people display difficulties in socio-communication and restricted interests [4] with high risk of mental health problems, trauma, suicidality and severe behavioural distress [5-7]. Autism is disproportionally represented among relatives of autistic children [8] and affects more than 2.8 million family members [9]. >70% of autistic individuals have mental health disorders and 40% have two or more. Mental health problems occur in >50% of parents [4, 10-14], who are more frequently hospitalised for mental disorders than other parents [15]. These families are more likely to experience stigma, victimisation and abuse, increased incidence of Adverse Childhood Events [16] and risk of traumatisation compared to others [17-20]. Around 50% of autistic people engage in self-injurious behaviour and suicidal ideation occurs in more than a third (34.2%) of autistic people and those with autistic traits, including relatives of autistic children [21]. Approaching a quarter of this population (24.3%) attempt suicide, with causes linked to poor mental health [22], poor socio-communicative skills, isolation, rigid thinking and unmet support needs [23, 24]. Suicidality begins early and is reported in over a third of autistic children including those < 8 years old [25]. Autism is a life-limiting condition with average life expectancy being 54 years. Reasons include comorbid conditions, self-injury, suicide and difficulty advocating for themselves, accessing support or explaining health needs [26].

Autistic individuals and relatives can experience lack of reflective thinking [27], compromised social communication, and isolation [28], factors associated with poor coping, depression and suicidality [29]. Challenges of parenting autistic children increases risk of psychiatric problems in siblings and parents [30] exacerbating child behavioural distress [31] and maintaining negative cycles [32, 33]. Families can struggle to communicate needs to each other and to external agencies [34, 35]. Early support makes a difference, and these families can experience positive family life [36-40]. Resilient families [41, 42] show key attributes: good communication between family members including collaborative responses to challenges [43], capitalising on strengths, pulling in resources, finding shared positive meaning in adversity, and flexibility in solving problems [44, 45]. Families of autistic children highlight the importance of working with the whole family [46], early intervention and support for mental health and behaviour issues [46, 47].

SAFE is a systemic therapy intervention [48] designed to address these gaps in care and provide a preventative intervention targeting multifaceted escalation towards crisis amongst these families. SAFE sessions involve the whole family addressing autism-related mental health difficulties, poor coping, communication, and behavioural distress.

1.2 Research Importance

Current care is inappropriate, ineffective and disjointed with little regard for associated mental health issues [49-51], resulting in crisis, escalation and increase in residential care [7, 49], contributing to an annual economic burden of > £32B [52, 53]. The Westminster Commission on Autism [53] identifies autism as a life-limiting condition [54] with substantial unmet health needs, highlighting urgent need for new treatments [53].

1.3 Review of Existing Evidence

Systemic Family Therapy is used in the NHS, is an evidence-based approach [55], and recommended treatment for conduct disorder [56], ADHD and Anorexia [57]. Two large Meta analyses of RCTs evaluating family therapy for these and other conditions indicate that it is effective

(d = >.64) [58, 59]. Despite evidence that family therapies have potential to benefit autistic children and their families [60-65] a search of clinical trial registries including ISRCTN Registry, clinicaltrials.gov and World Health Organisation (WHO) trials using search terms 'autism' and 'Family Therapy' revealed no on-going or completed trials assessing Family Therapy as a treatment for autism except our own published feasibility study [48] and a study in Iran focusing solely on mother and autistic child interaction and using a 'family eclectic model' with 30 participants [66]. RCTs have, however, found Family Therapy to be effective for both internalizing (d = .78) and externalizing problems (d = .68) associated with behavioural distress [50], anxiety (d = 1.24), depression (d = 1.21) and suicidal ideation (d = .52) [67] among families of non-autistic adolescents. A meta-review [68] for Multi Family Therapy in autism found no completed RCTs and a Cochrane Review [69] found no RCTs and few studies assessing the use of Family Therapy for families of autistic children, concluding that: "*More research studies are needed to evaluate the effectiveness of family-focused interventions to enhance communication, reduce stress and improve coping*."

1.4 Plain English Summary

Background: Autism affects around 2% of people in the UK. Autistic children often struggle with communication and social interaction, and may experience distress or challenging behaviour. This can be hard for families, who often face poor mental health. Support after diagnosis is often not enough or suitable.

A new support programme (called SAFE) has been developed with families of autistic children . SAFE includes proven approaches to help families manage the challenges of autism, such as so-called meltdowns. SAFE supports the whole family. Sessions are led by trained therapists and use talking, images, and play to explore autism-related challenges, behaviour, wellbeing, and coping.

In the SAFE programme, there are two sessions where all the parents from about 12 families meet with the therapists as a group, and five sessions where each family meets with the therapist separately. These seven sessions take about 20 weeks.

Aim: This study will test whether SAFE improves family mental health and coping compared to usual care, and whether it is feasible and affordable for the NHS. Usual care is what families receive from the NHS or local authority.

Design and methods: Around 500 families who are in the care of NHS services for autism will take part. The autistic child and their main carer must take part; families can choose who else in their family takes part. Families will be randomly split into two groups: Two thirds of families will receive SAFE plus usual care, and one third will receive usual care only.

All families will complete questionnaires at the beginning and about 5 months later (after the SAFE programme ends) and at 12 months. In this way, we will measure changes in family mental health family strengths, communication and coping. Families will also share their experiences in group discussions with a researcher.

2 RISK ASSESSMENT AND MANAGEMENT

SAFE is a new intervention designed to address autism-related needs including problem-solving, poor communication, mental health difficulties and challenging behaviour.

SAFE has been developed from well-recognised, evidence-based approaches: Systemic Family Therapy, Multi-family therapy and family models. Systemic Family Therapy is widely used in the NHS for complex cases where family members may have been diagnosed with a range of conditions such as eating disorders, psychosis or ADHD. SAFE differs in that it is tailored specifically to families of autistic children, but it draws from the same evidence base and employs commonly used systemic activities, adapted for this population. Family Therapy is a low-risk intervention especially where it includes playful experiential activities [70] (which SAFE does). A systematic review of 47 RCTs exploring systemic therapies found “no indication for adverse effects of systemic (family) therapy” [71]. The SAFE therapists will check with families that they are comfortable with what is asked of them and they will not be asked to do anything they are not happy to do. At the start of each session the therapists will ask each family member if any significant events have arisen for them (Positive or negative). This will inform ways forward. The therapists will offer opportunities to discuss anything that has been triggering or upsetting for them. At the end of every session Families complete the helpful Aspects of Therapy Questionnaire which asks them about what was helpful or unhelpful and this will also inform future discussions and ways forward. At each trial location there will be clinicians who can offer support as part of usual care which may also include GP practices including those families who self-refer. In addition, families will be signposted to further support including that provided by NHS, local authority and third sector during the intervention.

In preliminary work, the design of SAFE had extensive input from Families of autistic children, NHS and third sector service providers working with this population, Senior Family Therapists and academic experts in autism and has been optimised for use in the SAFE2 trial, benefiting from substantial and ongoing PPI review.

The SAFE intervention is autism-friendly and will be delivered by experienced Family Therapists who have received additional specific training from consultant systemic practitioners with extensive experience in working with this population. Therapists will also receive fortnightly supervision from experienced systemic practitioners conversant with SAFE principles and approaches.

In the SAFE Feasibility RCT [48], the intervention was delivered to 34 families at two locations in the UK. Participant safety was monitored via reporting of SAEs, and assessment of the relatedness of any SAEs to the intervention or to trial procedures, over the 12-month follow-up period. No detectable harm related to the intervention or trial procedures was detected.

We consider this a low-risk intervention; similarly, trial procedures are non-invasive and pose no significant risk to participants.

A risk protocol will be developed to be initiated by research staff if a participant is perceived to exhibit new instances of suicide risk, i.e., expresses suicidal ideation, thoughts of self-harm, or thoughts of harm to others. Risk may present through responses to questionnaire items, or the participant may disclose information during study visits, e.g., SAFE sessions.

3 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

The overarching aim of this study is to test the effectiveness of SAFE in reducing family autism-related mental health including distress associated with child behaviour focusing on: coping with challenges (including behavioural distress), improving family communication and wellbeing, and increasing perceived family strengths compared with TAU alone. Also, to test whether any effects on primary and secondary outcomes are reported at 22 weeks and 52 weeks post randomisation.

This protocol describes a randomised controlled trial to compare the effectiveness and assess the cost-effectiveness of SAFE+TAU with TAU alone on family functioning and mental health.

3.1 Primary Objective

The primary clinical question of interest is:
What is the difference at 22 weeks post-randomisation in Systemic CORE (SCORE-15) in the primary caregiver in families with a child aged 3-16 years with a diagnosis of autism (as defined by the trial inclusion/exclusion criteria) in families receiving SAFE+TAU (intervention) compared to TAU alone (control), regardless of non-attendance of any number of SAFE sessions for any reason.

The primary estimand has the following attributes:

- **Population**: families including a child aged 3-16 years with a diagnosis of autism (as defined by trial inclusion/exclusion criteria).
- **Endpoint**: SCORE-15 total score at 22 weeks post-randomisation.
- **Treatment condition:** SAFE+TAU (intervention) compared to TAU alone (control) regardless of non-attendance of any number of SAFE sessions for any reason (treatment policy strategy).
- **Key intercurrent events:** The intercurrent event “non-attendance of any number of SAFE sessions for any reason” is addressed by the treatment condition of interest attribute. There are no remaining intercurrent events anticipated at this time.
- **Population-level summary:** Difference in mean SCORE between treatment conditions.

Rationale for estimand: to compare the effectiveness of SAFE+TAU against TAU alone as would be observed in routine practice.

3.2 Primary Outcome Measure

The Systemic CORE-15 (SCORE-15) [72] has been found acceptable by our PPI families, is endorsed by the Association of Family Therapy, and CAMHS Outcome Research Consortium with established reliability and validity as an index of therapeutic change [73]. The SCORE-15 is the gold standard in the UK for evaluating impact of family-based interventions on family mental health, defined as a state of mental well-being that enables people to cope with the stresses of life, realise their potential, learn well, be productive, and take part in their social environment. The SCORE-15 provides scores for overall family mental health and mental health of individuals [72]. SCORE-15 also generates ‘sub-scale’ scores for components of mental health from the 5 items on each of three dimensions 1. Strengths and adaptability (whether families are able to build on strengths, knowledge and resources available and respond flexibly to life events), 2. Coping with difficulties and problem solving (whether families can effectively tackle everyday challenges including behavioural distress, reflect on problems and use techniques and strategies learnt to overcome them), 3. Communication and understanding (whether families can communicate effectively with each other and with outsiders to ensure needs are met). These sub-scales align well to the known autism-related difficulties of

these families and our aim and first objective. In addition, the SCORE-15 can distinguish between families that are i. non-clinical (functioning well and children and young person's difficulties are managed effectively), ii. clinical (children within the family have significant emotional or behavioural problems impacting negatively on the family) and iii. severe clinical (families are in crisis, unable to address child or young person's difficulties and at risk of family disintegration) [74, 75]. Consequently, the SCORE-15 can identify change over time, but also whether families have moved out of crisis or become non-clinical.

The SCORE-15 consists of 15 Likert scale items with a minimal clinically important difference of 3 scale points between total scores at two timepoints reflecting better family mental health evidenced by capitalising on family strengths and resources, increased ability to communicate with each other and outside agencies and improved ability to reflect and resolve difficulties including behavioural distress. The SCORE-15 will be our primary outcome measure at 22 weeks post randomisation, to be completed by the Primary Caregiver (PC).

3.3 Secondary Objectives

To compare the effectiveness of SAFE+TAU against TAU alone with respect to:

1. Family functioning measured by the SCORE-15 and Child SCORE-15.
2. Child-parent attachment measured by the Coding of Attachment-Related Parenting for use in children with Autism (CARP-A).
3. Anxiety and depression measured by the Patient Health Questionnaire – 9 (PHQ-9) and Generalised Anxiety Disorder – 7 Questionnaire (GAD-7) score.
4. Frequency and severity of extreme behavioural outbursts (meltdowns) experienced by the AC.

3.4 Secondary outcome measures

Secondary outcome measures:

- SCORE-15 at 52 weeks post randomisation. To be completed by the PC.
- Child SCORE-15 a version of the SCORE-15 with simplified language and colourful presentation suitable for children >7 years with established reliability and good internal consistency [76]. This will be completed by child participants (e.g. siblings).
- PHQ-9 and GAD-7 [77, 78]. The PHQ-9 measures depression and the GAD-7 measures anxiety. These are short, self-report questionnaires, sensitive to change, widely used in research and clinical practice, and with established correspondence to clinical diagnoses. Both questionnaires will be completed by adult participants, including the PC.
- Mutuality subscale of the CARP-A [79]. The CARP-A is a validated observational measure of mutuality (identifying each other's communicative signals and responding to support a positive interactive communication flow) between an autistic child and their caregiver during a collaborative playful task. This will be completed by the AC and PC to assess family connection and communication and will be video recorded.
- Frequency and severity of extreme behavioural outbursts among AC (meltdowns) recorded by the PC.

All secondary measures have been found acceptable by our PPI families. The CARP-A task was reported as ''fun' and 'enjoyable' by autistic children in our feasibility trial [48].

Where child participants move into the next age category during study participation, e.g. 16 years at baseline to 17 years at follow-up, the same measure completed at baseline will be repeated at

the follow-up assessments (e.g. Child SCORE-15). This also applies for the economic evaluation outcome measures (see Section 10).

3.5 Economic evaluation objectives

Assess the cost, cost-effectiveness and cost-utility of SAFE+TAU compared to TAU alone.

3.6 Economic evaluation outcome measures

Economic evaluation measures:

- EQ-5D-5L assessing health-related quality of life and estimating quality-adjusted life-years (QALYs). To be completed by adult participants, including the PC.
- Child Health Utility 9 Dimensions (CHU-9D) assessing health-related quality of life and estimating QALYs of children. To be completed by child participants if ≥7 years of age, PC proxy report if child 5-6 years of age, or CHU-9D proxy version if child under 5 years of age.
- ICEpop CAPability measure for adults (ICECAP-A) assessing wellbeing via dimensions of Attachment, Stability, Achievement, Enjoyment and Autonomy, estimating wellbeing-adjusted life-years. To be completed by adult participants, including the PC.
- Resource Use Questionnaire (RUQ) to capture health, social care, family and wider societal resource use. To be completed by the PC in relation to the AC.

3.7 Process evaluation objectives and outcome measures

Mixed methods process evaluation objectives and outcome measures described in Section 9.

3.8 Summary of objectives and outcome measures

Objectives	**Outcome Measures**	**Timepoint(s) of evaluation of the outcome measure (if applicable)**
Primary Objective: To compare the effectiveness of SAFE+TAU (intervention) with TAU alone (control) on family functioning and mental health of the primary care giver	Systemic CORE-15 (SCORE-15) total score	(i) Baseline (ii) 22 weeks post randomisation
Secondary Objectives: To compare the effectiveness of SAFE+TAU (intervention) with TAU alone (control) with respect to:		
1. Family functioning	SCORE-15 total score	(i) Baseline (ii) 52 weeks post randomisation
	SCORE-15 strengths and adaptability dimension score	(i) Baseline (ii) 22 weeks post randomisation; (iii) 52 weeks post randomisation.

	SCORE-15 coping with difficulties and problem-solving dimension score	(i) Baseline (ii) 22 weeks post randomisation; (iii) 52 weeks post randomisation.
	SCORE-15 communication and understanding dimension score	(i) Baseline (ii) 22 weeks post randomisation; (iii) 52 weeks post randomisation.
	If a child participant ≥ 7 years of age, Child Systemic CORE-15 (Child SCORE-15) total score	(i) Baseline (ii) 22 weeks post randomisation; (iii) 52 weeks post randomisation.
	Child SCORE-15 strengths and adaptability dimension score	(i) Baseline (ii) 22 weeks post randomisation; (iii) 52 weeks post randomisation.
	Child SCORE-15 coping with difficulties and problem solving dimension score	(i) Baseline (ii) 22 weeks post randomisation; (iii) 52 weeks post randomisation.
	Child SCORE-15 communication and understanding dimension score	(i) Baseline (ii) 22 weeks post randomisation; (iii) 52 weeks post randomisation.
2. Child-parent attachment	Coding of Attachment-Related Parenting for use with autistic children (CARP-A) score	(i) Baseline (ii) 22 weeks post randomisation; (iii) 52 weeks post randomisation.
3. Anxiety & depression	Patient Health Questionnaire - 9 (PHQ-9) score Generalised Anxiety Disorder – 7 (GAD-7) Questionnaire score	(i) Baseline (ii) 22 weeks post randomisation; (iii) 52 weeks post randomisation.
4. Frequency and severity of extreme behavioural outbursts (meltdowns) experienced by the AC participant	Non-validated measure	Monthly from baseline to 52 weeks post-randomisation.
CEA objectives: To assess the cost, cost-effectiveness and cost-utility of SAFE+TAU compared to TAU alone using:		
Resources required to provide the SAFE intervention	Participant-level intervention data	During course of the intervention

1. Health-related quality of life and quality-adjusted life-years (QALYs) for adult participants	QALYs based on the EQ-5D-5L	(i) Baseline (ii) 22 weeks post randomisation; (iii) 52 weeks post randomisation.
2. Health-related quality of life and QALYs of child participants.	If a child participant is ≥7 years of age, QALYs based on the Child Health Utility 9 Dimensions (CHU-9D) (i) from baseline to 22 weeks; (ii) from baseline to 52 weeks. If a child participant is 5-6 years of age, CHU-9D to be completed by Primary Caregiver as proxy. If child participant is <5 years of age, QALYs based on the CHU-9D proxy version.	(i) Baseline (ii) 22 weeks post randomisation; (iii) 52 weeks post randomisation.
3. Capability wellbeing and Years of Full Capability (YFCs).	YFCs based on the ICEpop CAPability measure for Adults (ICECAP-A)	(i) Baseline (ii) 22 weeks post randomisation; (iii) 52 weeks post randomisation.
4. Health, social care and wider societal resource use Questionnaire (RUQ)	Questionnaire based on previous RUQs and designed to be bespoke for this population with input from the PPI group.	(i) Baseline (ii) 22 weeks post randomisation; (iii) 52 weeks post randomisation.

Table 1: Summary of objectives and outcome measures

Also see the trial schedule (Table 3 and Table 4).

4 TRIAL DESIGN

A parallel, multi-centre randomised controlled trial of SAFE+TAU versus TAU alone with embedded economic evaluation, a mixed methods process evaluation and internal pilot, conducted in secondary care NHS Trusts in the UK.

4.1 Design considerations

4.1.1 Randomisation

Once twelve families have consented at a trial location and completed the baseline assessments (see section 7.3), they will be randomised *en bloc* to receive SAFE plus Treatment as Usual (SAFE+TAU) or TAU alone in a 2:1 (SAFE+TAU: TAU) ratio. The requirement for there to be twelve families in each cohort at each location may need to be flexible depending on the recruitment situation at each location. The minimum number of families required in a cohort before randomisation can take place is nine and the maximum is fifteen, allowing an even number of families to be allocated to the SAFE intervention (preferred for delivery of the family therapy sessions). If families decide to withdraw pre-randomisation additional families will be recruited to replace them to make up the total of at least nine families.

The randomisation sequence will be generated by a member of the PenCTU statistics team and implemented through a secure web-based system on REDCap, [80, 81] ensuring allocation concealment. The system will be developed in conjunction with a statistician independent from the trial team and will use random permuted blocks and stratified by recruiting location. The PenCTU data management team will run checks before and during the trial to verify the integrity of the randomisation system.

Advantages of 2:1 allocation include:

- Increased appeal for families deciding whether to consent to randomisation based on PPI feedback.
- Minimal reduction in statistical power for between-groups comparisons in a full-scale evaluation.
- Increased ability to recruit the required number of families within an area before randomising; which will be closer to the figure needed if and when the intervention is implemented. A group of 6 families is needed to deliver the intervention, but the artificial situation of a trial requires more to be recruited before randomisation – a 1:1 allocation would require 12 families, whereas the 2:1 allocation requires 9.

Only PenCTU data management staff who have been delegated the role of randomisation will be able to access the randomisation feature on REDCap. An unblinded automated confirmation email will be generated once a cohort has been randomised to the study and sent to each participant family and other unblinded members of the study team stating which families have been allocated to which treatment arm. A blinded confirmation email will be sent to the PI and other delegated members of study team.

4.1.2 Blinding

This trial is non-blinded to participants, as it is not possible to conceal the treatment allocation to them. Family therapists will also be aware of the participant's allocation to SAFE+TAU arm, and they will be discouraged from communicating with other members of the local research team about this.

Family therapists will be responsible for scheduling intervention sessions for those allocated to SAFE+TAU to protect the blind as much as possible from the outcome assessors.

The coordinating trial management team will be blinded to treatment allocation. Best endeavours will be made to ensure the staff members at each location delegated to perform the follow-up assessments remain blinded. It is possible that participants will disclose if they have received the study intervention prior to or during such an appointment. Families will be asked not to reveal their allocation to outcome assessors. The success of outcome assessor-blinding will be evaluated at each follow-up visit by asking assessors to record the treatment group to which they think a participant has been allocated in the case report form (CRF). Outcome assessors will also be asked to report any cases of inadvertent unblinding (e.g., as a result of a participant disclosing their allocated treatment). Families will be reassured that they will not be withdrawn from the trial in the event of inadvertent unblinding. Where the follow-up visits are being conducted by RAs, the treatment allocation will be revealed during the focus groups performed by the RAs at W22, meaning the blind can only be protected for the baseline and W22 visits. The data collection at all follow-up assessments is largely self-reported by the participant families, which reduces the possibility of introducing reporter bias for these assessments. The CARP-A is an observational measure, therefore, to minimise bias, a sub-sample of videos of the participant families will be viewed and assessed by a Research Fellow in the central team at the University of Plymouth.

PenCTU will hold the key to the allocation. The trial statistician responsible for undertaking the analyses will be blinded to allocated groups at least until the statistical analysis plan (SAP) is finalised and signed off by an independent statistician. An unblinded statistician will assist with preparation of the DMEC report and perform treatment allocation balance checks. The data management team at PenCTU will be unblinded for central coordination.

4.1.3 Internal pilot

An internal pilot, lasting for 6-months after recruitment commences, will be conducted. Pre-defined progression criteria for the internal pilot will be used to determine whether the trial will progress. The pre-defined rates for each progression criteria and RAG ratings are given in in **Table 2**.

The pilot phase will be conducted with a subset of three recruiting locations, supported by participant identification from community pathways. The target for the average rate per location per month will include a 50% reduction for the first three months of location opening, allowing for recruiter experience to develop and initial problems to be resolved.

Status at the close of the internal pilot will be reviewed by the Trial Steering Committee, with input from the Data Monitoring Committee. For amber ratings, guidance will be sought for remedial action. With no obvious mitigating factors, red ratings will terminate the project.

Progression Criteria	Red (likely termination of the trial)	Amber (progression of the trial with remedial action)	Green (progression of the trial)
Number of locations opened	<33% (n<1)	= 33-66% (n=1-2)	100% (n=3)
Recruitment rate per month based on average number of families recruited per trial location over first six months	<50% <1.9	50%-80% 1.9-3.04	>80% 3.04-3.8
Total number of families recruited	n < 34	n = 34-55	n = 56-68

Table 2. Internal Pilot progression criteria after 6 months of recruitment

5 TRIAL SETTING

The study will be conducted in approximately six participating NHS Trusts in England. The SAFE intervention will be delivered in community settings.

Trial locations will be identified through research, clinical practice and training networks established by the co-applicants including those associated with Autistica, The National Autistic Society and The Centre for Family Attachment Narrative Training. The prevalence of autism differs for ethnic and socio-economic groups and is highest among black children and children with low socio-economic status (SES). SES also mediates the effect of ethnicity on autism diagnosis. Participating locations will be specifically selected to ensure a spread of patient demographics, including social deprivation status and ethnicity.

Participant Identification Centres (PIC) in autism-related services including autism diagnostic pathways, women and children services and mental health services will be used to identify and approach potentially eligible families about participation in the study. PICs will make use of existing routes to access and contact families.

The study will also be advertised in community-based settings such as local support groups (see section 7.1.1.2).

5.1 Study personnel

Each trial location will be overseen by a local Principal Investigator. The SAFE intervention will be delivered by location-specific NHS Family Therapists (FTs) to provide continuity for participating families. Each location will have two FTs and both will be present at every intervention session. Additional FTs will be trial trained at each location for cover purposes.

Each location will be supported by two location-specific Research Assistants who will consent families, collect outcome data, run focus groups and undertake qualitative data analysis. The latter will be overseen by a Research Fellow within the central team at the University of Plymouth. Where capacity allows, some activities (e.g. consent, baseline questionnaires) may be performed by the local research team, including research nurses and trial coordinators.

There will be two senior FTs in the coordinating team who provide supervision for local FTs. Each location is allocated three live supervisions sessions to enhance treatment fidelity. Supervision sessions will be remote and local staff will be encouraged to schedule these to align with treatment of the first cohort of families. This is to maximise support for the local FTs in the beginning stages.

SAFE intervention sessions will also be recorded with family consent and videos will inform fortnightly, remote supervision sessions addressing therapist drift and competence.

All study personnel working with families will be required to have an enhanced Disclosure and Barring Service (DBS) check before working with children. Local staff will also be required to complete cultural competency training to facilitate recruitment of families of Black autistic children and low SES. FTs will be required to attend a 4-day training session in delivering the SAFE intervention and a 2-day training session in administering the Parent Development Interview (PDI). Staff members delegated to undertake outcome assessments will be required to complete trial-specific training, specifically with regards to performing the CARP-A assessment and initial analysis.

6 PARTICIPANT ELIGIBILITY CRITERIA

6.1 Inclusion criteria

Families must satisfy all the following criteria to be enrolled in the study:

- Family includes autistic child, aged 3-16 years*
- Diagnosis of autism, severity level 1 or 2 (in accordance with DSM-5[1]).
- If other diagnoses are present (e.g., ADHD, OCD, ED), autism must be primary diagnosis
- Family are willing and able to comply with study requirements

*In families with more than one eligible child, only one can be the family index case.

6.2 Exclusion criteria

Families who meet any of the following criteria will be excluded from study participation:

- Serious concomitant illness in the child or family, or other circumstances affecting compliance with study requirements
- Risk to safety of research staff*
- Family currently or due to take part in a family therapy-based intervention during study participation.
- Individual family members already taking part in the SAFE trial as part of another family unit.
- Unable to understand or communicate in English**

***Examples of risk:** violent behaviour causing injury that requires treatment, or a family member that has a serious infectious disease.
****English language**: This is due to delivery of the SAFE intervention being in English. Those who speak English as an additional language will be eligible to take part but will be encouraged to attend appointments with a conversational partner if necessary to assist with study delivery.

7 TRIAL PROCEDURES

7.1 Recruitment

7.1.1 Participant identification

7.1.1.1 *Clinical pathway*

The pathways used to identify and recruit families will vary according to local practice, and the needs of the individual families being approached. Initial identification will depend upon the timing of the diagnosis of the AC; some families will receive a diagnosis during the SAFE recruitment period (new diagnosis), and others will have been diagnosed before the SAFE study recruitment period starts (older diagnosis).

Families with a diagnosis during the SAFE recruitment period will be identified as potentially eligible for the study (and initial approach made) by the diagnosing paediatrician or another suitable member of the clinical team.

Families with a diagnosis before the SAFE study recruitment period (older diagnosis) will be identified as potentially eligible from clinic records by a suitably qualified member of the clinical team at each centre (e.g., research nurse).

[1] DSM-5 ASD Levels: Levels 1-2 – requires support or substantial support, e.g., the child has spoken language and could attend mainstream school with support. Level 3 – requiring very substantial support, e.g., the child may have an intellectual disability and limited spoken language.

Where possible, for continuity, clinical staff who have had prior contact with the identified family during the diagnostic pathway will be involved in the recruitment process.

Potentially eligible families will be provided with participant information documents (PID) and a letter of invitation, either in-person during a routine appointment, or via email or post by the clinical team. The PID will be supplemented by a video explaining the study developed in collaboration with PPI. Primary Caregivers (PC) will be asked to explain the study information to younger children in a way which is appropriate for their child, and suggestions for how to do this will be included in the PID.

If approached in person, potential participant families will be asked if they wish to receive a follow-up call from a member of the research team. If they agree, their contact details will be passed on to the research team who will conduct a telephone call. This call will take place after the family has had sufficient time to consider participation. Usually, this will be at least 24 hours after provision of the study information but may been sooner if the family wishes.

A member of the clinical team may contact families directly to ascertain interest if they do not respond to the letter of invitation sent via email or post.

If the family does not wish to receive a follow-up call, they will be advised that, should they reconsider, they can use the information on the PID to contact the research team directly, or self-refer via the SAFE2 webpage on the PenCTU website.

For families whose first language is not English, translated versions of the PIS can be provided on request. Such families will be encouraged to bring a 'conversational partner' to all study visits; this is a trusted person who speaks both the family native language and English. All participant reported outcome measures must be completed in English and by the participant to ensure the validity of such measures. Conversational partners may also assist families in other contexts, e.g. families with hearing impairments or single parents who would benefit from additional support in sessions.

7.1.1.2 *Community pathway*

The study will be advertised via community channels in our trial locations. Appropriate means for approaching local community members will be established with our PPI networks. This may include, for example, posters and leaflets in community venues and sharing study information via social media. Information about the study will be provided through such means and families will be invited to self-refer to the research team, either by using the research team contact details provided in the PID or via the SAFE2 webpage. The SAFE2 webpage comprises of Participant Information Documents and an expression of interest (EOI) form. Upon submitting a completed EOI, the family agrees that 1) they have read the PIS, 2) they are happy to be contacted by the research team using the contact details provided, and 3) the local trial location and PenCTU will receive their EOI.

7.1.1.3 *Equality, diversity and inclusion (EDI)*

Families of Black autistic children and families with low socioeconomic status are typically overrepresented in autism prevalence and underrepresented in research [82-84]. Informed by the NIHR Research Inclusion Strategy and other literature and toolkits [85-88], and in consultation with PPIE partners, a range of strategies to recruit such underserved families is embedded in the study. Inclusive recruitment will be monitored and strategies reviewed 6 months into the recruitment phase.

7.1.2 Telephone contact

A member of the local research team will contact families who have consented to be contacted and

have expressed an interest in taking part to discuss the study further and answer any questions they may have. If the family is interested in participating and initially eligible, they will be invited to attend an in-person visit to confirm eligibility, provide informed consent and complete baseline assessments (see Section 7.3).

During the telephone call, any families who decline to participate will be asked if they would be happy to take part in an interview, as part of the qualitative part of the study (described in Section 9.3).

If it is not possible to contact the family after three telephone calls, the researcher will document on the screening log that the family was 'not contactable'.

Participants will be reminded that they can bring a 'conversational partner' to any or all study visits.

7.2 Screening

A screening log must be maintained at each location to document all participants considered for the trial, including those subsequently excluded, to enable population of a CONSORT flowchart for the study. Where possible, the reason for non-entry to the trial should be documented. Recruitment pathway (clinical or community), Index of Multiple Deprivation (IMD) score (via partial postcode of the AC, to determine socioeconomic status) and ethnicity of the AC and PC will also be documented.

No specific trial-related screening tests are required. A researcher at each trial location will confirm eligibility of the family at the baseline visit and obtain informed consent (see sections 7.2 and 7.3).

Each trial location should keep a separate enrolment log linking trial ID and identifiable patient data, i.e., family member names).

7.1 Payment

Families will not be compensated for their participation in this study. Families experiencing financial hardship will be able to claim reimbursement for travel costs to study visits.

7.2 Consent

The Principal Investigator (PI) retains overall responsibility for the conduct of research at their trial location, this includes the receiving of informed consent of participant families at their location. They must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki. Informed consent may be obtained by local research staff, SAFE Research Assistants (RA), or other suitably trained members of the SAFE study team, where delegated by the local PI.

The PI takes responsibility for ensuring that all vulnerable participants are protected and participate voluntarily in an environment free from coercion or undue influence.

Informed consent must be obtained prior to the participant families undergoing procedures that are specifically for the purposes of the trial and are out-with standard routine care at the participating location, including the collection of identifiable participant data.

The right of a participant to refuse participation without giving reasons must be respected.

Participating family members remain free to withdraw at any time from the trial without giving reasons and without prejudicing further care and will be provided with a contact point at the trial location where they may obtain further information about the trial. Data collected up to the point of withdrawal

will be retained and used in analysis as outlined in the participant information sheet. Any intention to utilise such data will be outlined in the informed consent form. Where a participant is required to re-consent, or new information is required to be provided to a participant it is the responsibility of the PI to ensure this is done in a timely manner.

If the family meets the eligibility criteria and wishes to take part in the study, written informed consent will be obtained at the baseline visit, once the details and implications of the study have been explained, and families have had the opportunity to ask questions.

Participating adults will be asked to complete a study-specific consent form and the primary caregiver will be asked to give consent for the autistic child, and any additional siblings that are <16 years of age. Children who are <16 will be given the option of completing a separate study-specific assent form if they wish. Where the child does not provide assent, the researcher will work with the PC to address the child's concerns.

Participating children who turn 16 during study participation and have capacity to consent for themselves will be asked to reconsent using an adult consent form.

As part of the consent process, the primary caregiver will be asked to agree to the GP of their autistic child being informed of their involvement in the study. If the AC has capacity to consent for themselves, they will be asked to agree to this.

The original consent form(s) must be filed in the Investigator Site File. Copies must be provided to the participant family and a copy filed in the medical records of the AC (via notification to the GP). The researcher obtaining consent will document the consent process on the SAFE database and in the participant folder of the AC in the ISF.

7.3 Baseline Visit (pre-randomisation)

The trial schedule is given in Table 3 and Table 4**.**

Initially eligible and amenable families will be invited to attend a face-to-face visit with the research team at a community venue (this may include venues provided by the local trial location). For community referrals, eligibility must be confirmed via diagnostic letters and reports held by the family.

If eligible and willing to participate, a delegated member of the research team will obtain informed consent / assent from the family members (see Section 7.2) and continue with the baseline assessments.

The composition of the family will be defined at this visit, including confirming the Primary Caregiver (PC). All family members participating in the study must attend the baseline visit. The minimum requirement for each family unit is the AC and the PC, and the maximum number is 7 family members.

Participants will be given the option to complete self-report measures digitally (e.g., direct entry into survey or the MyCap app) or using paper CRFs, which will be uploaded to the study database by the researcher.

Baseline data collection (approximately 2 hours):

Following receipt of informed consent / assent, family history (date of autism diagnosis of the index case and family composition) and demographic data of all family members (age, gender, sex at birth, ethnicity and socio-economic status measured by IMD) will be collected and entered onto the study database by the researcher. The family will also be asked the following open-ended questions: 1) How did you hear about the study? 2) Why did you choose to take part in the study? And 3) How could recruitment to the study be improved for families like your own?

At the same visit, the RA will support the participant family to complete the following baseline assessments:

- Systemic CORE 15 (SCORE-15)
- Child SCORE-15
- Patient Health Questionnaire – 9 (PHQ-9)
- Generalised Anxiety Disorder-7 Questionnaire (GAD-7)
- Coding of Attachment-Related Parenting for use in children with Autism (CARP-A)
- (EQ-5D-5L
- Child Health Utility 9 Dimensions (CHU-9D)
- ICEpop CAPability (ICECAP-A)
- Resource Use Questionnaire (RUQ)

Primary caregivers will also be given a template to record monthly incidence of meltdowns.

The above baseline data must be collected and entered onto the study database prior to randomisation. Where families have completed self-report measures digitally, the researcher must review each eCRF for completeness. Where outcome measures have been completed on paper CRFs, the researcher must enter the data onto the REDCap database. It is important that the data is entered contemporaneously so as not to delay randomisation of cohorts, i.e., within 1 week of the visit.

All assessments should be completed during a single visit, however if this is not possible, families will be given the option to complete the remaining assessments either online (via REDCap) or using paper booklets within 2 weeks of the baseline visit. If additional support is required, the RA may schedule a second in-person study visit with the family. In all cases, the primary outcome measure (SCORE-15) must be completed by the PC at the first in-person visit.

Randomisation

Once a cohort of 12 families (+/- 3) has been recruited to the study at a trial location, the families will be randomised to undertake either SAFE+TAU or TAU alone. It is anticipated that it will take approximately 8-9 weeks to recruit the required number of families at a single trial location. During this time, the researcher will maintain contact with the families to remind them about the study.

Randomisation will be carried out by PenCTU following greenlight from the local researcher(s) and Chief Investigator or delegate to confirm readiness and appropriateness of cohort size. This will only occur once all families within the cohort have provided informed consent and completed all baseline data collection. Once randomised, families will be informed of their treatment allocation via an automated email or text message by the REDCap system, using the contact details provided at the baseline assessment. If allocated to the SAFE+TAU group, one of the Family Therapists (FT) at the relevant trial location will telephone the families to arrange the initial interview and subsequent SAFE intervention sessions (see Section 7.4 and 11). The RA will separately arrange the subsequent follow-up visits for both the SAFE+TAU and TAU alone groups (see Section 8). The RA will need to confirm with the FT that all intervention sessions have concluded prior to the follow-up assessments.

7.4 Post-randomisation assessments and intervention sessions (SAFE group only; Weeks 1 - 20)

At an introductory visit, which is expected to take approximately 2 hours, the FT will explain the intervention schedule and answer any questions they family may have. The FT will conduct the Parent Development Interview (PDI) with each parent in preparation for the SAFE therapy sessions. Where the PC is not a parent, the PDI will be conducted with the PC instead. The PDI is an audio recorded interview consisting of 20 items and taking approximately 40 minutes to complete. The full

interview schedule provides background information on the relationship between the PC and the child, which will inform the SAFE sessions. If both parents are participating, they should both be interviewed, but if not then a single parent should be interviewed.

The FT will also check during this visit that the family can attend the next scheduled group therapy session, explain the family reflection activity and answer any questions the family may have. The FT will also provide a schedule of the subsequent SAFE sessions scheduled for the relevant cohort to the family (2 multi-parent group sessions and 5 individual family therapy sessions).

SAFE can be delivered in 13 weeks but family therapy sessions build in flexibility as standard practice to account for family availability and rescheduling hence 20 weeks will be allocated for the intervention. The aim is to schedule the first SAFE intervention session within two weeks of randomisation, but this will depend on family availability and time to recruit a full cohort at each trial location.

At a minimum, the AC and PC from each family must attend each intervention session. Where this is not possible, the FT session (including group sessions) must be rearranged. Individual catch-up sessions may be arranged for other family members who are unavailable to attend a session, though best endeavours should be made for all family members (as defined at the baseline visit) to attend every session. The number of sessions a family may reschedule will be at FT discretion, based on family circumstances, motivation and levels of problems/distress.

8 FOLLOW-UP ASSESSMENTS

8.1 Week 22 and 52 post randomisation assessments – all families (+ / - 3 weeks)

All families will be followed up at 22 weeks and 52 weeks post-randomisation via a face-to-face visit with an RA. The visit will take place in a community venue or at another setting such as a venue provided by the trial location, if convenient and acceptable to both the family and the RA.

All outcome measures conducted at the baseline visit will be repeated at both follow-up visits, with support from the RA (SCORE-15, Child SCORE-15, PHQ-9, GAD-7, CARP-A, EQ-5D-5L, CHU-9D, ICECAP-A, RUQ). Families will be reminded to bring their diary of behavioural meltdowns to each follow-up visit.

All assessments should be completed in one single visit for each follow-up assessment, however if this is not possible, families will be offered the same options as the baseline visit (digital completion, paper booklets, or second in-person visit). In all cases, the primary outcome measure (SCORE-15) must be completed by the PC at each of the first in-person follow-up visits.

8.2 Early discontinuation and withdrawal criteria

A family may withdraw from the intervention or the study itself at any time without giving a reason, and without it affecting the child's clinical care. Families will be asked to give a reason for withdrawal from the intervention or study but do not have to provide one. Families who wish to withdraw from the SAFE intervention sessions should always be followed up provided they are willing, and they should be encouraged to not leave the whole trial.

The study intervention should be discontinued if there is an occurrence of an AE or SAE that suggests an unacceptable risk to any participating family member, in the judgement of the Investigator.

Withdrawal from the study may take place if the family requests to withdraw or the Sponsor decides to terminate the study and/or the internal pilot progression rules are not met and the study is terminated on that basis.

Those who withdraw completely from study intervention or follow-up post-randomisation will not be replaced. Families who fully withdraw pre-randomisation will be replaced. The PenCTU data management team will ensure that participants who formally withdraw from the study are not contacted for any subsequent follow-up data collection (aside from any partial follow-up arrangements made with individual families). Data collected prior to withdrawal will be included in the study analysis as described in the PIS and ICF.

Withdrawals will be recorded by completing a digital withdrawal form in REDCap. This form allows the collection of withdrawal, partial withdrawal, loss-to-follow up and participant death events.

8.3 Loss to follow-up

At the baseline visit, contact details will be obtained from the participating family members to include mobile phone number, home landline number, email address and postal address. Families will be asked to confirm their preferred method of communication and at each visit, contact details will be checked and updated. The RAs will provide a telephone helpline for all participating families to answer any questions, but also to be notified of any changes to the family circumstances (e.g. moving home address).

Automated alerts will be sent to participant families reminding them about the study. Researchers at trial locations will also maintain contact with families directly, particularly during the period between the baseline visit and randomisation to keep them updated about study progress.

Based on learning from the feasibility study, participant families will be provided with a document depicting the planned dates of each visit and a description of the activities at each session. Additional time has been factored into the planned intervention period to ensure there is flexibility to suit each family's availability and encourage attendance. Intervention sessions should be attended in-person, and at a minimum by the AC and PC, but where this is not possible, sessions will be rescheduled. If other family members are unable to attend, they will be offered the option to join remotely, or an individual catch-up session may be scheduled. Families will also be offered the option to complete some patient reported outcome measures after the study visit. Where this is being completed digitally, automated reminders will be sent by REDCap until the eCRF is marked as complete. Where the window for assessment is closing and the data is still outstanding, the researcher will be prompted to contact the family directly to assist with completion.

If a family is no longer contactable and has missed at least one study visit, location staff should attempt to contact the family at least three times using at least two methods, e.g., text message, phone and letter. If the family remains uncontactable, location staff should contact the AC's GP to gain further information and check contact details.

8.4 End of Trial

The end of the trial is defined as completion of data collection for the final family in follow-up. The study may be terminated early if the internal pilot progression criteria are not met, as detailed in Section 4.1.3.

The Sponsor delegate will notify the REC of the end of the trial within 90 days of completion. The final report to REC will be written within 12 months of the end of the trial.

	Timepoint	Pre-baseline	Baseline	Randomisation (day 0)	Post-randomisation		
					Weeks 1 to 20	Week 22 +/- 3 weeks*	Week 52 +/- 3 weeks
Enrolment							
Whole family	Eligibility screen	X	X				
	Informed consent		X				
	Family history		X				
	Demographics		X				
	Randomisation			X			
Treatment	**period**						
Intervention group	SAFE (solid line) TAU (dotted line)				←		→
Control group	TAU (dotted line)				←		→
Assessments							
Primary Caregiver participant	SCORE-15 (primary outcome measure)		X			X	X
	Proxy CHU-9D if a child participant is <7 years of age		X				
			X				
	CARP-A (session is video recorded)		X			X	X
	Incidence of AC's autism-related meltdowns		X			Monthly	
	ICECAP-A		X			X	X
	RUQ		X			X	X
All adult family participants	PHQ-9 & GAD-7		X			X	X
	EQ-5D-5L		X			X	X
Each parent participant / PC. Intervention group only.	PDI				X**		
Child participants	Child SCORE-15 if a child participant is ≥ 7 years		X			X	X
	CHU-9D if a child participant is aged 7 to 17 years of age		X			X	X
	CARP-A		X			X	X
Safety reporting							
SAE reporting					X	X	X
Capture TAU							
Invitation/Engagement/Attendance for TAU					←		→

Table 3: Tabulated summary of trial

Activity applies to both trial arms unless otherwise stated.
*The final SAFE intervention session must have taken place before this assessment is undertaken for participants in the cohort (i.e. intervention and control participants alike). **After randomisation and before first SAFE session.

	Timepoint	Pre-baseline	Baseline	Randomisation	Post-randomisation		
					Weeks 1 to 20	Week 22 +/- 3 weeks *	Week 52 +/- 3 weeks
Treatment period							
Intervention group	SAFE (solid line) TAU (dotted line)						
Control group	TAU (dotted line)						
Assessments							
Whole family	Interviews with families who declined to participate in the trial	X					
	Interviews with families who withdraw from the trial						
	Qualitative focus groups with subset of families					X	
	Qualitative interviews with families not attending focus groups					X	
Whole family. Intervention group only.	HAT				X (after each session)		
Therapists	Training and Checklist Questionnaire (TCQ)				X (at each session)		
	Live supervision for treatment fidelity assessment. Sessions used in supervision are video recorded.				X (3 sessions per location)		
	Focus group session					X	

Table 4: Tabulated summary of process evaluation

Activity applies to both trial arms unless otherwise stated. Table does not cover process evaluation activities related to stakeholders; please see Section 9.3 for further details on this.

*The final SAFE intervention session must have taken place before these assessments are undertaken for participants in the cohort (i.e. intervention and control participants alike).

	SAFE sessions*						
For <u>each cohort</u> of families at a location* **	e.g. Fortnightly sessions over 13 weeks	Week 1**	Week 3	Week 5	Week 7	Week 9	Week 11	Week 13
	Nominal schedule over 20 weeks	Week 2**	Week 5	Week 8	Week 11	Week 14	Week 17	Week 20
		SAFE 1	**SAFE 2**	**SAFE 3**	**SAFE 4**	**SAFE 5**	**SAFE 6**	**SAFE 7**
Group**: Multi-parent therapy of parents (3 hours per session)		X						X
Individual family***: Family session for all family members (2 hours per session) for each family			X	X	X	X	X	

Table 5: SAFE session schedule

Randomisation takes place at Day 0 of Week 1.

* The seven fortnightly SAFE sessions can be delivered in a minimum of 13 weeks but, to account for family and therapist availability, a 20-week period is provided to complete the intervention. Outcomes are assessed for the whole cohort at Week 22 +/- 3 weeks (but only once the once the SAFE intervention period has concluded) and at Week 52 +/- 3 weeks post-randomisation.

** The first SAFE session takes place during the two weeks after randomisation.

*** The minimum number of families required in a cohort at a trial location before randomisation can take place is nine and the maximum is fifteen.

**** At a minimum, half of the Parents / Carer's in each group are required for a Group Session to take place, e.g., where 6 families are allocated to SAFE, 3 sets of Parents / Carer's must attend.

*****At a minimum, the Primary Caregiver and AC must be present at an Individual Family Session.

9 PROCESS EVALUATION

9.1 Overview

This study includes an embedded mixed method process evaluation based on MRC guidance [89, 90]. The process evaluation will have the following three interconnected main components which will work synergistically and be conducted concurrently:

1. *Implementation Study*: A mixed method implementation study theoretically informed by Participatory Action Research and Concept Mapping techniques [91, 92]. The implementation study and design including implementation outcomes will be based on the Consolidated Framework for Implementation Research (CFIR) [93] and implementation strategies refined and mapped against the Expert Recommendations for Implementing Change (ERIC) framework [94]. In preparation,150+ NHS autism related Diagnostic Pathways and Child and Adolescent Mental Health Services were surveyed. 97% felt SAFE was needed and their service would use it if available. Facilitators included availability of experienced Family Therapists already working in NHS contexts, and barriers were access to SAFE training, supervision and need for flexible use of SAFE. Four focus groups were carried out with PPI and Commissioners to explore how SAFE fits with needs, priorities and legislation informing this study. This preliminary data resulted in the following implementation objectives: a. Explore barriers and facilitators to training existing NHS staff in SAFE. b. Explore barriers and facilitators to supervision for SAFE. c. Explore avenues for flexibility and sustainability in SAFE delivery including means of engaging underserved populations and online options. These objectives alongside CFIR guidance informed the initial design/framework of the implementation study (see Table 6). A series of focus groups and interviews with stakeholders and participating families will include a focus on the five domains of the CFIR as appropriate in relation to the objectives. Focus groups will utilise principles of nominal group technique [95, 96] to help identify and refine implementation strategies drawn from the ERIC framework [97] judged to be the most impactful and important in relation to the five domains related to implementation in the CFIR. Early identification of strategies will be supported by use of the CFIR-ERIC matching tool [98] and with input from stakeholders and PPIE these will be refined and feed into an implementation guide which will be utilised and developed as the trial progresses.

2. *Fidelity Assessment:* The Training and Checklist Questionnaire (TCQ) assessing protocol adherence, ease of delivery, and therapist confidence will be completed by SAFE family therapists after every intervention session. Video analysis of intervention sessions will also be used for supervision of therapist adherence, and independently rated using adapted UKATT PRS [99] based on the SAFE intervention manual. The Helpful Aspects of Therapy (HAT) questionnaire will be completed by families after each SAFE session [100] capturing satisfaction with sessions and events between sessions feeding into both fidelity and processes of change for SAFE+TAU families.

3. *Qualitative Investigation:* The qualitative study will employ focus groups to inform theories of change and develop a logic model. This research takes a Critical Realist stance [101] and aims to capture rich data on mechanisms and contexts involved in change related to intervention associated with SAFE or TAU, through exploring family's opinions of whether positive or negative change has occurred and if so, how and why? Topic guides and prompt questions for focus groups will be developed in collaboration with PPI and IDPPI, and barriers and facilitators to focus group attendance will be explored and remedied where possible. For SAFE+TAU participants, topic guides will include reference to the HAT data (collected after each therapy session). Prompts will seek to facilitate discussion of change in family life and beliefs regarding process of family change for SAFE+TAU compared to TAU. Exploration will include experience of activities and approaches in SAFE or in TAU and specific examples of

contribution to change. Representation of target groups (black and low SES families) will be monitored and participants who do not attend will be asked how they would like to share feedback to the prompt questions, with interviews conducted if required. Focus groups will include breakout groups for parents and children. This model worked well in the feasibility study and children were able to contribute to feedback effectively through drawing, modelling and indicating choices in response to visual stimuli. Responses to images relevant to SAFE or TAU will also be employed for adults.

Domains	**Constructs**	**Key Methods (to be refined with PPI and stakeholder input)**	**Indicative implementation strategies from the ERIC framework (to be refined with PPI and stakeholder input)**
Innovation	• Existing evidence • Comparison with TAU • Flexibility • Complexity of intervention • Quality of design packaging • Training, supervision • Costs	Literature search, outcome data, focus groups, observation	• Identify and prepare champions • Conduct educational meetings • Inform local opinion leaders • Conduct educational outreach visits
Outer setting	• Possible disruption • Legislation • NHS priorities and capacity • Commissioning • Social pressures/ facilitators • Campaigns, advocacy groups	Interviews, focus groups, simulation, observation	• Involve executive boards • Conduct local needs assessments • Capture and share local knowledge • Conduct local consensus discussion
Inner Setting	• NHS priorities, policy, capacity • Autism Pathway, CAHMS, Family Therapy clinics • Shared values • Information sharing • Competing approaches • Funding and space	Interviews, mapping, doc search, observation	• Assess for readiness and identify barriers and facilitators • Alter incentive/allowance structures • Promote adaptability • Develop a formal implementation blueprint
Individuals	Roles: • Leaders, Influencers & champions, PPI all levels • Deliverers • Families	Interviews, focus groups, reflective logs, observation	• Develop educational materials • Conduct ongoing training • Facilitation

	Characteristics: • Recipients needs • Motivation, skills, time & space		• Provide ongoing consultation
Process	• Team working • Collect information • Define goals, roles & responsibilities • Encourage participation	Synthesis maps, feedback scales, mini trials/case studies	• Identify and prepare champions • Build a coalition 1. Use advisory boards and workgroups • Tailor strategies (toolkit)

Table 6: Initial implementation plan based on CFIR (2022)

9.2 Methods

The process evaluation will be conducted in such a way as to minimise burden on participants wherever possible and avoid duplicating data collection. The aim is to create a data corpus for the entire process evaluation which will be analysed with different interpretive lenses depending on the objective of each of the three components of the process evaluation. Focus groups and interviews will, where possible, be designed in such a way that issues related to the theory of change (core components) and the different domains of the CFIR related to the intervention are explored within the same focus group/interview. Conceptually the components are interrelated and impact one another (e.g., core components of the intervention (theory of change) could directly influence the innovation and individual domains of the CFIR). Issues identified via fidelity monitoring may also help understand issues related to the process of implementation among other domains.

9.3 Data Collection

All in-person and remote data collection for focus groups and interviews will be digitally recorded and transcribed verbatim.

Participant information sheets and informed consent forms will be provided specific to each group/source of data. Informed consent will be obtained by a suitably qualified member of staff prior to any data collection.

Focus groups with participating families (theory of change, implementation)
Week 22 (N = 18):
SAFE+TAU arm (n = 12): Two focus groups will be conducted in person at an acceptable and secure venue by the local RA at each trial location, for the 2nd and 6th (or final) cohorts, respectively. All participating families from cohorts 2 and 6* receiving the SAFE intervention will be invited (to represent earlier and later delivery) and this will occur following the week-22 post-randomisation visit of cohort 6. Each focus group will consist of 6-10 families and last up to 3 hours.

TAU arm (n = 6): One focus groups will be conducted at each location by the local RA following the week 22 post-randomisation visit of the 6th (or final) cohort, inviting all families who have participated in the TAU arm across all previous cohorts at each location (to compensate for the 2:1 randomisation). Each focus group will consist of 6-10 families.

*Purposive sampling principles will also be employed, where through therapist supervision any other cohorts which demonstrate unique challenges or exemplify practice will also be invited to participate in a focus group in addition to or instead of the planned 2nd and 6th cohorts (to be decided by the Trial Management Group).

Week 52 (N=2):
Following the week 52 post-randomisation visit of the 6th (or final) cohort at one trial location, two separate focus groups will be conducted for the *SAFE+TAU arm* and *TAU arm*. Invitations will extend backwards through the cohorts to recruit 6-10 families still engaged in the study.

Therapist focus groups (theory of change, implementation)
Once the week 22 post randomisation visit has been completed for the 1st cohort at all 6 trial locations, all of the study therapists will be invited to attend a focus group (~2 hours) to discuss their overall experience of taking part in the study, carrying out the SAFE sessions and the training and supervision (N = 1). The RF / RA will lead the focus group process, which will take place online so all therapists from across the country can discuss the experiences together.

Trial locations stakeholder interviews (implementation)
At each trial location (n=6), key stakeholders (e.g. service managers, commissioners) identified as playing a key role in the implementation of SAFE will be invited to participate in a one-to-one online interview (n~3, ~30 mins each) to explore issues related to the implementation of the SAFE intervention. Topic guides will be developed with PPIE and stakeholder input to explore implementation issues guided by the domains of the CFIR. Interviews will be conducted following the initiation of the first cohort at each trial location and again following the completion of the last cohort at each location. The same participant may be interviewed at both timepoints.

Additionally, up to 6 interviews will be conducted with stakeholders in locations NOT involved in the delivery of SAFE who may have declined participation to understand barriers to implementation and possible solutions. This will occur once all participating trial locations have opened to the study.

Stakeholder survey (implementation)
An electronic survey (developed with PPIE and stakeholder input) will be developed to reflect possible issues related to implementation reflecting the 5 domains of the CFIR. This will be shared through national networks who are involved in the support of people and families living with autism. Responses will include open and closed responses and will be analysed in line with the objectives of the implementation study. The broad scope will contribute to knowledge regarding implementation beyond those locations and stakeholders directly involved in the study. The survey will be completed using the secure JISC online platform and will be distributed after the internal recruitment pilot is complete.

Interviews – declined participation (implementation)
When an eligible family declines to participate in the study, the primary care giver will be invited by the local RA to engage in a short, focussed telephone interview (~10 mins) to discuss their decision not to participate. Findings from these interviews will be feedback at regular trial management meetings.

Interviews – withdrawn participation (implementation)
When a family withdraws from the study the local RA will make a phone call to invite the primary care giver to engage in a short, focused telephone interview (~10mins) with them to discuss the

reasons for their decisions, and how the main trial can be designed to address these issues. Findings from these interviews will be feedback at regular trial management meetings.

9.4 Analyses

Two separate but complimentary analyses will be undertaken, one focussed on implementation and one focussed on refining the theory of change/logic model using the same methodological approach. Implementation analysis will begin following the first round of data collection, whereas analysis for the refinement of the theory of change will be conducted following completion of all data collection.

Focus groups and interviews will be audio-recorded and transcribed verbatim, and summaries prepared which will be sent to participants for comment (excluding the interviews with declining and withdrawn families, unless requested by the participant). Transcription will be digital and may include the use of Artificial Intelligence. For focus groups utilising nominal group technique for identifying and prioritising implementation strategies, summary lists of strategies ranked by importance will be produced. NVivo 14 will be used to assist qualitative Reflexive Thematic Analysis [102, 103] for focus group and interview transcripts. Validity enhancement will include 'member validation' and multiple independent analysis. Discrepancies between analysts will be addressed using Practical Thematic Analysis [104] with memos shared between analysts with discussion as needed at each stage of the process. Findings, alongside relevant previous evaluations and PPI input will be used to develop Theory of Change/Logic Model including causal pathways of specific intervention components and support the production of an implementation guide/toolkit.

9.5 Outcomes

1. *Implementation study*: The implementation study will produce an 'implementation guide' (or 'toolkit') which will be continually developed and deployed throughout the trial. It will support effective implementation of the intervention responding to barriers and challenges as they arise. The guide will be designed to support implementation of the intervention post-trial across clinical and community settings and will form an important part of the subsequent dissemination activity.

2. *Fidelity assessment*: Fidelity monitoring will be ongoing and used to identify deviations in delivery away from the planned and manualised intervention. Identified deviations will be used to support practitioner supervision in order to minimise practitioner 'drift', whilst also identifying deviations which may contribute unexpected but effective and acceptable practices. Findings will be recorded and reported as appropriate. Such deviations will be used to inform the qualitative study which seeks to refine the theory of change and identify the active components of the intervention (i.e. fidelity monitoring will help identify challenges in delivery for which possible solutions will then be explored in the qualitative component).

3. *Qualitative investigation:* The primary outcome will be a refined theory of change/logic model for the intervention which will describe the active and effective components of the intervention. Producing a set of 'core components' for the intervention which are fundamental to its effectiveness and therefore considered immutable within the context of adapting the 'innovation' domain within any implementation guide.

9.6 Stakeholder/Community Engagement and Involvement/PPIE

The study PPIE group will be used to consult and guide development of all participant facing materials and topic guides. It will also be used to support interpretation of findings and the development of outputs. An NHS Trust in the Southwest not involved in the study, that is delivering

the SAFE intervention, will be regularly consulted and engaged to help guide and form questions related to the objectives of the implementation study.

9.7 Contamination

The data corpus will also be scrutinised and regularly discussed for any evidence of contamination between SAFE+TAU therapists and the TAU therapists. Contamination is considered extremely unlikely and SAFE therapist training will include emphasis not to share practice with other therapists not delivering the intervention. If any indication of contamination is observed, responsive lines of investigation and possible remediation will be explored.

10 ECONOMIC EVALUATION

A within-trial cost-effectiveness analysis (CEA) will estimate the incremental cost-effectiveness of SAFE+TAU compared to TAU alone. Resources (e.g., staffing, training etc.) and associated costs of providing SAFE will be established. Health, social care and broader societal resource use will be captured at baseline, 22 and 52 weeks post randomisation follow-up using the resource use questionnaire (RUQ). The RUQ will be developed for the population, with input from the PPI group and study team, ensuring resources/costs of care particular to these families are included. Nationally recognised UK health and social care unit costs will be applied to the resource use data.
The CEA will be undertaken from a primary perspective of NHS/Personal Social Services and two primary analyses will be undertaken based on: i) quality-adjusted life-years (QALYs) estimated using EQ-5D-5L data collected from Primary Carers at baseline, 22 and 52 week post randomisation follow-up and; ii) QALYs estimated using CHU-9D data collected from children with autism if the child is >7 years or the Primary Carer as a proxy if the child is <7. The CEA will present incremental cost-effectiveness ratios for: i) the trial primary outcome, SCORE-15, and ii) the policy relevant economic endpoint, cost-per-QALY at 52-week post randomisation follow-up. Sampling uncertainty will be accounted for, and the pattern/potential mechanisms of missing data explored in considering multiple imputation. Cost-effectiveness acceptability curves will be presented as appropriate using the net-benefit approach, showing the probability that SAFE+TAU is cost-effective (as compared to TAU) over a range of cost-per-QALY thresholds (including the £20,000 and £30,000 thresholds considered by NICE). For EQ-5D-5L data, QALY weights will be applied in accordance with the 'position statement' of NICE at the time of analysis. Regression models will test for differences in costs and QALYs in line with the Statistical Analysis Plan (SAP) and adjusting for baseline costs and EQ-5D-5L/CHU-9D values.

Broader perspectives will be considered in sensitivity analyses. The impact of including wider care costs beyond health/social care will be assessed. The cost-per-year of full capability wellbeing of the intervention will also be estimated based on the ICECAP-A from Primary Caregivers. The ICECAP-A is explicitly recognised by NICE for use in cost-effectiveness analyses of interventions with a social care element. Additional sensitivity analyses will also draw on the emerging 'health spillovers' literature in considering effects for multiple family members [105]. Over a longer time, benefits may continue/accrue in the SAFE+TAU group and costs to health, social and wider care systems may be less compared to those in the TAU group. There may be an initial greater uptake of other services as a result of the enabling impact of the intervention, including integrated continuation of care. If there is indication of the intervention's effectiveness, a decision analytic model will be used to estimate the cost-effectiveness of the intervention over participants' lifetimes. A Markov model will be used, populated using data from the trial supplemented with evidence on longer term costs and outcomes drawn from related literature. Sensitivity analyses will be conducted to explore the effects of adjusting model parameter estimates and assumptions, and probabilistic sensitivity analysis performed in relation to the longer-term estimates of costs, effects and cost-effectiveness. A Health

Economics Analysis Plan (HEAP) will be developed which will be fully concordant with the SAP, and the internationally recognised CHEERs guidelines for reporting CEA studies.

11 TRIAL INTERVENTION

11.1 The SAFE intervention

SAFE is a novel, preventative, manualised intervention addressing autism-related mental health difficulties. Good mental health is a complex state of well-being that enables people to cope with the stresses of life, realise their potential, learn well, be productive, and take part in their social environment [106]. Many families of autistic children do not enjoy good mental health with difficulties coping with life challenges, poor communication, isolation, rigid thinking and difficulties expressing and securing support for unmet needs. Left untreated these risk factors result in suicidality, behavioural distress, mental health conditions such as anxiety, depression and psychosis, as well as family breakdown and the need for residential care. SAFE seeks to prevent and address these escalations, drawing on the evidence base for Systemic Family Therapy [55, 107], Attachment Narrative Therapy [108], Multi-Family Therapy [109] and the strengths and preferences of autistic people [110, 111] to provide a unique intervention with activities and modes of delivery designed specifically for this population.

SAFE can be regarded as a toolkit with activities adapted from well used Family Therapy techniques [57] and combined in new ways so that it can be tailored to the needs of families of autistic children. As an example, our previous research [48, 112] indicates that families found the following three activities adapted for SAFE to be particularly helpful:

1. Tracking Circularities [113]: This activity directly focuses on recurrent problematic and highly distressing negative cycles which often include challenging behaviour among autistic children (meltdowns). Specific examples are explored in detail to develop better mutual understanding and strategies for avoiding escalations. Tracking examines in depth each family member's understandings, feelings and intentions which also assists to build an awareness of relationship patterns and mutual awareness which is linked to a key feature of autism - difficulties with executive functioning, reflective thinking. This promotes the creation of coherent family narratives which can be drawn upon in future similar difficult circumstances.

2. Self-Autism Mapping [114]: The autistic child is supported through visual representations and modelling to share with family members their understandings, fears and hopes about autism, how different contexts impact on their experience of autism and how they see their current life and the future. Positive and challenging aspects of autism are discussed with the family to develop strategies together to reduce the risk of future problems and distress. It assists family communication and helps to clarify misunderstandings in their explanations of autism.

3. Sculpting: Many families are unable to cope with present challenges and see a bleak future for their child and the family. This technique involves mapping family and wider relationships over time: before the diagnosis, now and into the future, to examine the impact of autism on their lives. Visual objects are used to represent needs, closeness and distance in relationships, supporting exploration of how relationships have developed or deteriorated, how new relationships might be forged and how to plan for needs to be met in the future. This can contribute to instilling an increased sense of confidence and hopefulness about the future and preparing their child for independent living.

SAFE can be delivered by family therapists employed in NHS services following a 4-day training programme. Therapists support families to manage current difficulties and crises, and to prepare for future challenges and opportunities. Sessions are delivered jointly by two therapists. Between weeks

1 (randomisation) and 20, families allocated to SAFE+TAU complete the Parent Development Interview [115], providing therapists with background information. They then attend fortnightly sessions (allowing for availability) comprising two 3-hour multi-parent sessions for 8 +/- 2 sets of parents (without children) and five 2-hour single family sessions (with children). Sessions take place in community settings and are video recorded with family consent. Live supervision will be used for 3 sessions per location, enhancing treatment fidelity. Videos will inform monthly supervision addressing therapist drift and competence. Intellectual Property rights (IP) for SAFE will be available to use during the study.

For our feasibility study we developed a four-day training course in delivery of SAFE for family therapists. This course is being refined, including online delivery options, on the basis of therapist feedback from our feasibility study. We will work with our collaborating organisation, The Centre for Family Attachment Narrative Training, to develop and deliver an inclusive, bespoke online Continuing Professional Development (CPD) four-day training course for all therapists

11.2 Control arm (Treatment as Usual alone)

Autism care across the UK varies by region and by severity of symptoms. A comprehensive search, however, of "local offers" suggests similarities. The descriptions below reflect core similarities across our trial locations for post-diagnostic care. As the recent Children's Commissioner report outlines [116], waiting times for referral and on the pathway are too long and family difficulties often become exacerbated and entrenched by the time a diagnosis is received.

Diagnosis is provided either in clinic or by written letter and a detailed report sent to the family. The family are also given recommendations and details of what post-diagnostic support is available to them often through an information pack or web page. This is followed up by invitations to attend at least two further appointments or group sessions to discuss the report and next steps. Where families have reached crisis point, characterised by an inability to cope with a child or young person who is experiencing a deteriorating mental health condition, failure to eat, self-injury, violent behaviour, suicidality or other serious difficulty further intervention though CAMHS may be provided including psychological intervention, psychotherapy, behavioural interventions and psychiatric assessments and reviews. Where a family member is experiencing depression or anxiety, treatment is not usually linked to autism-related care. Initial referral is often through the GP. Patients may receive Cognitive Behavioural Therapy as part of IAPT, medication or a period of hospitalisation or in-patient treatment.

In line with the Health and Care Act 2022 and the creation of statutory integrated care systems, current post diagnostic care for autistic children and their families involves the NHS, Local Authorities (LAs), and third sector organisations. There are long-standing initiatives to provide group-based parent psychoeducation and peer support courses post-diagnosis including Incredible Years, Early Bird Plus and Teen Life National Autistic Society Family Support Programme. Currently, additional courses are being developed to be more individualised with workshops available to parents with various emphases (mental health, sensory needs, information about autism, behaviour, attachment etc). These workshops may be face-to-face or online. Integrated Care Boards may commission neurodiversity support teams, for children and young people, who provide helplines, online resources and links to LA and third sector support networks. CAMHS neurodiversity teams or equivalent services also often provide information and support for autistic children, young people and parents including advice and strategies regarding managing child distressing behaviour and support via activities for children and young people focusing, for example, on social skills games for children or videos and articles for young people on topics such as autism and gender. These resources are available to families long-term, and most families also join voluntary support groups which offer opportunities for ongoing advice, activities and peer support. Despite improvements to provision

many families still feel the process of diagnosis and support post-diagnosis is fraught with long waiting times and support is insufficient, inappropriate and difficult to navigate [116].

Families of children and young people with an autism diagnosis may also apply for an Education Health and Care Plan (EHCP) which professionals from the diagnostic pathway may feed into. In principle an EHCP enables special education provision including therapies needed such as speech and language, occupational therapy or physiotherapy and involvement of health and social workers to assist with needs beyond education, up to the age of 25. Despite the intentions of the SEND reforms around EHCPs some families are dissatisfied with the process of acquiring an EHCP and the support it promises. A recent review of family experience revealed a lack of integration with health and social care leading to unmet needs, lack of knowledge and understanding of the process and the plan itself by schools, Local Authority staff and families, particularly families living in areas of deprivation and those with a low level of educational attainment. In addition, the involvement of parents and children in the EHCP process was often minimal, and the demands placed on the professionals involved were unachievable [117].

12 SAFETY REPORTING

12.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a trial participant which may or may not have a causal relationship with the research. An adverse event can be any unfavourable and unintended sign, symptom, or disease that occurs during the time a participant is involved in the study, whether or not it is considered to be related to the intervention.
Serious Adverse Event (SAE)	A serious adverse event (SAE) is any untoward occurrence that fulfils one or more of the following criteria: a) results in death; b) is life-threatening;* c) requires hospitalisation or prolongation of existing hospitalisation (i.e., admission to a hospital ward for an overnight stay. Attendance at Accident & Emergency is not itself serious until there is a requirement for a medical intervention to prevent one of the other 'serious' outcomes from occurring); d) results in persistent or significant disability or incapacity (defined as a substantial disruption of a person's ability to conduct normal life functions); e) consists of a congenital anomaly or birth defect**; or f) is otherwise considered medically significant by the investigator (e.g., a participant's safety is jeopardised) **Life-threatening, by definition, refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it was more severe.* ***Not applicable to the current trial.*
Related SAE	An Adverse Event that is both serious and, in the opinion of the investigator, resulted from administration of any of the research procedures.
Unexpected and related SAE	SAEs that have been assessed by the investigator as having a possible causal relationship to the administration of the research procedures and has not been listed in the protocol as an expected occurrence.

12.2 Operational definitions for (S)AEs

The safety reporting period will commence from the point of randomisation until the final study visit (Week 52).

Any AEs self-reported by the AC and / or PC will be recorded in a participant file of the ISF. No onward reporting (to the Sponsor or otherwise) is required for non-serious AEs.

The risks associated with study participation are considered minimal, with no adverse events anticipated in any participant. In the feasibility study, only one SAE was reported which was unrelated to the research procedures.

For those in the SAFE+TAU group, there is a slight chance that the SAFE intervention sessions could lead to an initial increase in family disagreements as family members learn how to change the way they solve problems and talk with one another. However, the purpose of the intervention is ultimately to equip families with skills to handle these difficulties by learning how to change the way they solve problems and talk with one another, and the SAFE family therapists will be available to provide support and will be trained to handle any emerging problems. Should any issues arise the SAFE family therapists will have access to a senior clinical practitioner such as consultant clinical psychologist, psychiatrist or consultant family therapist to provide further support and advice. All SAEs will be reported in this study via eCRF (as per Section 12.3), including new incidences of suicidal or self-harm behaviour not previously displayed by the participant. Where the latter pre-specified events do not meet any of the standard SAE criteria, they should be reported as (f) medically significant events.

Any reported SAEs which are ongoing at the point of the final visit, must be followed up until the event has resolved, stabilised or has been fully investigated to the satisfaction of the PI and Sponsor. This may require contact with healthcare providers of the participant family members. The GP of the AC participant will be notified of the family's participation and will be provided with a copy of the ICF.

Any new SAEs which occur after the final visit will not be sought or captured in the eCRF. If the Investigator becomes aware of any related SAEs that occur after the end of the safety reporting period (week 52), these should be reported to PenCTU as per Section 12.3.

Events should be recorded using V5.0 of the Common Terminology Criteria for Adverse Events (CTCAE) provided in the National Cancer Institute (NCI).

12.3 Recording and reporting of SAEs

Serious adverse events (SAEs) occurring from the time of randomisation until the week 52 visit must be reported by the Investigator within the eCRF as per the work instruction for reporting safety events. SAEs may be volunteered by the participant or discovered by the SAFE Family Therapists (in the intervention group), RAs or other member of the research team. All delegated study team members are responsible for checking for SAEs at every study visit post-randomisation, in the AC participant or any participating family member.

SAEs must be reported using the digital PenCTU SAE reporting form **within 24 hours of the research team first becoming aware of the event,** even if not all information is available at the time of reporting.

For each **SAE** the following information will be collected

- Full details of the event, including a diagnosis
- MedDRA coding (system organ class and preferred term)
- Duration (start and end dates, if applicable)
- Action taken
- Outcome
- Seriousness criteria

- Causality (i.e. relatedness to administration of research procedures), in the opinion of the Investigator
- Expectedness

CTU contact information	
Email	Safe2.penctu@plymouth.ac.uk
Telephone	01752 439831

All SAEs suspected to have resulted from administration of any of the research procedures **and** is unexpected in accordance with the trial protocol will be subject to expedited reporting to the Research Ethics Committee (REC) which issued the favourable ethical opinion of the research. This will be actioned by the CI / Sponsor within 15 calendar days of the CI becoming aware of the event using the non-Clinical Trials of Investigational Medicinal Product report form provided on the Health Research Authority (HRA) website. The allocation of the family will be unblinded by the Sponsor as part of this reporting process. Once a report has been made to the REC, PenCTU in collaboration with the CI, may inform participating trial locations of the unexpected and related SAE where appropriate, using methods that reflect the urgency of the event.

12.4 Assessment of (S)AEs

12.4.1 Severity

The investigator should determine the severity of the SAE as per NCI CTCAE (V5.0):

	Severity	Definition
1	*Mild*	Aware of sign/ symptom but easily tolerated
2	*Moderate*	Discomfort enough to cause interference with usual activity
3	*Severe (or medically significant)*	Incapacitating, unable to work or perform usual tasks
4	*Life-threatening*	Risk of death at the time of the event, urgent intervention required
5	*Death*	Death related to AE

NOTE: to avoid confusion or misunderstanding the term “severe” is used to describe the intensity of the event, which may be of relatively minor medical significance, and is NOT the same as “serious” which is described in the safety definitions.

12.4.2 Causality

Clinical judgement should be used to determine whether the event is likely to be related to the administration of any of the research procedures as defined in the protocol.

- **Related** to the study (i.e., resulted from the administration of any of the research procedures)
- **Not related** to the administration of any of the research procedures.

Causality assessments should be performed by the Principal Investigator / delegate within 3 working days of the trial location becoming aware of the event.

12.4.3 Expectedness

The expectedness assessment is only required if the event is deemed to be related to the administration of any of the research procedures.

- **Expected**: Event previously identified and described in the protocol*
- **Unexpected**: Event not previously described in the protocol.

The expectedness assessment is delegated to the Chief Investigator who will perform a clinical review.

*The participating AC may have ongoing issues related to severe tantrum behaviour (meltdowns), as well as suicidal ideation or self-harm behaviours. Mental health problems may be present among all family members, anxiety in particular.

12.5 Responsibilities

Researchers at trial locations

- Checking for SAEs at each study visit and escalating to PI for assessment of causality.

Principal Investigator (PI) / delegate:

- Using clinical judgement in assigning severity, seriousness and causality.
- Ensuring all SAEs are recorded and reported to the Sponsor within 24 hours of becoming aware of the event and provide follow-up information as soon as it becomes available. Ensuring SAEs are chased with the Sponsor if a record of receipt is not received within 2 working days of initial reporting.

Chief Investigator (CI) / delegate or independent clinical reviewer:

- Clinical oversight of the safety of all participants in the trial, including an ongoing review of the risk / benefit.
- Using clinical judgement in assigning seriousness, causality and whether the event was anticipated as documented in the trial protocol.
- Immediate review of all related SAEs.
- Review of specific SAEs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan (TMP).
- Assigning Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding to all SAEs.

Sponsor (NB where relevant these can be delegated to the CI or PenCTU):

- Central data collection and verification of SAEs according to the trial protocol onto a database.
- Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing risk / benefit according to the TMP.
- Reporting safety information to the independent oversight committees identified for the trial (DMEC & TSC) according to the TMP.
- Expedited reporting of related and unexpected SAEs to the REC within the required timelines.
- The unblinding of a participant for the purpose of expedited SAE reporting.
- Notifying investigators of unexpected SAEs that occur within the trial (where appropriate).

Trial Steering Committee (TSC):

In accordance with the TSC charter, periodically reviewing safety data and liaising with the DMEC regarding safety issues.

Data Monitoring and Ethics Committee (DMEC):

In accordance with the DMEC charter, periodically reviewing overall safety data to determine patterns and trends of events, or to identify safety issues which would not be apparent on an

individual basis. To facilitate this, a monthly report of any SAEs graded 4 or 5 will be sent to the DMEC chair.

12.6 Notification of deaths

All deaths should be reported to PenCTU within the eCRF. 'Death' in itself is not an SAE, but the outcome of an SAE, and should be reported in line with section 12.3.

12.7 Reporting urgent safety measures

The Sponsor, Chief Investigator or local Principal Investigator (PI) at a trial location, may take appropriate urgent safety measures (USM) in order to protect research participants against any immediate hazard to their health and safety.

If any USM's are taken, the CI and / or Sponsor shall immediately and in any event no later than seven days from the date measures are taken, submit written notice to the REC of the measures taken, the circumstances giving rise to those measures and the plan for further action. Where the USM(s) requires a modification to study documents, a substantial modification will be submitted to the REC as soon as possible thereafter.

The CTU will notify all participating trial locations within 24 hours of USM(s) being implemented and acknowledgement of receipt from each local PI will be recorded and filed in the TMF. The trial funder and oversight committees will also be notified accordingly.

12.8 Type and duration of the follow up of participants after SAEs

All SAEs which occur during study participation will be followed up until resolution, stabilisation (i.e., the participant's status is unlikely to change) or to the satisfaction of the Sponsor.

Any change in outcome (e.g., a resolution is reached) or additional information, including an increase in severity or change in causality assessment, should be entered onto a digital SAE resolution form as soon as it is available and within 24 hours of the information becoming available.

13 STATISTICS AND DATA ANALYSIS

13.1 Sample size calculation

The target sample size is 494 families (330 in the SAFE+TAU group and 164 in the TAU only group). For a minimal clinically important difference of 3 on our primary outcome measure, (SCORE-15) based on the literature [72, 73, 75, 118] and 8 for the SD (7.3 obtained in the SAFE feasibility study). To account for a possible multi-parent group effect in the intervention group we will use a conservative 0.1 for the intragroup correlation and an assumed mean group size of 6 with variance 2. Using the conventional 2-sided 5% alpha and 90% power, and retaining the 2:1 allocation, gives a requirement for 405 families. We anticipate a 18% loss to follow up. This increases the requirement to 494 families. We have looked at a number of sensitivities to our assumptions, e.g. if the SD is 9 then we would still have 82% power.

13.2 Planned recruitment rate

494 families will be recruited via 6 trial locations and associated community pathways (CP). Our six locations vary in size and diversity, on average they see a minimum of 10 eligible families per week. We predict we can comfortably meet a target of 4.12 families per location + CP, per month across 20 months.

13.3 Statistical analysis plan

A detailed statistical analysis plan (SAP) will be developed during the delivery phase and approved by an independent statistician (Trial Steering Committee) prior to database lock. Reporting and presentation of trial data will accord with CONSORT 2010 extension for cluster randomised trials [119].

13.4 Summary of baseline data and flow of patients

A CONSORT diagram will be used to summarise the flow of participating families (clusters) and participants through the trial. Baseline characteristics of participants will be summarised descriptively using means and standard deviations (or medians and interquartile ranges) for continuous variables and numbers and percentages for categorical variables. Summary measures will be calculated as appropriate, for baseline, 22 weeks and 52 weeks post randomisation follow-up.

13.5 Primary outcome analysis

The main comparison for the primary outcome (SCORE-15 total score at 22 weeks post randomisation follow up) will be between trial arms (SAFE+TAU versus TAU only) and will be based on the intention-to-treat (ITT) principle with participants analysed according to the trial arm their family was allocated to. The ITT principle is defined as an assessment of participants taking part in the trial, based on the group they were initially (and randomly) allocated to. Participants will only be included in the analysis if data are available (i.e. no imputation will be done).

The primary analysis will be programmed and undertaken by a trial statistician blinded to allocated groups, under the ITT principle. SCORE-15 total scores will be analysed using a heteroscedastic partially nested mixed-effects model [120] to account for the variation within individual families in both arms and within multi-parent groups in the intervention arm. It also accounts for the variation in the individual errors within treatment arms. This model also facilitates the inclusion of participants with at least one post-baseline data point (i.e. 22 weeks and 52 weeks post randomisation), maximising use of available outcome data and minimising effects of loss to- follow-up. Primary analysis will estimate the between-group difference in SCORE-15 total scores at 22 weeks post randomisation follow up. The analyses will be adjusted for key prognostic factors (e.g. baseline

SCORE-15 total score), the time (in days) between baseline and randomisation and the factors on which the randomisation was balanced (i.e., location).

13.6 Secondary outcome analysis

Comparisons will be based on the ITT principle with participants analysed according to the trial arm their family was allocated to. Participants will only be included in the analysis if data are available (i.e. no imputation will be done). Continuous outcomes will be compared using a heteroscedastic partially nested mixed-effects models, reporting mean differences with 95% confidence intervals and p-values, and binary outcomes will be compared using marginal logistic regression models using Generalised Estimating Equations with information sandwich ("robust") estimates of standard error, specifying an exchangeable correlation structure, reporting odds ratios with 95% confidence intervals and p-values. For each outcome, the intervention effect estimate will be adjusted for key prognostic factors (e.g. baseline score), the time (in days) between baseline and randomisation and the factors on which the randomisation was balanced (i.e., location).

13.7 Subgroup analysis

Subgroup analyses will be undertaken using tests of interaction to investigate whether the effect of the intervention differ across categories defined by ethnic group and socio-economic status, if a sufficient number of families are recruited from black ethnicities and low socio-economic status groups. The SAP will contain full details of this and any other agreed subgroup analyses of interest. These analyses will be exploratory given their secondary nature and that the trial has not been powered to detect subgroup effects.

13.8 Interim analysis and criteria for premature termination of the trial

There is no planned formal, comparative interim analysis for this trial. An internal pilot (Section 4.1.3) will be used to make the decision to progress to the main trial. The progression recruitment criteria will be summarised descriptively.

13.9 Participant population

The primary analysis population will include all participants for whom the primary outcome can be derived (i.e. no imputation) with the main comparison based on the ITT principle with participants analysed according to the trial arm their family was allocated to.

13.10 Procedure(s) to account for missing or spurious data

For each outcome measure, relevant scores will be calculated with published guidelines (if available) used to process, score, and summarise measures which may include imputation in the event of missing items.

Reasons for being unable to collect data during an assessment will be recorded on the electronic case report form (eCRF), where appropriate. eCRFs will be assessed for missing data by the CTU and trial locations will be regularly chased for missing data. The CTU will maintain a record of local compliance with eCRF completion. If data completion is poor, a monitoring visit may be scheduled. The eCRFs will include mandatory fields; if a form is saved without these fields being completed an automatic flag will be displayed to the user. Where questions may need to be left blank, options such as 'Not applicable' or 'Prefer not to say' will be available, to differentiate these from missing data. Validations will be written into the study database, to raise queries with particular data field, such as flagging if the date of a visit does not correspond to the correct timepoint. Periodic reminders will be

sent out to participants to complete questionnaires, if they have selected to complete these electronically.

The PenCTU data manager will write a series of R scripts to perform data tasks to aid data completeness, including checking overall completeness by field of all CRFs, checking all visits have been recorded in a logical order and checking SAE forms have been completed. The scripts will be run on a weekly basis and any concerns will be raised individually with trial locations.

The RA will be required to check participant completed measures to confirm completeness, and automated field sin the form will flag where forms are incomplete. Licensed measures will only be given a calculated score where all fields are complete, unless the official useage guidance states otherwise.

13.11 Other statistical considerations

Any deviations from the original statistical plan will be documented fully.

14 DATA MANAGEMENT

Data management activities are summarised in this section. Detailed data management activities are described in a separate Data Management Plan (DMP). The main study database will be developed by PenCTU, using the commercial electronic data capture system REDCap.

14.1 Data collection tools

The REDCap database will be used to collect participant screening and outcome data. It will be a web-based, fully validated system, compliant with MHRA guidance and ALCOA+ principles. Data will be captured in accordance with the best principles of clinical data management and the relevant standard operating procedures on Clinical Data Management System Specification and Validation. PenCTU will be responsible for the database build and system validation. Inbuilt validation features will be utilised alongside post-entry monitoring, performed using validated R scripts to ensure data quality and completeness.

Data will be hosted externally by ARO on MS Azure datacentres located within the UK (Liverpool, England). ARO are NHS DSP Toolkit compliant and hold ISO27001 and Cyber Essentials Plus certifications. Microsoft Azure datacentres are Service Organisation Control (SOC) type 1 and 2 compliant. Data will be stored on hardware dedicated to PenCTU's instance of REDCap. All electronic data are regularly backed up and stored with a full audit trail.

14.2 Source records

Source data will include the AC's care records (e.g., for certain eligibility criteria and medical history), participant completed documents (e.g. informed consent forms), worksheets provided by PenCTU, eCRFs and video and audio recorded data at baseline and post-intervention assessments, intervention sessions, focus groups and interviews.

Source data will be compliant with ALCOA+ guidance (attributable, legible, contemporaneous, original, accurate, complete, consistent, enduring, available). The CTU will verify source data and source documents as stipulated in the study monitoring plan (see Section 14 Monitoring, Audit and Inspection).

In the context of clinical care, local investigator staff will notify the GP of the AC of their involvement in the study to ensure a record is present in their medical notes. Otherwise, trial locations should keep a participant folder in the investigator site file (ISF) which at a minimum, should be updated to include:

• Consent and eligibility for trial

• Dates of all trial visits and follow ups

• Serious adverse events

• Completion or discontinuation of trial

The participants' identity will be protected at every stage of their participation in the trial, according to the Caldicott principles. If any patient information needs to be sent to a third party the trial team will adhere to maintaining pseudo-anonymous participant parameters in correspondence.

14.3 Case Report Form and questionnaire completion

Study data will be recorded on eCRFs on REDCap. Patient Reported Outcomes (PROs) will be completed via digital survey link or on paper. If completed on paper, these will be entered to the

eCRF by local staff. Any paper forms completed by local staff or participants will be retained in the investigator site file (ISF).

14.4 Video and audio recorded data

Video data will be collected at baseline, 22 and 52 weeks for all study participants for CARP-A assessments carried out by RAs; and at each intervention visit for treatment fidelity assessment by designated supervising therapists. Audio data will be collected at participant and therapist focus groups and interviews, including the PDI prior to intervention sessions All video and audio files will be password protected and stored on Microsoft SharePoint on the University's secure server. Video and audio data will not be left stored on recording devices. Audio data will be transcribed, pseudonymised and deleted as soon as is practicable. Those participants who have not given their consent for their video data to be used for subsequent supervision and training purposes, will have their video files deleted at the end of the study. Data retained at trial locations will be securely stored for the duration of the study prior to archiving.

14.5 Access to data

Direct access to investigator location records will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits, and inspections, in line with participant consent.

14.6 Archiving

Following completion of trial data analysis, the Sponsor will be responsible for archiving the study data and Trial Master File in a secure location for the period of 20 years beginning with the day after conclusion of the trial. PenCTU will prepare the Trial Master File for archiving in accordance with the requirements of the Sponsor's SOP. PenCTU will prepare a copy of the final dataset for archiving according to the requirements of the CTU's SOP.

Principal Investigators at trial locations will be responsible for archiving Investigator Site Files and trial data generated at the location according to local policy. No trial-related records should be destroyed unless or until the Sponsor gives authorisation to do so. Medical records containing source data or other trial related information should be labelled, physically or electronically, so as to ensure retention until the Sponsor gives authorisation to destroy. e.g. "Keep until dd/mm/yyyy" (where the date given is five years after the last participant's final visit).

15 MONITORING, AUDIT & INSPECTION

15.1 Monitoring plan

In accordance with PenCTU standard operating procedures for risk assessment and monitoring, a specific trial monitoring plan will be generated by the PenCTU, based on the PenCTU's risk assessment. The monitoring plan will be signed off by the CI and Sponsor before implementation.

PenCTU will perform ongoing central monitoring, outputs from which will be discussed by the TMG, and used to identify areas of poor performance at trial locations. Central monitoring will include close supervision of participant recruitment rates, attrition rates, data completeness (missing data), data quality (using range and consistency checks), protocol non-compliance and calendar checks (to identify deviations from participants' visit schedules).

Remote monitoring will also be performed and will include consent process checks (through collection of completed de-identified consent forms) and appropriateness of delegated duties at trial locations (through collection of local delegation and training logs). Poor performance at locations may trigger on-site monitoring visits, hosted by the local PI and relevant members of the PI's team. On-site monitoring (if applicable) will be conducted by PenCTU staff according to established PenCTU SOPs. The Investigator(s) must ensure that source documents and other documentation for this study are made available to study monitors, the REC or regulatory authority inspectors. Authorised representatives of the Sponsor may visit the trial locations to conduct audits/ inspections.

15.2 Quality assurance

The CI (Dr Rebecca Stancer) will be responsible for the overall running of the trial. The CTU will coordinate trial-related activities and assist with overall trial management, monitoring and production of progress reports. The CTU will also organise the web-based randomisation, prepare the database, and oversee safety-reporting activities.

Prior to activating a location to recruitment, it is necessary for all staff members working on the trial to participate in an induction session. This will be carried out via a site initiation visit. A location set-up checklist will be completed for all locations to confirm that pre-activation activities have been actioned and all relevant staff members are able to participate. Support will be offered to staff at trial locations to ensure they remain fully aware of trial procedures and requirements. Additional support and training will be offered to locations as appropriate where necessary (e.g. if the recruitment rate is lower than expected).

A Trial Master File will be set up and held securely at the CTU, in accordance with CTU SOPs.
CTU will produce and provide each trial location with an Investigator Site File. Any updates to essential trial records will be circulated to all trial locations – it is the responsibility of the local team to update their Investigator Site File as necessary.

16 ETHICAL AND REGULATORY CONSIDERATIONS

16.1 Research Ethics Committee (REC) review & reports

The study will be undertaken subject to appropriate Research Ethics Committee (REC) and Health Research Authority (HRA) approvals. The trial will be conducted in accordance with the protocol, the principles of the Declaration of Helsinki and ICH GCP. Any modifications of the protocol will be submitted to the Sponsor, HRA and REC for approval.

The CTU will notify the REC of the end of trial within 90 days of completion. If the study is ended prematurely, the CTU will notify the REC within 15 days, including the reasons for the premature termination. This will also apply for temporary suspensions.

Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

16.2 Peer review

This study has been peer reviewed and approved as part of the NIHR HTA funding application process, including two PPIE representatives, and by Dr Nick Pratt (Senior Lecturer in Education) as part of University of Plymouth local procedures.

16.3 Public and Patient Involvement

The SAFE intervention has been developed in extensive collaboration with PPI to meet the need for novel interventions for the whole family.

There are three PPI co-applicants with relevant expertise on the project.

During study design, meetings were held with a PPI group. Their input and assistance was sought, including the selection of the outcome measures for the study and the development of participant-facing documents, and a video explaining the PIS by a PPI member for families to view on the SAFE webpage.

PPI meetings will be held quarterly to ensure regular PPIE throughout the trial life-cycle. A subgroup with a focus on Inclusion and Diversity (IDPPI) has also been established, including community groups and Autism Voice who support families of autistic children from the global majority.

The study team will liaise with PPI members to engage community groups and services in the geographical areas of the trial locations, to advertise the study through multiple media outlets, including community newsletters, social media, signposting by word of mouth, local support groups, posters and flyers.

A series of focus groups with key stakeholders and PPIE members will be used to identify and refine implementation strategies to develop an implementation guide as the trial progresses. Topic guides will be developed in collaboration with the PPI group for the qualitative investigation of the process evaluation.

PPIE representatives will sit on the TSC for independent oversight.

16.4 Regulatory compliance

The trial will not commence until HRA approval has been issued and a favourable REC opinion is received. The protocol and trial conduct will comply with the principles of the Declaration of Helsinki and ICH GCP.

Before any trial location can enrol patients into the study, PenCTU will ensure that appropriate approvals from participating organisations are in place.

If changes to the study are required, these must be discussed with the Sponsor, who is responsible for deciding if a modification is required and the substantiality of the modification. PenCTU will work with trial locations (R&D departments at NHS locations as well as the study delivery team) so they can put the necessary arrangements in place to implement the modification to confirm their support for the study as amended.

16.5 Protocol compliance

Non-compliance with protocol will be captured on study specific non-compliance report forms, according to instructions provided by PenCTU and in accordance with PenCTU standard operating procedures. Protocol non-compliances will be reviewed periodically by the Trial Management Group as part of central monitoring, with the aim of identifying and addressing recurrent episodes of non-compliance. Each reported non-compliance will be reviewed by the PenCTU trial manager. PenCTU staff will immediately inform the PenCTU QA Manager and CI if they believe that a serious breach has occurred (see below). Where the trial manager and/or PenCTU QA Manger believes that a non-compliance might constitute a serious breach, PenCTU will ensure that a completed non-compliance report form is provided to the Sponsor immediately (i.e., within 1 working day of first awareness).

16.6 Notification of serious breaches of GCP and/or the protocol

A “serious breach” is a breach of the protocol or of the conditions or principles of Good Clinical Practice, which is likely to effect to a significant degree –

- The safety or physical or mental integrity of the trial participants; or
- The scientific value of the trial

The Sponsor will be notified immediately of any case where the above definition applies during the trial period. The Sponsor is responsible for notifying the REC of a serious breach in any study within seven days of the matter coming to their attention.

16.7 Data protection and patient confidentiality

Data will be collected and retained in accordance with the UK Data Protection Act 2018 and the General Data Protection Regulation (GDPR) 2016. The trial Sponsor is the Data Controller for the trial data. PenCTU is a data processor, centrally managing trial data generated at trial locations. The University of Plymouth is the data custodian, since data are stored on databases managed by the University of Plymouth.

Data including the number of patients screened, approached and interested in taking part will be collected via a log completed by staff conducting screening. Local staff will ensure that the participants’ anonymity is maintained through protective and secure handling and storage of patient information in accordance with ethics approval.

Any paper-based data collection tools (e.g. questionnaires, source data worksheets) for capturing source data will remain at trial locations. Local staff will enter participant data into purposed designed data capture systems. Access to the system for all users (including PenCTU staff) is via a secure password-protected web-interface with two-factor authentication. Each participant will be allocated a unique system-generated study number. Participants will be identified in all study-related documentation by their study number and initials. Data collected and analysed during the study will be pseudonymised by the use of this unique identifier.

In order to facilitate central coordination of the study, participants' contact details will be entered into the data capture system by local staff (after consent). Only limited staff at PenCTU will have access to these details and these details will not be made available in any form to any persons unless needed for study conduct. Datasets prepared for transmission to statisticians (for analysis), co-applicants or Sponsor will be pseudonymised and will not contain any direct identifiers or participant contact details.

All video and audio data will be password protected and stored on Microsoft SharePoint on the University's secure server using a unique study number. All data will be deleted from digital recorders as soon as it is securely transferred. Video and audio recordings will only be accessible to designated individuals for the purposes outlined in Section 14.4: Video and Audio recorded Data.

Transcription of audio recordings of interviews or sessions will only be carried out by members of the research team or professional services with confidentiality agreements in place. Direct identifiers will be removed from transcripts.

16.8 Financial and other competing interests

The Chief Investigator, PIs at each trial location and TSC/DMEC committee members will sign a declaration form to disclose any financial or other competing interests including, but not limited to:

- any ownership interests that may be related to products, services or interventions considered for use in the trial or that may be significantly affected by the trial
- commercial ties including, but not restricted to, any pharmaceutical, behaviour modification, and/or technology company
- any non-commercial potential conflicts e.g. professional collaborations the may impact on academic promotion.

Declaration forms will be filed in the Trial Master File (TMF). At the time of protocol writing, there are no known financial or other competing interests of the Chief Investigator or team.

16.9 Indemnity

This study is sponsored by an NHS/HSC organisation (Devon Partnership NHS Trust) and no additional insurance for design or management of the research is required. The NHS indemnity scheme will apply.

16.10 Modifications

Any modifications to the study will be submitted to the Sponsor, HRA and REC for approval. Substantial modifications that require review by REC will not be implemented until HRA approval is issued and the REC grants a favourable opinion.

PenCTU will notify the relevant stakeholders of any substantive modifications, including the Funder, trial registries, and external vendors, where contractually required. PenCTU will maintain a modification history log documenting changes to trial documents and implementation date(s). All correspondence with the REC and HRA will be recorded and retained in the Trial Master File.

16.11 Post trial care

All participants will continue to receive the standard care for their condition during and post-trial, and their participation in this study will not affect or delay this care. Participants will not receive any

additional SAFE intervention once the programme is complete. Voluntary organisations will receive training so they are 'SAFE informed' to support any participant families using these services post-trial participation.

16.12 Access to the final trial dataset

During the study, the PenCTU data team will have access to the trial dataset, including identifiable participant data. Other members of the CTU and the wider study team will have restricted access to pseudonymised study data. Access to the dataset will be granted to the Sponsor and host institution on request, to permit study-related monitoring, audits and inspections. Access will be overseen by the CTU data manager and trial manager. Access to the final dataset will be provided to the trial statisticians for analysis.

After the trial has been reported, the anonymised individual participant data that underlie the results will be available on request from the CI and Sponsor, along with supplementary files as required (e.g. data dictionaries, blank data collection forms, analysis code, etc.). Data will be shared with (or access to the data will be provided to) requestors whose proposed use of the data has been approved by the CI and Sponsor, under an appropriate data sharing agreement. It will not be possible to identify participants personally from any information shared.

17 COMMUNICATION AND DISSEMINATION POLICY

As part of the embedded implementation plan and in liaison with PPIE representatives, the study team will inform and engage key stakeholders and the public about the study and the results. This will include patients/service users, community and advocacy groups, NHS autism service providers, family therapists, commissioners and policy makers (including registered stakeholders informing NICE guidelines related to autism).

Existing connections will be developed further to plan for dissemination of study results through presentations at local, national and international events, as well as posters, flyers, newsletters, news items, online platforms, podcasts, informal discussion groups, and publications in international and practice journals. This will include targeted outputs in appropriate formats to ensure inclusivity of dissemination activities (black and low SES families), and recruitment of influencers and champions to enthusiastically share and promote the research.

The data arising from the trial will be owned by the Sponsor. On completion of the trial, the data will be analysed and tabulated and a Final Trial Report prepared. This report will be submitted to the trial Sponsor and Funder and will be publicly available. Participating investigators will not have rights to publish any of the trial data without the permission of the CI and Sponsor.

The trial will be reported in a manuscript that will be submitted to a peer-reviewed practice journal as open access. The trial will be reported in accordance with the relevant CONSORT guidelines. All publications arising from this trial will acknowledge the Funder and a copy of all manuscripts will be provided to the Funder for review at the time of submission to a journal. However, the Funder does not have the right to revise any submission prior to publication. The trial protocol will also be submitted for open access publication to a peer-reviewed journal. Other publications will include an analysis of processes of change including Theory of Change and Logic Model, and contributions to inclusive recruitment strategies.

A dedicated study webpage hosted by Peninsula Clinical Trials Unit will highlight the project aims, objectives, methods and partners and provide a location for potential participants to view the Participant Information Sheet, register their interest in participating and view regular study updates. The study webpage will provide a platform with potential to generate a range of written, visual and video content to showcase and promote the study and will be promoted by utilising the University of Plymouth's extensive following on various social media platforms.

An anonymised participant level dataset will be produced and held within PenCTU.

This study has potential to improve autism care and reduce the current economic burden to the NHS. If the study results indicate that SAFE is an effective and cost-effective intervention, the study group aims to:

- Implement SAFE as a new intervention for families of autistic children in the NHS.
- Encourage inclusion of SAFE in NICE guidelines as a recommended intervention to be offered to families of autistic children at the point of diagnosis
- Develop a practical implementation guide covering contextual factors for delivery including what, how, who, where for distribution across clinical and community settings.
- Make the SAFE intervention & a 4-day CPD training programme freely available to NHS Family Therapists in Autism Services (Copyright currently held jointly by Professor Rudi Dallos and The University of Plymouth)

17.1 Authorship eligibility guidelines and any intended use of professional writers

Authorship of all manuscripts and papers relating to this trial will be determined according to the International Committee of Medical Journal Editors criteria. All members of the TMG who have contributed to trial design, management, analysis and interpretation will be granted authorship of the Final Trial Report. The CI will retain lead author status on the Final Trial Report. There is no intention to use professional writers.

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19 APPENDICES

APPENDIX 1 – SAFE THERAPY SESSIONS

More detailed information about each of the SAFE therapy sessions is as follows:

Session 1 (3 hours in a community session – multi-parent therapy including 8+/- 2 sets of parents)

Families act as 'consultants' for each other and will:

- Present a typical day in their life and the challenges they face
- Explore the understandings of the nature of autism and associated typical challenges and problems
- Draw their family tree (genogram) and explore with other families their family networks and sources of support
- View videos of typical problematic family scenarios and share practical and emotional coping strategies
- Develop a relational/attachment model of the interaction in the video
- Discuss how this connects with their own experiences of how problems are related to family life
- Learn about and discuss the Circle of Security model
- Discuss coping strategies in terms of parents' own childhood experiences
- Learn about and discuss family and attachment approaches applicable to autism care

Session 2 (2 hours– individual family session including all family members)

Discussion of how things have been since the last session, followed by:

- As a family draw a picture of a 'day in our life' - discuss the challenges and opportunities they face as a family
- Discussion of a successful interaction where a potential problem was averted. Something that went well
- Map the successful event they have recently experienced
- Draw a family genogram together: focus on transitions, similarities and differences between family members parenting styles, attachment patterns, coping with emotional needs and comfort

Session 3 (2 hours– individual family session including all family members)

Discussion of how things have been since the last session, followed by:

- Map a difficult event experienced recently and discuss how things could have been done differently
- Sculpt (using buttons). Mapping of changes in family relationships, intimacy, connections, family patterns a) prior to diagnosis, b). current family configuration, c). ideal/hoped for family configuration. Use this to discuss the needs of all the family members, including the siblings.
- Explore the Circle of Security (CoS) to consider their child and their own needs for safety, comfort and exploration. Discuss how parents' childhood experiences shape parenting styles and emotional responses

Session 4 (2 hours– individual family session including all family members)

Discussion of how things have been since the last session, followed by:

- Consider systems the child and family are involved in, school, community, clubs, activities, friendships etc. and sources of support and anxieties these can generate. Relate to CoS
- Self-Autism Mapping (SAM): The child maps parts of themselves they see as influenced by and not influenced by autism. Exploring how the influence of autism may alter/ reduce/ expand in different contexts and over the course of development
- Return to the family genogram. Focus on family stories and looking at trans-generational pattern of 'autistic' traits. How families responded

Session 5 (2 hours– individual family session including all family members)
Discussion of how things have been since the last session, followed by:

- Map any notable events including discussion of how things could have been done differently
- Further discussion of the CoS model. Exploration of parents own attachment histories
- Corrective and replicative scripts. What they have learnt from their own childhood. What they want to do differently and similarly. How scripts relate to their responses to the child's 'typical' and 'autistic' behaviour
- Mapping of parents' experience of being parented. Continuing role that their parents (grandparents) play in their lives

Session 6 (2 hours– individual family session including all family members)
Discuss how things have been since the last session, followed by:

- Map and Role-play core parts of a typical current problematic sequence at home and explore different ways of managing, especially the importance of naming emotions and feelings at difficult moments.
- Autistic child and siblings invited to give a 'presentation' of an area of their special interest
- Return to a discussion of SAM and understandings of autism – challenges and opportunities, when is autism helpful/unhelpful?
- Make links to parents' own childhood histories and how they influence their parenting
- Return to a discussion of the family sculpt to consider transitions and changes they will be facing

Session 7 (3 hours in a community setting – multi-parent therapy including 8+/- 2 sets of parents)

Representatives of local support groups, trained in SAFE will be present at this meeting.

- Feedback about how they have been able to use core techniques
- Reflecting discussion from the therapists about their experience of the sessions
- Revisit examples of difficult patterns of interaction – meltdowns and share what they have learnt with each other
- View video of young adult with Asperger Syndrome reflecting on his childhood and how he has learnt to cope
- Discuss similarities/differences in perceptions, changes in relationships, impact of diagnosis, refer to SAM
- Create a future orientated timeline and discuss problems that may arise and how to overcome them
- Feedback from parents or carers regarding implementing ideas from the programme
- Future challenges and developmental stages that will face the families.
- On-going support available from peers and local voluntary support workers.