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SHIFT

Self-Harm Intervention, Family Therapy: a randomised controlled trial of family therapy vs. treatment as usual for young people seen after second or subsequent episodes of self-harm

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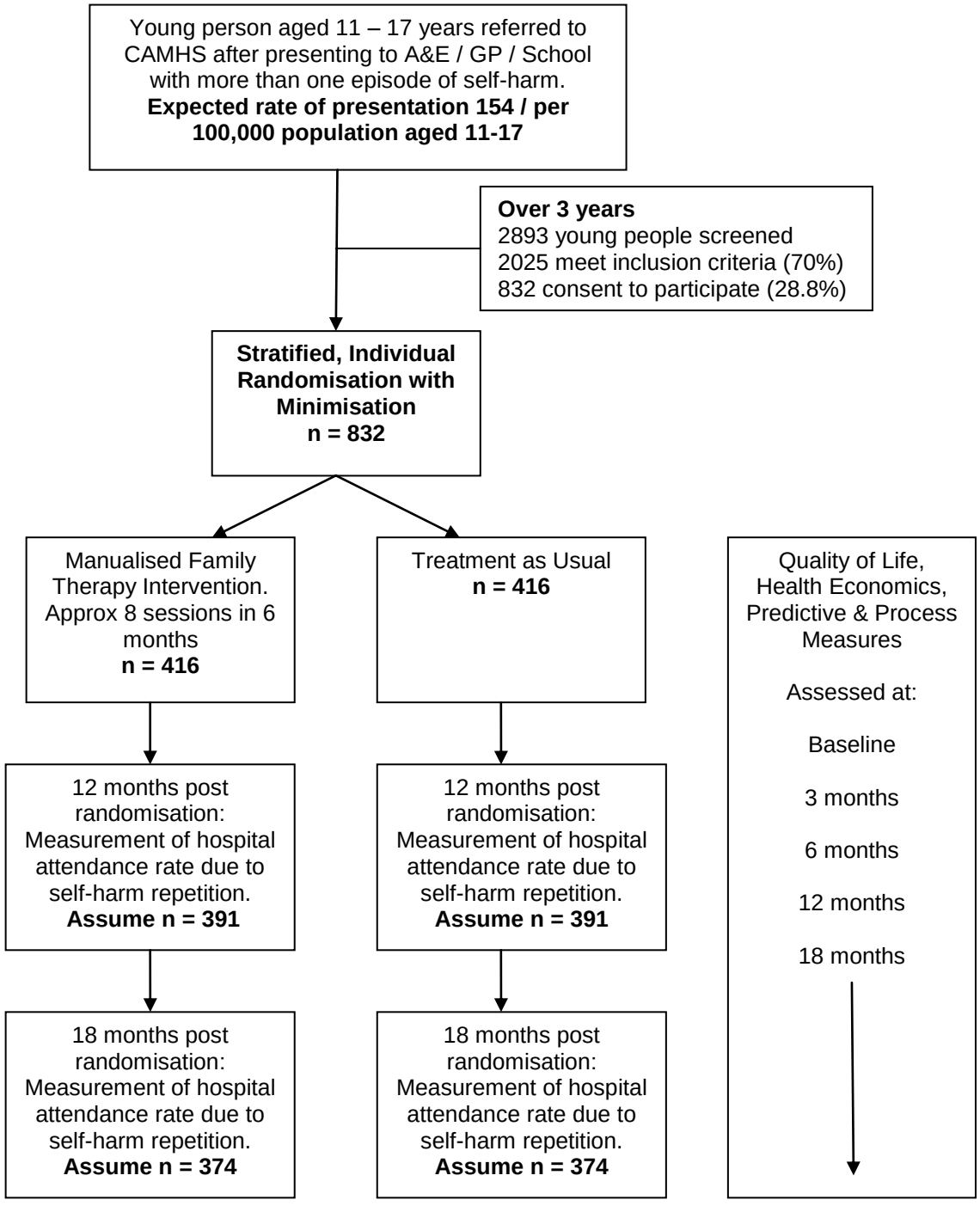
1 CONTENTS PAGE

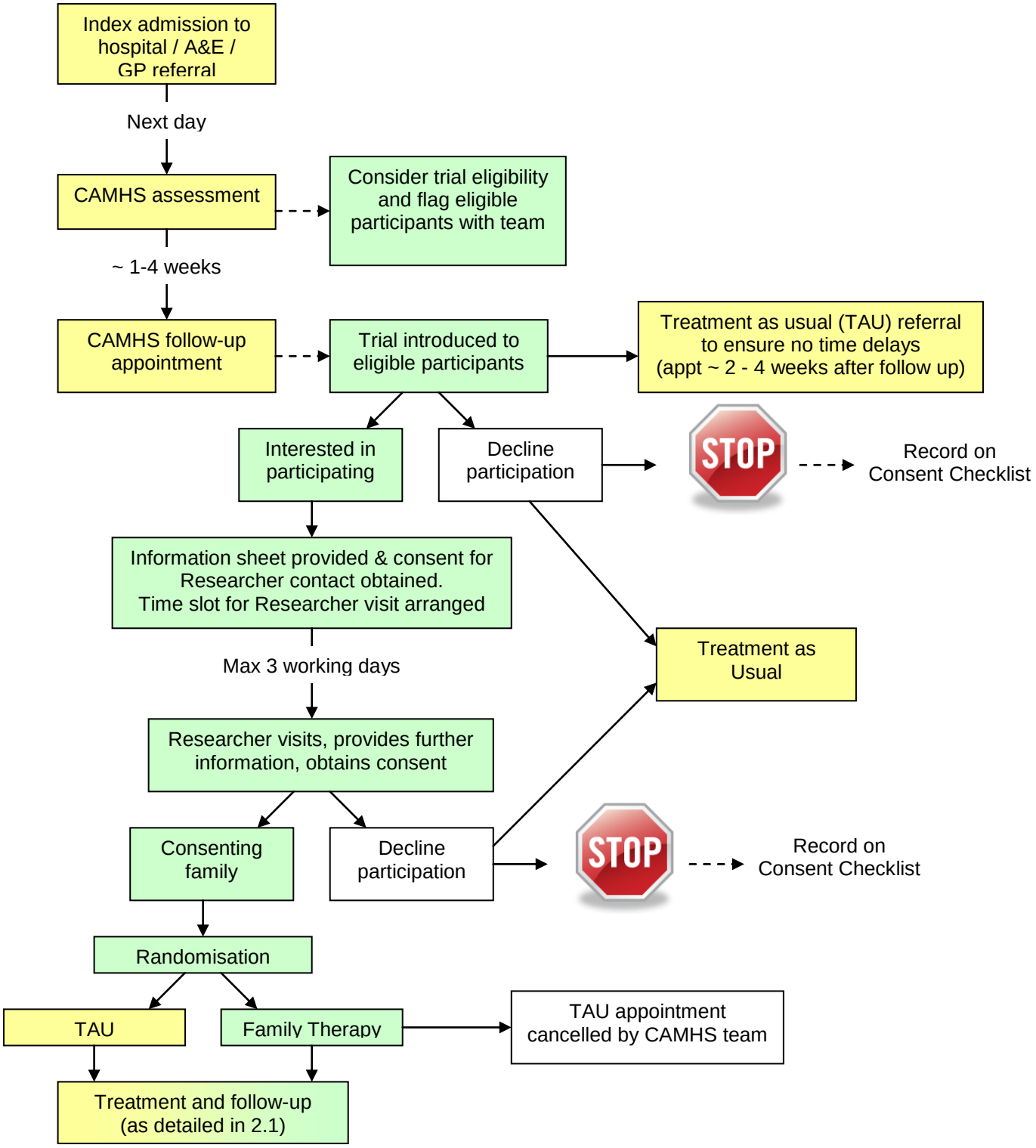
2 TRIAL SUMMARY

The SHIFT Trial has been designed as a pragmatic, individually-randomised, controlled trial comparing Family Therapy (FT) with Treatment as Usual (TAU) for adolescents aged 11 – 17 years who have engaged in at least one previous episode of self-harm. The trial aims to recruit 832 participants from centres in Yorkshire, Greater Manchester and London. Family therapy will be delivered by qualified family therapists using a modified version of the Leeds Family Therapy & Research Centre Systemic Family Therapy Manual (LFTRC Manual), the development of which was funded by the MRC to support trials of FT. The primary outcome is rate of repetition of self-harm leading to hospital attendance 18 months after randomisation. Secondary outcomes include rate of repetition at 12 months, cost-effectiveness, quality of life, and predictive / process measures.

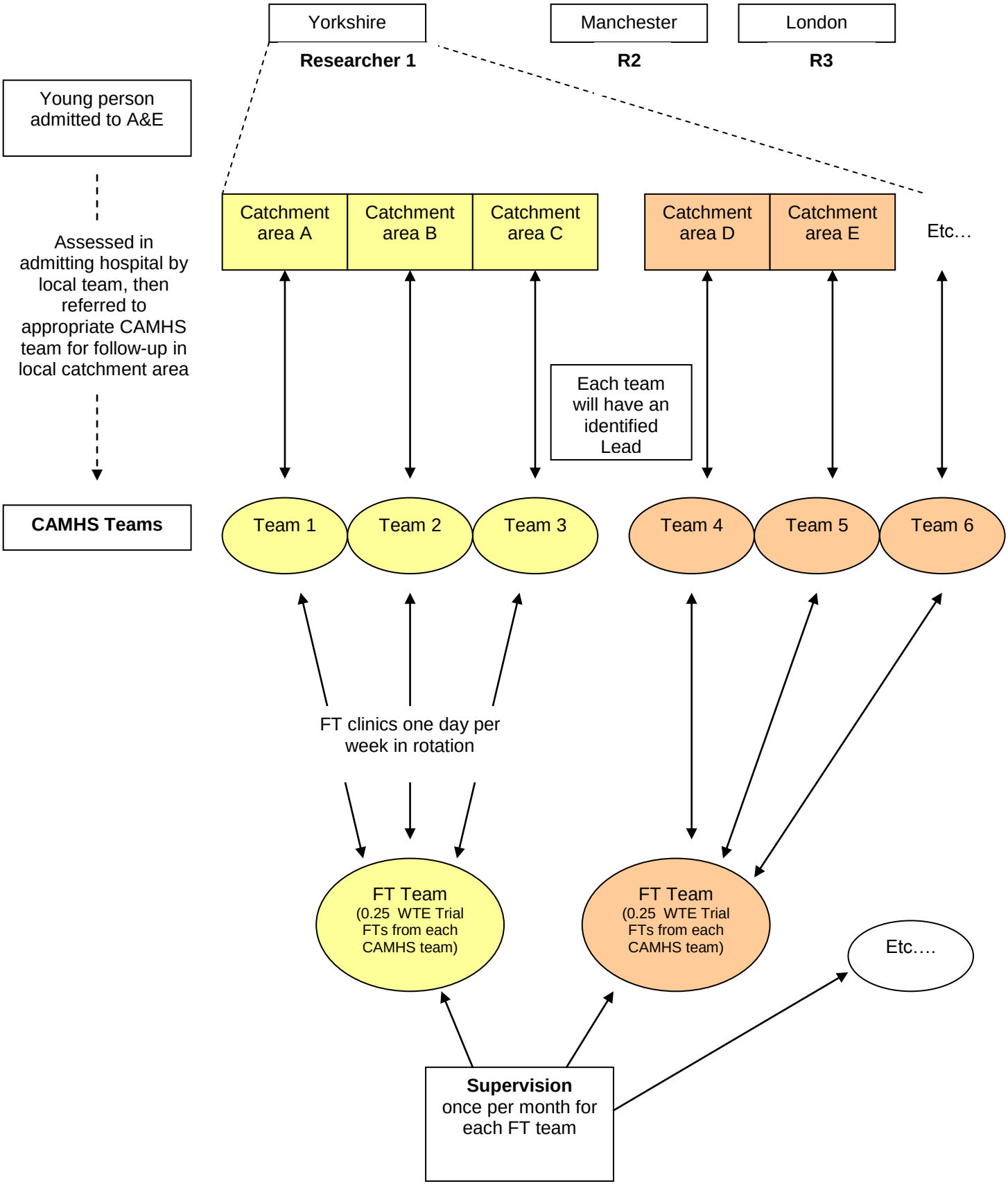
2.1 TRIAL DESIGN FLOW DIAGRAM



2.2 PATIENT PATHWAY FOR IDENTIFICATION AND CONSENT



2.3 BASIC MODEL OF TRIAL STRUCTURES



3 BACKGROUND

In this study self-harm is defined as any form of non-fatal self-poisoning or self-injury (such as cutting, taking an overdose, hanging, self-strangulation, jumping from a height, and running into traffic), regardless of motivation or the degree of intention to die. A large number of adolescents in the community engage in self-harm; a recent systematic review demonstrated that 26% of adolescents had self-harmed in the previous year. Rates of self-harm are higher amongst females than males during adolescence [16].

Self-harm is associated with an elevated risk of overall mortality [9, 22, 23, 58] and suicide. In one follow-up study of 15 – 24 year olds who had presented to hospital following an episode of self-harm the overall number of deaths from all causes was 3% of cases, four times higher than expected. This was mainly due to an excess number of suicides (2%), which were ten times more frequent than expected. The main risk factors for suicide were male gender, previous self-harm, prior psychiatric history and high suicide intent [33]. Due to the young ages at which these deaths occur, the life years lost to the community due to suicide are significant.

In young people only one in eight episodes of self-harm lead to a hospital presentation [36]. Even so around 20,000 – 30,000 adolescents present to hospital each year having harmed themselves [35]. Based on hospital attendances in Leeds the rate of self-harm among 12 – 17 year olds was 335.24 per 100,000 per year. The rates of self-harm are rising rapidly [31], and the epidemiology of self-harm appears to be shifting with dangerous methods such as hanging rising in females [28] and higher rates among South Asian young women [59]. People who harm themselves are high users of public services [11] and increasing rates of self-harm will lead to an even greater demand for services over time.

In studies based on presentations to general hospitals in the UK, the majority of adolescents have harmed themselves by taking an overdose, self-poisoning with analgesics being particularly common [32] and dangerous due to the risk of death due to liver failure. A common and preventable reason for requiring a liver transplant is overdose [38]. At the community level the most common methods of self-harm are cutting and overdose [36]. Young people have a poor understanding of the potential lethality of methods of self-harm, so interventions to prevent further episodes of self-harm is one approach to reducing both the morbidity and mortality associated with these acts.

The estimates of risk of repetition are between 5 – 15% per year [8], although this may be much higher where repetition that does not come to clinical attention is considered [35] and when one focuses on young people who have a prior history of self-harm. Based on our multi-centre study in the UK [31] we estimate that among 12 – 17 year olds with a known history of self-harm repetition is 25% at one year after presentation at hospital for a new act. The risk of repetition is highest in the first year, but may remain high for many years after an episode [22, 55]. There are mixed findings on whether repetition rates are higher in one gender or the other [22, 23] although high levels of repetition are associated with death by suicide among females [30]. The later finding indicates that targeting interventions to this particular group may be of benefit.

Family factors are particularly important risk factors associated with fatal and non-fatal self-harm among children and adolescents [8]. Difficulties in parent-child relationships, including those related to early attachment problems, perceived low levels of parental caring and communication are related to increased risk of suicide and self-harm among children and adolescents [20]. A family history of self-harm is associated with increased risk for suicide deaths [2, 6, 26] and non-fatal self-harm by adolescents [36, 41]. Parental mental illness and

substance abuse are significant risk factors [8]. A strong association exists between self-harm and both childhood sexual abuse and physical abuse [17]. Young people who self-harm experience higher rates of exposure to recent stressful life events such as rejection, conflict or loss following the break-up of a relationship, conflicts, and disciplinary or legal crises [32]. The nature of the stressors seems to vary according to age. For example, children and younger adolescents describe familial stress, whereas older adolescents typically describe peer-related stressors [27, 32]. Interventions to enhance family functioning, communication and coping are therefore indicated.

Depression is the most prevalent mental health disorder associated with suicide [7, 41, 56] and non-fatal self-harm [15]. Hopelessness is an important mediating variable between depression and self-harm [60]. Depression is also a key factor associated with repetition of self-harm in adolescents [34] and is thus measured in the current study.

Family factors such as parental psychopathology, disturbed attachment, parent-child relationships and living situations form part of the risk matrix for adolescent self-harm and have an impact on treatment outcomes [39, 45]. Family therapy is one mechanism of intervening with self-harm behaviour among adolescents given that family issues are implicated in the aetiology [57]. Family therapy focuses on the relationships, roles and communication patterns between family members. It is surprising therefore that there have been relatively few studies of psychotherapeutic interventions with this population [37] and that there is only a very small literature on the use of family therapy with young people who self-harm. Two well-conducted studies are particularly relevant to this trial.

In a treatment study [4], 107 depressed adolescents aged 13 – 18 years were randomly allocated to cognitive behaviour therapy, systemic behavioural family therapy or non-directive supportive therapy. Participants received 12 -16 sessions of therapy. Those who were currently or previously suicidal were more depressed at the start of therapy and were significantly less likely to complete therapy. In addition, supportive therapy did not appear to ameliorate the depression of these adolescents, although cognitive behaviour therapy and family therapy were equally effective. The three treatments did not produce significant differences in reducing suicidality although the focus of the study was the treatment of depression so it is difficult to draw conclusions about the effectiveness of this treatment approach in reducing further self-harm.

The most informative study to date has been conducted by Harrington, Kerfoot and colleagues in Manchester [44]. In a randomised controlled trial 162 adolescents aged 10 – 16 years who had poisoned themselves, were allocated routine care or routine care plus a brief (5 sessions), structured, home-based intervention with the suicidal adolescent and their family. Non-depressed adolescents in the home-based group had less suicidal ideation than controls, but the home-based intervention was no more effective for depressed adolescents [29]. Parents of adolescents who received the home-based intervention were more satisfied with treatment. This study was powered to detect between group differences in suicidal ideation, not repeat self-harm and only included adolescents who had taken an overdose which reduces the generalisability to those who use other methods of self-harm.

In conclusion, there are community-based and hospital-based studies which estimate that approximately one in four adolescents harm themselves each year. Only one in eight episodes leads to a hospital presentation but this accounts for 20,000 – 30,000 presentations annually and the number of presentations is rising year on year. In line with NICE guidelines these adolescents should receive psychosocial assessments from child and adolescent mental health

practitioners [49] and many go on to receive input from Child & Adolescent Mental Health Services. Family factors are particularly important risk factors associated with non-fatal repetition of self-harm and death by suicide in children and adolescents. Family therapy is therefore one obvious mechanism of intervening. However, to date there has been no study which has been designed to evaluate the effect of family therapy on repetition of self-harm by adolescents. Young people who self-harm are heavy users of public services. Repeated acts of self-harm are associated with elevated rates of all-cause mortality and death by suicide placing a huge burden of life years lost on the community, so establishing an effective intervention is an important clinical and public health issue.

4 AIMS AND OBJECTIVES

The aim of the SHIFT trial is to determine whether there are differences between Family Therapy (FT) and Treatment as Usual (TAU) for adolescents aged 11-17 years who have self-harmed with respect to 1) repetition rates of self-harm, 2) cost effectiveness, 3) characteristics of further self-harm, 4) suicidal ideation and 5) quality of life.

An additional aim is to determine the moderators and mediators of engagement with and response to treatment.

Primary Objective
The primary objective is to assess the effectiveness of FT compared to TAU as measured by rates of repetition of self-harm leading to hospital attendance 18 months after randomisation.

Secondary Objectives
Secondary objectives are:

- to assess the effectiveness of FT compared to TAU as measured by repetition rates of self-harm leading to hospital attendance at 12 months after randomisation
- to document the cost per self-harm event avoided due to FT, measured using a structured questionnaire
- to assess the characteristics of further episodes of self-harm (all episodes, not just those resulting in hospital attendance) as measured by the number of subsequent self harm events, time to next event, severity of event (fatal, near fatal or not) and dangerousness of method used, as measured by the Suicide Attempt Self-Injury Interview [47]
- to assess suicidal ideation in each arm as measured by the Beck Scale for Suicide Ideation [5]
- to document differences in quality of life as measured by the Paediatric Quality of Life Enjoyment and Satisfaction measure, PQ-LES [14].
- to identify mediator and moderator variables which influence engagement with and benefit from treatment

5 DESIGN

SHIFT has been designed as a pragmatic, multi-centre, individually-randomised, controlled trial of FT versus TAU for adolescents aged 11-17 years who have engaged in more than one episode of self-harm. 832 participants will be recruited to receive either FT which will be delivered by qualified family therapists using a modified version of the Leeds Family Therapy & Research Centre (LFTRC) Systemic Family Therapy Manual, or TAU which will be delivered by local CAMHS teams. Participants and therapists will, of necessity, be aware of treatment

allocation but collection of outcomes will be blind. Outcome measures will be obtained at 12 and 18 months following randomisation, with additional assessment for health economics outcomes at 3 and 6 months. Engagement with treatment will be assessed at 3 months.

An individually randomised design has been chosen over a cluster randomised design as the risk of contamination between the two treatment arms is thought to be minimal. Different teams of therapists will deliver the two interventions in each Child and Adolescent Mental Health Service (CAMHS) and there will be little opportunity for participants to meet and discuss treatment. Any family-orientated clinical interventions in the TAU group are likely to be very different to the trial FT intervention as this requires adherence to the LFTRC manual and fully-trained family therapists eligible for UKCP registration (see section 8.2 for further details). TAU will involve a wider range of treatment techniques and modalities (such as supportive counselling or cognitive behaviour therapy) that will not be delivered to the FT group as part of the clinical intervention, unless indicated during or after family therapy.

6 ELIGIBLITY

6.1 INCLUSION CRITERIA

Children / adolescents meeting the following criteria are eligible for this trial:

1) Aged 11-17 years (from date of 11th birthday to the day prior to 18th birthday)
2) Self-harmed prior to assessment by the CAMHS team
3) Engaged in at least one previous episode* of self-harm prior to current presentation by self-injury or self-poisoning (or both)
4) Assessed in hospital following current episode, or referred directly to CAMHS from primary care with recent self-harm as a key feature of presentation
5) Where the presenting episode is due to alcohol or recreational drugs, the young person has explicitly stated that he / she was intending self-harm by use of alcohol / recreational drugs
6) Where it is intended to offer CAMHS follow-up for self-harm
7) Lives with primary care-giver
8) Both child / adolescent and primary care-giver have given written informed consent, where appropriate**

* this can be via self-report

** there may be some children (under 16) where there are concerns regarding Gillick competence, in which case parental consent alone will be accepted, provided the child does not actively object [66]. Where children are competent, consent will always be obtained. This approach mirrors normal practice. Consent would always be obtained for those aged 16 and 17.

6.2 EXCLUSION CRITERIA

Children / adolescents meeting any of the following criteria are <u>not</u> eligible for trial entry:

1) Currently at serious risk of suicide
2) A current ongoing child protection investigation within the family, which would make treatment (TAU or FT) difficult to deliver
3) Would not ordinarily be treated in generic CAMHS but rather by a specific service (e.g. psychiatric inpatient care for severe major depressive disorder, schizophrenia and other psychotic disorders, bipolar disorders, eating disorders (anorexia and bulimia nervosa),

significant substance misuse where this is the primary diagnosis)
4) Pregnant at time of trial entry (would make adherence to protocols and prescribing difficult)
5) Is actively being treated in CAMHS
6) In a children's home or short term foster placement*
7) Moderate to severe learning disability or lacks capacity to comply with trial requirements
8) Involved in another research project - currently or within the last six months
9) Sibling has been randomised to the SHIFT trial, or is actively receiving family therapy within CAMHS
10) The child / adolescent and one main care-giver have insufficient proficiency in English to contribute to the data collection required for the research.

* Young people who have been in the same foster family for at least 6 months and where there is no plan for them to move for at least another 6 months can be included if foster families are willing to engage with family therapy. It will also be necessary to ensure that appropriate consent can be obtained from those with parental responsibility – either birth parents, or social services if the young person is on a care order.

Participants may not be randomised for trial participation more than once.

7 RECRUITMENT AND RANDOMISATION

7.1 RECRUITMENT DETAILS

832 patients in total (416 in each arm) will be recruited over at least a 3 year period. It is predicted that recruitment will be slower during the first year as a consequence of the variable timescales for Trust approvals to be granted.

7.2 RECRUITMENT PROCESS

Participating sites (i.e. CAMHS teams) will be required to have obtained all relevant local ethical and management approvals and have undertaken a site initiation meeting with the CTRU or appropriate Lead Investigator prior to the start of recruitment into the trial.

Participants will be recruited following a referral to CAMHS from either secondary or primary care. In line with NICE guidance, young people who self-harm in collaborating CAMHS teams will be assessed in the acute hospital and discharged to local CAMHS for follow-up. If the young person self-harms but does not present to hospital it is possible that their school or GP will become aware of this and refer direct to local CAMHS. Referrals following a recent self-harm episode will also be included allowing direct recruitment from primary care. Recruitment for this study will be initiated at the first follow-up contact with CAMHS. Adolescents and families deemed eligible for participation will be informed in outline of the proposed research by CAMHS clinicians, who will provide a copy of the participant information sheets and seek permission (written, wherever possible) for contact from a researcher. Verbal permission must be documented in the young person's case notes. If agreement is given for Researcher contact, he/she will meet with the family and young person within three working days to explain the research in detail and seek formal consent (from both the primary care-giver and young person, where appropriate) for participation. Thereafter, consenting participants will be randomised to TAU or FT.

Leeds data suggest that 30% of adolescents receive a follow-up appointment within 1 week of

their hospital presentation for self-harm, 38% within 2 weeks, and 25% within one month. We thus anticipate that adolescents will be approached for study participation with 1 to 4 weeks of presentation with the index event.

The arrangements proposed for FT will allow appointments within a similar timescale to TAU and participants will thus not be disadvantaged nor have their waiting time for follow-up appointments extended.

7.3 INFORMED CONSENT

An outline verbal explanation of the trial and the Participant Information Sheets will be provided at the first follow-up appointment by the relevant CAMHS team member for the young person and primary care-giver to consider. These will include detailed information about the rationale, design and personal implications of the trial. Consent (written wherever possible) will also be obtained for contact by the Researcher who will arrange to meet with the family and young person within three working days to discuss the trial in more detail.

Following information provision by the CAMHS team, the young person and primary care-giver will have as long as they need to consider participation (normally a minimum of 24 hours) and will be given the opportunity to discuss the trial with their family and healthcare professionals before they are asked whether they would be willing to take part in the trial. The right of the young person and primary care-giver to refuse consent without giving reasons will be respected.

Assenting families will then be invited to provide written informed consent for trial participation. Informed consent and formal assessment of eligibility will be undertaken by the Researcher or other appropriate member of the team.

There may be some children under the age of 16 for whom there are concerns regarding Gillick competence. In such cases parental consent alone will be accepted, provided the child does not actively object [66]. Where children are competent, consent will always be obtained from both the child and primary care-giver. This approach mirrors normal practice when obtaining consent for treatment within CAMHS. Written informed consent will always be obtained for those aged 16 and 17. It should be noted that the primary care-giver may not necessarily be someone with parental responsibility and that, as long as the young person is 'Gillick competent', parental consent is not mandatory.

Should a young person under 16 be deemed to have lost capacity at any stage throughout the trial, parental / primary care-giver consent will remain in place and he / she will have the right to judge whether continued participation is appropriate and in line with the wishes of the young person. Where a young person aged 16 or over loses capacity, the parent / primary care-giver will act as Consultee in accordance with the requirements of the Mental Capacity Act 2005. Follow-up of the primary endpoint would continue, unless consent for further follow-up was withdrawn.

The participants will remain free to withdraw from the study at any time without giving reasons and without prejudicing any further treatment. The original consent forms will be sent to CTRU and will form part of the central study archive. Copies of the young person's and primary care-giver's consent forms will be given to the relevant participant to keep. A third set of copies will be sent to the treating clinician for filing in the participant's notes.

Written informed consent for trial entry must be obtained prior to participant randomisation and trial-specific baseline assessments.

The responsibility for the overall care of the participant remains with the attending CAMHS teams.

7.4 RANDOMISATION

Participants will be randomised using the 24-hour automated randomisation system based at the CTRU, University of Leeds. Authorisation and PIN codes, which will be provided by the CTRU when all relevant study approvals are in place, will be required to access the randomisation system.

Participants who fulfil the eligibility criteria, and have given written informed consent (as appropriate), will be randomised on a 1:1 basis to receive either FT or TAU and will be allocated a trial number. A computer generated minimisation programme that incorporates a random element will be used to ensure treatment groups are well-balanced for the following characteristics of the young person, details of which will be required at randomisation:

- Centre (i.e. local CAMHS team which will be responsible for patient follow-up)
- Gender (M/F)
- Age (11-14 / 15-17)
- Living arrangements (with parents or guardians / foster care)
- Number of previous self-harm episodes (including index event) (2 / ≥3)
- Type of most recent episode (self poisoning, self injury, combined).

The following information will also be required at randomisation:

- Young person's details including initials, date of birth, and NHS number (if available)
- Primary care-giver's details including initials and date of birth
- Name of CAMHS clinician who undertook the first follow-up appointment
- Name of person who undertook baseline assessment and consent
- Name of person undertaking randomisation
- Confirmation of eligibility
- Confirmation of written informed consent for both young person (if appropriate) and care-giver
- Date of written informed consent for both young person (if appropriate) and care-giver.

Participants from CAMH Services in Greater Manchester (and other CAMHS as appropriate) randomised to receive Family Therapy will have an additional randomisation to 'Lead Family Therapist'. This is appropriate for sites where there is not an obvious 'lead' family therapist by virtue of location – e.g. there is a centralised Family Therapy team in Manchester covering at least 12 CAMHS, so randomisation of the lead is appropriate to avoid biased selection of cases.

Where there is a 'lead' family therapist clearly attached to one specific service, he / she will take on this role for all families randomised to family therapy in that service wherever possible.

DIRECT LINE FOR 24-HOUR RANDOMISATION: +44 (0)113 343 6986

7.5 SCREENING

The CAMHS team and Researcher will complete Screening and Eligibility Forms for all young people screened for eligibility who are not randomised either because they are ineligible or because they decline participation. Anonymised information will be collected on a regular basis including:

- Date screened
- Age
- Gender
- Ethnicity
- Type and severity of self-harm episode
- Number of previous episodes of self-harm (if available)
- Source of referral (hospital, GP surgery, school, other)
- The reason for non-entry (not eligible, eligible but declined, other)

8 INTERVENTION DETAILS

All participants within this study will be treated within Child & Adolescent Mental Health Services (CAMHS) local to the participants and their family. Family therapists will be formally linked with specific CAMHS teams to ensure lines of clinical responsibility are clear, and all clinicians in both arms of the trial will have access to local child and adolescent psychiatrists if medication or hospitalisation needs to be considered.

8.1 TREATMENT AS USUAL (CONTROL GROUP)

TAU is the care offered by local CAMHS teams to adolescents aged 11 – 17 who have harmed themselves. This treatment is likely to be diverse and may involve individual and/or family-orientated work, delivered by a range of practitioners with various theoretical orientations. The average duration of treatment in CAMHS is approximately 6 sessions. This will be a pragmatic trial involving a number of collaborating CAMHS teams and so it will not be possible to specify what treatment as usual should be, although it is expected that CAMHS practitioners will be working in line with best practice as per several pertinent NICE guidelines (for example, guidance on self- harm and depression in childhood). In addition, as per best practice guidelines, practitioners delivering TAU will also be in receipt of supervision at a similar frequency to those delivering FT and this will be monitored.

8.2 FAMILY THERAPY (INTERVENTION GROUP)

FT will be delivered by qualified family therapists using a modified version of the Leeds Family Therapy & Research Centre Systemic Family Therapy Manual (LFTRC Manual), the development and validation of which was funded by the MRC to support trials of FT [53]. This manual, which is flexible enough to deal with the diverse situations likely to be encountered in the trial, will be reviewed and updated by the Trial Management Group to ensure it is appropriate for work with families following self-harm.

Adolescents and their families will attend FT sessions of approximately 1¼ hours duration each, delivered over 6 months at approximately monthly intervals but with more frequent initial appointments. This will equate to approximately 8 sessions. It is expected that, as with TAU, some participants will receive fewer sessions because of drop-out or mutually agreed termination of treatment. Equally some may receive more sessions where this is deemed clinically appropriate.

FT will be delivered by qualified, trial-specific family therapists (registered with the United Kingdom Council for Psychotherapy as Family Therapists). Family therapists will work in teams of 3-4 and provide trial FT as a team for a cluster of services. Each local CAMHS will identify a named Case Manager for the Family Therapists to link with to provide assurance about clinical governance. Where a Family Therapist is a full-time employee within the local CAMHS, the Family Therapist and Case Manager may be one and the same person.

The family therapist and family therapy team members will not be allowed to see participants in the TAU arm of the trial for the duration of the trial.

Family therapists will receive training (including the use of video and role play) in the use of the manual and adherence to it, delivered by those members of the Trial Management Group who are experienced FT trainers. Supervision of FTs to ensure quality of care and adherence to the manual will be conducted face-to-face once per month by a senior family therapist (a member of the Trial Management Group). A senior family therapist will be allocated to undertake the supervision for each research hub (i.e. Yorkshire, Greater Manchester and London). Training and supervision protocols will be developed to ensure consistency of approach throughout the duration of the trial.

These arrangements will ensure a fair test of family therapy by using qualified therapists, using a manual, regular supervision, and a team approach that is required by systemic family therapy theory and accepted best practice in CAMHS.

In addition, it is intended that there will be central review (by appropriately qualified members of the Trial Management Group) of a selection of family therapy tapes to ensure, and allow reporting of, overall adherence to the manual.

Family therapy sessions will only be recorded where consent for this has been obtained from all family members present. Consent will be obtained once from each family member for the duration of therapy, unless local governance requirements specify the need for more frequent consent. Recorded sessions will be saved in an encrypted format onto appropriate movable media prior to transfer between the NHS Trust and the University of Leeds. Detailed guidance will be provided to Family Therapists / CAMHS by the University of Leeds regarding appropriate processes for transfer from NHS to University of Leeds. Local Trust policies for transfer between NHS locations within the Trust should be followed.

8.3 WITHDRAWAL

In line with usual clinical care, cessation or alteration of regimens at any time will be at the discretion of attending CAMHS teams, clinicians or the participants themselves. Withdrawal from, or non-attendance for, treatment will be documented in the CRF. Where participants wish to withdraw from trial follow-up the type of withdrawal will be clarified (one or more of: withdrawal from clinical records follow-up, Researcher interviews or CTRU postal follow-up) and subsequent data collected accordingly.

9 DATA COLLECTION / ASSESSMENTS

Participating CAMHS teams will be expected to maintain a file of essential trial documentation (Investigator Site File), which will be provided by CTRU, and to keep copies of all completed CRFs for the trial, except participant questionnaires which will be sent to CTRU and stored centrally.

Participant assessments will be undertaken at the following time points:

- Baseline (prior to randomisation)
- 3-months post-randomisation
- 6-months post-randomisation
- 12-months post-randomisation
- 18-months post-randomisation

Required data, assessment tools, collection time points and processes are described in detail in sections 9.1 to 9.4. This is summarised in table 1 below.

Table 1: Summary of Assessments

Assessment (including who is involved)	**Timeline (months post-randomisation)**				
	Baseline	3	6	12	18
Eligibility and consent					
- Eligibility (assessed by Clinician)	X				
- Consent (YP, P, R*)	X				
Background and demographics (YP, P, R - interview and case notes)					
- Personal details	X				
- Outline 'index' event details	X				
- Current co-morbid physical / mental health	X				
- Current psychotropic medications	X				
- History of abuse	X				
Follow-up data (collected from case notes)					
- Therapy details (provided by therapist)			X	X	
- Therapist supervision details (provided by therapist / supervisor)			X	X	
- Details of further self-harm episodes since consent (R)				X	X
- Psychotropic medication details (R)				X	X
- Referrals to other MH services (R)				X	X
- Re-referral to CAMHS (R)				X	X
- Admissions to hospital relating to mental health (R)				X	X
- All-cause mortality (CTRU to collect via MRIS flagging)					X
- Serious adverse event reporting	Ongoing collection				
Questionnaires (completed at Researcher visit unless otherwise stated)					
- Family Questionnaire (P self-report, CTRU postal admin at 3 & 6 months)	X	X	X		
- System for Observing Family Therapy Alliances (completed by the family therapist and participants at Family Therapy session 3)		X			
- Suicide Attempt Self-Injury Interview (Interview with YP)	X			X	X
- Beck Scale for Suicide Ideation (YP self report)	X			X	X
- Hopelessness Scale for Children (YP self-report)	X			X	X
- McMaster Family Assessment Device (YP & P self report)	X			X	X
- General Health Questionnaire 12 (P self-report)	X			X	X
- Strengths and Difficulties Questionnaire (YP & P self-report)	X			X	X
- Children's Depression Rating Scale (Interview with YP)	X			X	X
- Paediatric Quality of Life Enjoyment and Satisfaction (YP self-report)	X			X	X
- Inventory of Callous Unemotional Traits (YP self-report)	X				
- EQ-5D (YP self report, CTRU postal admin at 6 months)	X		X	X	X
- Health Utilities Index 3 (P self-report, CTRU postal admin at 6 months)	X		X	X	X
- Health Economics questionnaire (YP & P self-report, CTRU postal admin at 3 & 6 months)	X	X	X	X	X

* YP = Young Person, P = Parent / care-giver, R = Researcher

9.1 RANDOMISATION AND BASELINE DATA

Young people and primary care-givers who satisfy the eligibility criteria and provide written informed consent (as appropriate) will enter the trial.

The CAMHS team and Researcher will provide data at randomisation / baseline as detailed in section 7.4 and will also record the following:

- NHS number
- GP address and telephone number
- Participants' contact details, as appropriate: address, telephone number, mobile numbers, email addresses
- Family / friend telephone / mobile numbers (to aid follow up if the family are non-contactable)
- Education and employment of young person and of primary care-giver
- Date of index event
- Hospital name (for admitting hospital)
- Date of hospital admission, or date of assessment and of referral by GP / school if not admitted to hospital
- Assessing CAMHS team, if different from randomising team
- Date of first CAMHS follow-up appointment
- Current co-morbid physical / mental health, including antisocial behaviour and history of abuse
- Current psychotropic medications.

The following questionnaires will be completed at baseline, prior to randomisation, by either the child, parent / care-giver or both, via face-to-face Researcher administration:

- Family Questionnaire (FQ) [62] (expressed emotion)
- Suicide Attempt Self-Injury Interview (SASII) [47] (suicidal ideation)
- Beck Scale for Suicide Ideation [5] (suicidal intent)
- Hopelessness Scale for Children [43] (hopelessness)
- McMaster Family Assessment Device (FAD) [13] (family functioning)
- General Health Questionnaire 12 [24] (GHQ 12) (parental mental health)
- Strengths and Difficulties Questionnaire (SDQ) [25] (emotional and behavioural problems)
- Children's Depression Rating Scale (CDRS-R) [54] (depression)
- Paediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q) [14] (quality of life)
- Inventory of Callous Unemotional Traits (ICU) (antisocial behaviour)
- EQ-5D and HUI3 [18, 67] (young person's health-related quality of life and parental health-related quality of life, respectively)
- Health Economics questionnaire (trial-specific - cost-effectiveness of family therapy).

CAMHS clinicians directly involved in provision of therapy to trial participants will be asked to complete a baseline form detailing their areas of expertise and training to enable accurate description of therapeutic expertise in the treatment as usual arm of the trial. Return of this CRF will be taken as each Therapist's explicit consent to provision, use and storage of this data.

9.2 FOLLOW-UP DATA

9.2.1 PATIENT-COMPLETED DATA

Questionnaires will be completed at 3 and 6 months post-randomisation via postal administration from CTRU, unless otherwise stated.

Questionnaires will be completed at 12 and 18 months post-randomisation at the Researcher's visit to the participants' home. If the Researcher (after repeated attempts) cannot get hold of the family at one or both time points, questionnaires will be posted, along with a covering letter requesting that the family contact the researcher to arrange a visit.

Where participants withdraw from further researcher visits, but have not withdrawn from receipt of postal questionnaires, the 12 and / or 18 month questionnaires will be posted to participants by the CTRU team.

<u>At 3 months:</u>

- Family Questionnaire
- Health Economics questionnaire
- System for Observing Family Therapy Alliances (SOFTA) [65]. This will measure expressed emotion and therapeutic change in the Family Therapy arm of the trial, and will be provided for completion in clinic by both the lead family therapist and participants at the third therapy session. If the consenting primary care-giver does not attend the therapy sessions, this may be completed by another member of the family. If participants do not attend the third session it may be administered at a later session, or postally by CTRU.

<u>At 6 months:</u>

- Family Questionnaire
- EQ-5D and HUI3
- Health Economics questionnaire

<u>At 12 months:</u>

- Suicide Attempt Self-Injury Interview
- Beck Scale for Suicide Ideation
- Hopelessness Scale for Children
- McMaster Family Assessment Device
- General Health Questionnaire 12
- Strengths and Difficulties Questionnaire
- Children's Depression Rating Scale
- Paediatric Quality of Life Enjoyment and Satisfaction
- EQ-5D and HUI3
- Health Economics questionnaire

<u>At 18 months:</u>

- Suicide Attempt Self-Injury Interview
- Beck Scale for Suicide Ideation
- Hopelessness Scale for Children
- McMaster Family Assessment Device
- General Health Questionnaire 12
- Strengths and Difficulties Questionnaire
- Children's Depression Rating Scale
- Paediatric Quality of Life Enjoyment and Satisfaction
- EQ-5D and HUI3
- Health Economics questionnaire

9.2.2 CLINICAL DATA

Clinical follow-up data will be collected on an ongoing basis up to 18 months post-randomisation.

Therapy details will be collected directly from the Therapist / CAMHS team (or from the Researcher or authorised individuals from the research team with appropriate access) by CTRU or the trial Family Therapy Supervisors up to the point of completion of treatment. This will include:

- Therapy details (type, sessions offered and attended, dates, therapists involved, family members involved)
- Therapist supervision details (dates, supervisors)
- Liaison with other services
- Contact with families between sessions

Other clinical data, not relating directly to therapy, will be collected by the Researcher or requested from the Therapist (as appropriate) at 12 and 18 months. This will include:

- Further self-harm episodes since consent
- Psychotropic medication details
- Referrals to other mental health services
- Re-referrals to CAMHS
- All cause mortality via NHS IC MRIS flagging (18 months only)

Primary outcome & safety data will be collected on a regular basis by the study Researchers from hospital records at the relevant Acute Trusts. Researchers will either access notes / systems directly, or will liaise with appropriate Trust personnel who will provide this data for them. This includes:

- Admissions to hospital relating to mental health and other reasons
- Treatment on an emergency out-patient basis

Primary outcome & safety data may also be collected via the NHS Information Centre's A&E and in-patient central databases. (Participants have all consented to registration with the NHS IC.)

9.3 FOLLOW-UP PROCESSES

Where participants are followed-up directly by the CTRU, the Researcher will contact the family

via text (or phone if a mobile number was not provided) to alert them to forthcoming postal questionnaires. Follow-up will be supported by postal, telephone, text or email reminders (as appropriate) if questionnaires are not returned. One reminder will be sent two weeks after the initial mailing. If questionnaires are not received within the subsequent two weeks, Researchers will call families and attempt to collect the data over the telephone.

Where the Researcher is unable to contact a family at 12 or 18 months, CTRU will contact the GP to establish if there has been a change of address.

CAMHS clinicians will also be encouraged to inform CTRU when a participant's status or location changes.

All participants who enter the study will be considered part of the intention to treat population and efforts will be made to follow them up whenever appropriate. Where participants cannot be located for follow-up, contact will be made with the GP in order to obtain any available information regarding episodes of self-harm (where participants have consented to such follow-up methods).

9.4 ASSESSMENT INSTRUMENTS

The assessment instruments will be incorporated into visit-specific participant assessment packs for both the young person and parent / primary care-giver. All measures are appropriate to the age-range of participants and have been widely used in a range of ethnic communities.

Family Questionnaire (FQ)
The level of expressed emotion (EE) in participants' families will be assessed using the Family Questionnaire (FQ) [62] which is designed to measure the EE status (criticism, emotional over-involvement) of relatives of participants. It is an easily administered brief self-report questionnaire relating to the different ways in which families try to cope with everyday problems.

System for Observing Family Therapy Alliances (SOFTA)
The System for Observing Family Therapy Alliances (SOFTA) [65] will be used to assess the quality of participants' alliance with the Therapist. It is designed to measure behaviours in four dimensions: engagement in the therapeutic process, emotional connection with the therapist, safety within the therapeutic system and shared sense of purpose within the family. It consists of various brief self-report questionnaires appropriate to either family or individual therapy, and therapist or client completion.

Suicide Attempt Self-Injury Interview (SASII)
Suicidal ideation will be measured using the Suicide Attempt Self-Injury Interview (SASII) [47] designed to assess the factors involved in non-fatal suicide attempts and intentional self-injury. It contains 6 screening items, 9 open-ended questions to provide information for interviewer coding, and 22 items and associated sub-items measuring timing and frequency of self-injurious acts, methods used and lethality of the method, suicidal as well as non-suicidal intent associated with the episode, communication of suicide intent before the episode, impulsivity and rescue likelihood, physical condition, and level of medical treatment.

Beck Scale for Suicide Ideation
The Beck Scale for Suicide Ideation [5] will be used to examine suicidal intent in participants. It is a 21 item self-report instrument used for detecting and measuring the current intensity of the

participants' specific attitudes, behaviours, and plans to commit suicide during the past week. Individual items assess characteristics such as wish to die, desire to make an active or passive suicide attempt, duration and frequency of ideation, sense of control over making an attempt, number of deterrents, and amount of actual preparation for a contemplated attempt. The last two items assess the number of previous suicide attempts and the seriousness of the intent to die associated with the last attempt.

Hopelessness Scale for Children
The Hopelessness Scale for Children [43] will be used to measure the degree to which participants have negative expectancies about themselves and the future. It includes 17 items each of which children identify as true or untrue of them.

McMaster Family Assessment Device (FAD)
Family functioning will be measured using the McMaster Family Assessment Device (FAD) [13] which was designed to evaluate families according to the McMaster Model of Family Functioning. The FAD is made up of seven scales measuring Problem Solving, Communication, Roles, Affective Responsiveness, Affective Involvement, Behaviour Control and General Functioning.

General Health Questionnaire (GHQ-12)
The 12 item General Health Questionnaire (GHQ-12) [24] was developed to measure current mental health and will be used to screen for non-psychotic psychiatric disorders in the parents of study participants.

Strengths and Difficulties Questionnaire (SDQ)
Levels of emotional and behavioural problems will be assessed using the Strengths and Difficulties Questionnaire (SDQ) [25] which was designed to be an effective and efficient screener for child and adolescent mental health problems.

Children's Depression Rating Scale (CDRS-R)
The Children's Depression Rating Scale (CDRS-R) [54] will be used to assess the severity of the depressive syndrome in participants. It is a brief rating scale based on a semi-structured interview with the adolescent rating 17 symptom areas including impaired schoolwork, difficulty having fun, appetite disturbance, excessive fatigue and low self-esteem.

Paediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q)
Patient quality of life will be evaluated using the self-administered 15 item Paediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q) [14] which was developed to aid in the assessment of an important aspect of life experience in children and adolescents. Items inquire about satisfaction with health, mood/feelings, school, helping out at home, getting along with friends and with family, play/free time, getting things done, sense of love for life, having enough money, place of residence, ability to pay attention, energy level, and overall course of life.

Inventory of Callous-Unemotional Traits (ICU)
The ICU is a 24-item questionnaire designed to provide a comprehensive assessment of callous and unemotional traits. It has three subscales: Callousness, Uncaring and Unemotional, and there are self-report, parent report and teacher report versions of the scale. Measures of ICU are helpful in predicting different outcomes and developmental pathways in children with conduct disorder.

EuroQol-5D
EQ-5D from the EuroQol Group is a standardised, non-disease-specific instrument for describing and valuing health [68]. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status. It is made up of two components; a description of the patient's health status and a self-rating of their current status using a VAS, both of which can be used to derive a utility value. The descriptive component consists of 5 dimensions, each having three levels; mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The EQ-5D has been shown to have good consistency, convergent validity, and reliability [69] for children of 12 years old and over.

Health Utilities Index 3
Health Utilities Index 3 (HUI3) [67] is widely used in population health surveys, clinical studies and cost-utility analyses. HUI3 includes 8 attributes (vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain).

Health Economics Questionnaire
Within the Health Economics questionnaire designed for use in SHIFT, information will be collected on primary and secondary health care utilisation, any out of pocket expenses and productivity costs to both participants and their carers, and any use of education and justice services.

9.5 DEFINITION OF END OF TRIAL

The end of the trial is defined as the date of receipt of the last set of participant 18 month follow-up data, following the final visit to the final family by a trial Researcher.

10 PARTICIPANT SAFETY

10.1 GENERAL DEFINITIONS

An adverse event (AE) is:
- any unintentional, unfavourable clinical sign or symptom
- any new illness or disease or the deterioration of existing disease or illness

A serious adverse event (SAE) is defined in general as an untoward event which:
- results in death
- is life threatening
- requires or prolongs existing hospitalisation
- is significantly or permanently disabling or incapacitating
- constitutes a congenital anomaly or a birth defect or
- is otherwise considered medically significant by the clinician.

A SAE occurring to a research participant which, in the opinion of the Chief Investigator, is related and unexpected will be reported to the main Research Ethics Committee (main REC).

The National Research Ethics Service (NRES) defines related and unexpected SAEs as follows:

- 'related' – that is, it resulted from administration of any research procedures; and

- ‘unexpected’ – that is, the type of event is not listed in the protocol as an expected occurrence.

10.2 SHIFT TRIAL OPERATIONAL DEFINITIONS AND PROCEDURES

10.2.1 EXPECTED ADVERSE EVENTS

The following non-serious (by definition) AEs are expected within the child / adolescent study population and will be reported by the research team on the appropriate CRFs:

- Treatment on an emergency outpatient basis
- Re-referral to CAMHS

The following SAEs are not common but are expected within the child / adolescent study population and will be reported by the research team on the appropriate CRFs:

- Death
- Hospital admissions and re-admissions

Deaths
Epidemiological data suggest that, with a sample of this size, it is possible that some young people (perhaps as many as 5) will die as a consequence of self-harm during the course of the study. Additionally there may be deaths due to other causes within the trial population.

All deaths occurring from the date of consent up to eighteen months post-randomisation must be recorded on the Death Form and faxed to the CTRU **within 24 hours** of the research staff becoming aware of the event. The original form should also be posted to the CTRU in real time and a copy retained at site.

Reports will be reviewed by the Chief Investigator within one working day of receipt by CTRU. The Data Monitoring and Ethics Committee (DMEC), HTA and Sponsor will be informed of the death within one month of reporting by site.

It is possible that families and / or coroners may wish to speak to someone representing the trial about trial participant deaths, as well as to local CAHMS staff who have provided treatment. The Chief Investigator would be available for such meetings if required.

CTRU FAX NUMBER FOR REPORTING DEATHS: 0113 343 1471

As deaths are expected within the study population they will not be subject to expedited reporting to the main REC, unless the DMEC advises that the frequency of self-harm related and / or all deaths observed within the trial population is significantly higher than that expected in the general population.

10.2.2 RELATED AND UNEXPECTED SAES

All related and unexpected SAEs occurring to the young person from the date of consent up to eighteen months post-randomisation must be recorded on the Related Unexpected Serious Adverse Event Form and faxed to the CTRU **within 24 hours** of the research staff becoming

aware of the event. The original form should also be posted to the CTRU in real time and a copy retained at site.

For each Related Unexpected SAE the following information will be collected:

- full details in medical terms with a diagnosis, if possible
- its duration (start and end dates; times, if applicable)
- action taken
- outcome

Any follow-up information should be faxed to CTRU as soon as it is available. Events will be followed up until the event has resolved or a final outcome has been reached.

CTRU FAX NUMBER FOR REPORTING RELATED/UNEXPECTED SERIOUS ADVERSE EVENTS: 0113 343 1471

All Related / Unexpected SAEs will be reviewed by the Chief Investigator and subject to expedited reporting to the main REC and Sponsor by the CTRU on behalf of the Chief Investigator within 15 days.

Responsibilities of the Chief Investigator, CTRU, TSC, DMEC and Sponsor will be detailed in a study specific Work Instruction.

10.2.3 REPORTING

Safety issues will be reported to the MREC in the annual progress report.

An annual summary of all events will also be reported to the DMEC, TSC and Sponsor.

Expedited reporting of events (as detailed in section 10.2.2) to MREC and the Sponsor will be subject to current NRES guidance, CTRU SOPs and Sponsor requirements.

11 HEALTH ECONOMICS

The economic evaluation will examine the question 'What is the incremental cost effectiveness of FT compared to TAU in the management of self-harm in adolescents'. Two sets of economic evaluation will be undertaken – 1) a set of within trial analyses and 2) a long term cost effectiveness model-based set of analyses. The evaluations will adhere to the methods guidance produced by the National Institute for Health and Clinical Excellence [50].

11.1 WITHIN TRIAL COST EFFECTIVENESS ANALYSIS

Measurement of outcomes: The primary, within-trial analysis will estimate the expected incremental cost per self harm event avoided due to FT up to the end of trial follow-up. The time horizon for this analysis will be 18 months and it will adopt the NHS and Personal Social Services (PSS) perspective. A secondary analysis will have Quality Adjusted Life years (QALYs) as the outcome measure. Utility weights will be obtained from the Health Utilities Indices Mark 2 and 3 data, collected as part of the trial follow-up [18, 67] to report health-related quality of life in both parents / primary care-givers and young persons. The economic evaluation will adopt a societal perspective and consider the out-of-pocket expenses, the productivity costs

to the patients and carers as well as use of education and justice services. This analysis will also use QALYs as the outcome measure.

A further secondary analysis will use depression as the outcome measure (namely the Children's Depression Rating Scale) and calculate the incremental cost per case of depression avoided.

Measurement of resource use: Wherever possible unit costs for resources will be obtained from national sources such as the British National Formulary and the PSSRU Costs of Health and Social Care. NHS and social service resource use will be identified through direct observation of the treatment provided within the study and through a structured questionnaire for collection of all other service use by young persons and parents / primary care-givers.

Discounting: Costs and benefits will be discounted at 3.5% p.a.

11.2 LIFETIME HORIZON COST EFFECTIVENESS MODEL

The second set of economic analyses will adopt a lifetime horizon and involve constructing a decision analytic cost effectiveness model. As far as possible parameters in the model will be specified using data collected within the trial. Other parameters, such as the long term 'natural history' will be parameterised using the published literature, and where necessary formally elicited expert opinion. The outcome measure for these analyses will be the QALY. The utility weights will be calculated using the EQ-5D and HUI3 data collected within the trial.

Analysis of uncertainty: Parameter uncertainty in the cost effectiveness analysis will be explored using probabilistic sensitivity analysis and Monte Carlo simulation.

12 ENDPOINTS

12.1 PRIMARY ENDPOINT

The primary endpoint is repetition of self-harm leading to hospital attendance within 18 months of randomisation.

12.2 SECONDARY ENDPOINTS

Secondary endpoints are:

- Repetition of self-harm leading to hospital attendance within 12 months of randomisation.
- The cost per self harm event avoided due to FT, measured using a structured questionnaire.
- Characteristics of further episodes of self-harm (number of subsequent self harm events, time to next event, severity of event (fatal, near fatal or not) and dangerousness of method used, as measured by the Suicide Attempt Self-Injury Interview [47]).
- Suicidal ideation as measured by the Beck Scale for Suicide Ideation [5].
- Quality of life as measured by the Paediatric Quality of Life Enjoyment and Satisfaction measure, PQ-LES [14].

12.3 PREDICTIVE AND PROCESS MEASURES

Mediator and moderator variables which influence engagement with and benefit from treatment will also be measured.

13 STATISTICAL CONSIDERATIONS

13.1 SAMPLE SIZE

The power calculation is based on the predicted reduction of the expected repetition rates of self harm for adolescents who have previously harmed themselves. The anticipated rate of repetition at 18 months in those participants receiving TAU is 29% [31] and we predict that for those participants in FT the repetition rate will be 35% lower i.e.18.8%. Using a 5% significance level log-rank test for equality of survival curves, we will require 374 participants per group; with 172 total events, to give 90% power to detect such a reduction in 18 month repetition rates between TAU (29%) and FT (18.8%), providing a constant hazard ratio of 1.64. Assuming at most 10% loss to follow-up by 18 months for the primary outcome (repetition of self-harm resulting in hospital attendance), the total sample size required is 416 per group i.e. 832 in total.

Inherent clustering within the data structure (participants nested within therapists) will have an impact on the study power and is related to the level of the intra-cluster correlation coefficient (ICC) and the cluster size. We anticipate that the level of clustering will be low for this particular trial – possibly around 0.01 but no higher than 0.05 (due to use of therapy manuals; therapist selection, training, supervision and monitoring). In addition the numbers of participants per therapist are expected to be small. In the treatment as usual (TAU) arm, we estimate there will be between 8 and 15 therapists available in the team at any one centre, so across all 15 Trusts there will be 120 - 225 therapists available to treat 416 participants. Thus each therapist will treat between 2 and 4 participants (i.e. a maximum control cluster size of 4). In the family therapy (FT) arm, we estimate there will be approximately 35 therapists available across all the sites to treat 416 participants; these therapists will operate in teams of 3 or 4 therapists. Within each FT team, each therapist will take the lead for a subset of participants at that site (the other therapists in the team will act as observers and make only a small face to face contribution for those participants). Thus each FT therapist will have direct contact with approximately 12 participants (a maximum intervention cluster size of 12).

Thus the design effect is likely to be no greater than 1.55; (assuming an ICC of 0.05) effectively reducing the sample size from 416 per group to 270 per group and the power from 90% to around 75%. If the ICC were as low as 0.01, then the design effect would be 1.11, reducing the sample size to 374 per group and the power to around 85%. We anticipate the ICC will be towards the lower end of the possible range and therefore the trial will still be adequately powered with the sample size planned.

13.2 ACCRUAL

At the outset, based on data from the Manchester self-harm trial [44] it was anticipated that no more than 29% of those referred would enter the study. To recruit 832 adolescents aged 11-17 who had self-harmed at least once before their recent presentation we require approximately 3000 to be referred to CAMHS. Collaboration was agreed with centres having projected annual presentations for self-harm of 990 adolescents aged 11-17 who have self harmed at least once before. Actual recruitment was therefore estimated to be 280 per year, taking 3 years to recruit the 832 required participants.

14 STATISTICAL ANALYSIS

14.1 GENERAL CONSIDERATIONS

Statistical analysis is the responsibility of the CTRU Statistician. The analysis plan outlined in this section will be reviewed and a final statistical analysis plan will be written before any analysis is undertaken. The analysis plan will be written in accordance with current CTRU standard operating procedures and will be finalised and agreed by the following people: the trial statistician and supervising statistician, the Chief Investigator, the CTRU principal investigator and the senior trial coordinator. Any changes to the final analysis plan and reasons for change will be documented.

All analyses will be conducted on the intention-to-treat population defined as all participants randomised regardless of non-compliance with the intervention. A per-protocol analysis will be considered if there are a considerable number of protocol violators. This decision will be made jointly by the trial statistician in co-operation with other members of the Trial Management Group on examination of the population and without reference to the endpoint data.

An overall two-sided 5% significance level will be used for all endpoint comparisons. For the primary endpoint, this will be adjusted to account for the planned interim analysis. The O'Brien and Fleming (18) alpha spending function will be used, which suggests an alpha level of 0.047 for the final analysis and 0.005 for the interim analysis.

14.2 FREQUENCY OF ANALYSES

Interim reports will be presented to the Data Monitoring and Ethics Committee (DMEC) in strict confidence, at approximately yearly intervals or as soon as sufficient data have been accrued to make them meaningful. A single formal interim analysis is planned on the primary endpoint, repetition of self-harm leading to hospital attendance within 18 months of randomisation, when at least half the required number of events has been reached (86 events). The DMEC, in light of the interim data and of any advice or evidence they wish to request, will if necessary report to the Trial Steering Committee with a recommendation of trial adaption or early closure if, compared with TAU, the effect of FT is significantly inferior ($p<0.005$).

Apart from the interim analysis to the DMEC, no other formal analyses are planned until after the trial is closed to accrual. Final analysis is planned when at least 172 events have occurred.

14.3 PRIMARY ENDPOINT ANALYSIS

Cox's Proportional Hazards Model accounting for the minimisation factors will be used to test for differences in 18 month repetition rates. Hazard Ratios and corresponding 95% CIs will be presented. If a participant is lost to follow-up, they will be treated as censored. Kaplan-Meier curves will be constructed for each group and compared using a 2-sided log-rank test. Note that although the significance level has been slightly reduced to account for the interim analysis, confidence intervals will still be presented at the 95% level as these are for summary purposes. Multilevel survival frailty models will also be used in a sensitivity analysis to assess the extent of clustering on participant outcomes due to therapists and the impact on the precision of the treatment effect estimate.

14.4 SECONDARY ENDPOINT ANALYSIS

The analysis of 12 month repetition rates will follow that of the 18 months data detailed in the Primary endpoint analysis. Further episodes of self-harm will be analysed using a multiple

events analysis based on Andersen-Gill [3] methodology, making use of the timing and cumulative number of first and subsequent events. For other measures, such as suicidal ideation (Suicide Attempt Self-Injury Interview) and quality of life (PQ-LES), mean scores and 95% CIs (adjusted for baseline) will be presented for each time point, and repeated measures models will be used to estimate differences between the treatment groups. In addition we plan to model the relationship between process variables (for example, number of sessions, medication use, referrals, mediators, moderators) and outcomes.

Safety will be monitored at regular intervals and will be reported separately for each treatment group.

14.5 SUB-GROUP ANALYSES

No sub-group analyses are planned.

15 DATA MONITORING

15.1 DATA MONITORING

Data will be monitored for quality and completeness by the CTRU, using established verification, validation and checking processes. Missing data, except individual data items collected via the postal questionnaires, will be chased until it is received, confirmed as not available, or the trial is at analysis. Reminders will be sent to participants if postal questionnaires are not returned on time.

The CTRU and the University of Leeds (Sponsor) reserve the right to intermittently conduct source data verification on a sample of participants. Source data verification will involve direct access to patient notes at the participating centres, and other relevant investigation reports.

A monitoring schedule will be defined and agreed by the DMEC, TSC and TMG. This will detail the timing and content of reports to these committees and will include:

- Primary endpoint
- Repetition of self-harm between index episode and first therapy session
- Compliance
- Safety data
- Rates of recruitment and refusals for all sites
- Losses to follow-up due to death, withdrawal and loss of contact

The DMEC will review the number and frequency of hospitalisations and deaths as a consequence of self-harm. Where the DMEC identify significantly increased frequency of such events in one or both arms within the trial population they may recommend trial suspension or closure. Such a decision must be reported to MREC, the TSC and the Sponsor by CTRU within 15 days of the DMEC's response, and appropriate action taken.

15.2 DATA MONITORING AND ETHICS COMMITTEE

An independent DMEC will be established to review the safety and ethics of the trial. Contents of the unblinded reports will be agreed between the DMEC and CTRU at the initial DMEC meeting during set-up. These annual reports will be prepared by the CTRU for the DMEC during recruitment and follow-up. The formal interim analysis on the primary endpoint will be reported to the DMEC after 86 events have occurred. SAEs will be summarised by treatment

group in a regular safety report sent to the DMEC. This will enable monitoring of safety rates between the control and intervention arms.

15.3 TRIAL STEERING COMMITTEE (TSC)

A TSC will be established to provide overall supervision of the trial, in particular, trial progress, adherence to protocol, patient safety, and consideration of new information. The committee will meet once during the set-up period and six monthly thereafter for the duration of the trial.

15.4 CLINICAL GOVERNANCE ISSUES

To ensure responsibility and accountability for the overall quality of care received by participants during the study period, clinical governance issues pertaining to all aspect of routine management will be brought to the attention of the DMEC and where applicable to individual NHS Trusts.

16 QUALITY ASSURANCE AND ETHICAL CONSIDERATIONS

16.1 QUALITY ASSURANCE

The trial will be conducted in accordance with current MRC Good Clinical Practice (GCP) guidelines, NHS Research Governance Framework and through adherence to CTRU standard operating procedures (SOPs).

16.2 ETHICAL CONSIDERATIONS

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 52nd World Medical Association General Assembly, Edinburgh, Scotland, October 2000. Written informed consent will be obtained from the primary care-giver and the young person (where Gillick competence is present in those under 16, and for all 16 and 17 year olds) prior to trial entry. The right of young persons and care-givers to refuse participation without giving reasons must be respected. The young person and primary care-giver must remain free to withdraw from the study at any time without giving reasons and without prejudicing the young person's further treatment. The trial will be submitted to and approved by a main Research Ethics Committee (MREC) and the appropriate Local Research Ethics Committee (LREC) for each participating CAMHS team prior to entering participants into the trial. The CTRU will provide the MREC with a copy of the final protocol, patient information sheets, consent forms and all other relevant study documentation.

17 CONFIDENTIALITY

All information collected during the course of the trial will be kept strictly confidential. Information will be held securely on paper and electronically at the Clinical Trials Research Unit (CTRU). The CTRU will comply with all aspects of the 1998 Data Protection Act and operationally this will include:

- consent from participants to record personal details including name, date of birth, address and telephone numbers, NHS number, hospital number(s), GP name, address and telephone number
- appropriate storage, restricted access and disposal arrangements for participants' personal and clinical details

- consent from participants for access to their medical records by responsible individuals from the research staff or from regulatory authorities, where it is relevant to trial participation
- consent from participants for the data collected for the trial to be used to evaluate safety and develop new research.
- participants' names, address and telephone numbers will be collected when a young person is randomised into the trial but all other data collection forms that are transferred to or from the CTRU will be coded with a trial number and will include two identifiers, usually the participant's initials and date of birth.
- where anonymisation of documentation is required, sites are responsible for ensuring only the instructed identifiers are present before sending to CTRU.

If a participant withdraws consent for further trial treatment and / or further collection of data, their data will remain on file and will be included in the final study analysis.

17.1 ARCHIVING

At the end of the trial, data will be securely archived at the CTRU and CAMHS units for a minimum of 5 years.

18 STATEMENT OF INDEMNITY

This trial is sponsored by the University of Leeds and the University of Leeds will be liable for negligent harm caused by the design of the trial. The NHS has a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and the NHS remains liable for clinical negligence and other negligent harm to patients under this duty of care.

19 STUDY ORGANISATIONAL STRUCTURE

19.1 RESPONSIBILITIES

Sponsor
As defined by the NHS Research Governance Framework, the Sponsor is the organisation that takes responsibility for confirming there are proper arrangements to initiate, manage, monitor and finance the study.

Chief Investigator
As defined by the NHS Research Governance Framework, the Chief Investigator is responsible for the design, management and reporting of the study.

Clinical Trials Research Unit (CTRU)
The CTRU will have responsibility for conduct of the trial in accordance with the Research Governance Framework, MRC GCP standards and the principles of CTRU SOPs.

Health Economists
The Health Economics collaborators will assist the CTRU in protocol and CRF development and will be responsible for the selection and / or design of the economic questionnaires, collation of unit costs, and the conduct, interpretation and writing up of the economic evaluation.

Child and Adolescent Mental Health Services (CAMHS)

CAMHS will be the key collaborators for this study. Participants will be recruited following a referral to CAMHS from either secondary or primary care. Trial Family Therapists will be directly linked to each CAMHS, and those participants allocated 'Treatment as Usual' will be treated and followed-up within standard CAMH services. CAMHS therapists and clinicians will be asked to provide access to baseline participant data and also provide details regarding treatment and supervision. Each CAMHS will have close links with the trial Researcher and with CTRU.

Researcher
Trial-specific Researchers will have responsibility (alongside the relevant CAMHS team members) for the identification, assessment and follow-up of participants identified for inclusion in the trial. Each research hub (Yorkshire, Greater Manchester and London) will have an associate Researcher.

Family Therapists
Trial-specific Family Therapists will have responsibility for the provision of family therapy in accordance with the LFTRC Manual (see section 8.2) under the supervision of the lead Family Therapists for the trial. Family Therapists will be grouped across 3-4 CAMHS teams so that they can provide trial FT as a team for a cluster of services.

19.2 OPERATIONAL STRUCTURE

Trial Management Group (TMG)
The TMG, comprising the Chief Investigator, CTRU team and co-investigators will be assigned responsibility for the clinical set-up, on-going management, promotion of the trial, and for the interpretation of results**.** Specifically the TMG will be responsible for (i) protocol completion, (ii) CRF development, (iii) obtaining approval from the main REC and supporting applications for Site Specific Assessments (SSA), (iv) completing cost estimates and project initiation, (vi) appointing and facilitating the TSC and DMEC, (vii) reporting of serious adverse events, (vii) monitoring of screening, recruitment, consent, treatment and follow-up procedures, safety, data quality and compliance (viii) interpretation of results and contribution to publications.

Clinical Trials Research Unit (CTRU)
The CTRU will provide set-up and monitoring of trial conduct to CTRU SOPs and MRC GCP standards including randomisation design and implementation, database development and provision, protocol development, CRF design, trial design, monitoring schedule and statistical analysis of clinical endpoints for the trial. In addition the CTRU will support main REC, SSA and R&D submissions and clinical set-up, ongoing management including training, monitoring reports and promotion of the trial. The CTRU will be responsible for the database administrative functions, data management including postal follow-up and telephone reminders, safety reporting, all statistical analyses of clinical endpoints and drafting of publications. The CTRU will have responsibility for the conduct of the study in accordance with the Research Governance Framework and CTRU SOPs.

Trial Steering Committee (TSC)
The Trial Steering Committee, with an independent Chair, will provide overall supervision of the trial, in particular trial progress, adherence to protocol, patient safety and consideration of new information. It will include an Independent Chair, not less than two other independent members. The Chief Investigator and other members of the TMG will attend the TSC meetings and present and report progress.

Data Monitoring and Ethics Committee (DMEC)
The DMEC will review the safety and ethics of the trial by reviewing interim data during the recruitment and follow-up periods.

20 PUBLICATION POLICY

Authorship and acknowledgement

The success of the trial depends upon the collaboration of all participants. For this reason, credit for the main results will be given to all those who have collaborated in the trial, through authorship and by contribution. Uniform requirements for authorship for manuscripts submitted to medical journals will guide authorship decisions. These state that authorship credit should be based only on substantial contribution to:

- conception and design, or acquisition of data, or analysis and interpretation of data
- drafting the article or revising it critically for important intellectual content
- final approval of the version to be published
- and that all these conditions must be met (www.icmje.org).

In light of this, the Chief Investigator, Co-Applicants and senior CTRU staff will be named as authors in any publication, and an appropriate first author agreed through discussion amongst the Trial Management Group (TMG) members. In addition, all collaborators will be listed as contributors for the main trial publication, giving details of their roles in planning, conducting and reporting the trial. The SHIFT team should be acknowledged in all publications, as should the NIHR HTA programme (as detailed below). Other key individuals will be included as authors or contributors as appropriate and at the discretion of the SHIFT TMG. Any disputes relating to authorship will be resolved by the TSC.

The Chairs and Independent members of the TSC and Data Monitoring and Ethics Committee (DMEC) will be acknowledged, but will not qualify for full authorship, in order to maintain their independence.

Relevant NIHR Clinical Research Networks' (e.g. Mental Health Research Network) support should be acknowledged appropriately in trial publications.

Data source

Data from the CTRU database in Leeds must be used for data analyses for all abstracts and publications relating to the questions posed within the trial protocol. Furthermore, the statistical team at the CTRU must perform all such analyses. If any additional analyses outside the remit of the protocol are to be performed, the statistical team at the CTRU should be involved if it involves data held on the CTRU databases.

Data release

To maintain the scientific integrity of the trial, data will not be released prior to the first publication of the results of the primary endpoint analysis, either for trial publication or oral presentation purposes, without the permission of the DMEC and the TSC.

The TSC will agree a publication plan and must be consulted prior to release or publication of any trial data.

Individual collaborators must not publish data concerning their participants which is directly relevant to the questions posed in the trial until the main results of the trial have been published. Local collaborators may not have access to trial data until after publication of the main trial results.

Processes for the drafting, review and submission of abstracts and manuscripts

The agreed first author of abstracts is responsible for circulating these to the other members of the Trial Management Group (TMG) for review at least 15 days prior to the deadline for submission.

The agreed first author of manuscripts is responsible for ensuring:

- timely circulation of all drafts to all co-authors during manuscript development and prior to submission
- timely (and appropriate) circulation of reviewers' comments to all co-authors
- incorporation of comments into subsequent drafts
- communication with the TSC (i.e. ensuring submission is in line with TSC publication plan, and ensuring TSC receive the final draft prior to submission)

The first author is responsible for submission of the publication and must keep the SHIFT TMG and all authors informed of the abstract's or manuscript's status. The TSC will be kept informed of rejections and publications as these occur. On publication, the first author should send copies of the abstract or manuscript to the SHIFT TSC, the SHIFT TMG, the SHIFT Sponsor and to all co-authors, and ensure communication with the NIHR HTA programme as outlined below.

NIHR Health Technology Assessment (HTA) programme requirements

In accordance with the NIHR HTA programme's requirements, all materials to be submitted for publication (written, audio/visual and electronic) should be sent to the NIHR Co-ordinating Centre for HTA (NCCHTA) at the time of submission or at least 28 days before the publication date, whichever is earlier. This applies to all publications regardless of whether or not the primary results have been published.

All publications must acknowledge NIHR HTA as the trial's funding source and include an appropriate disclaimer regarding expressed views and opinions (example text is provided on the HTA website).

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Appendix 1: Glossary of Terms

CAMHS	Child and Adolescent Mental Health Services
CI	Chief Investigator
CTRU	Clinical Trials Research Unit
DMEC	Data Monitoring and Ethics Committee
FT	Family Therapy
LFTRC	Leeds Family Therapy Research Centre
TAU	Treatment as Usual
TMG	Trial Management Group
TSC	Trial Steering Committee

Appendix 2: Trial Management Group

The TMG includes those listed as key contacts and the following Co-applicants:

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Michael Rutter Centre for Children & Young People
The Maudsley Hospital
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Appendix 3: Committee Terms of Reference

Trial Steering Committee

1. To provide overall supervision of the trial.

2. To monitor and supervise the progress of the trial towards its interim and overall objectives, adherence to protocol and patient accrual within the set time-frame.

3. To review at regular intervals relevant information from other sources (e.g. other related trials), and recommend appropriate action (e.g. changes to trial protocol, stopping or extending the trial).

4. To consider the recommendations of the Data Monitoring and Ethics Committee.

5. To recommend appropriate action in the light of points 1, 2, 3 and 4 to ensure that the rights, safety and well-being of the trial participants are the most important considerations, and prevail over the interests of science and society.

6. In light of 1, 2, 3 and 4 to inform the HTA programme and relevant Research Boards on the progress of the trial.

7. To advise the HTA programme on publicity and presentation of all aspects of the trial.

Data Monitoring and Ethics Committee

1. To determine if interim analyses of trial data should be undertaken.

2. To consider the data from interim data monitoring/analyses plus any additional safety issues for the trial and relevant information from other sources.

3. In the light of 2 (above), and ensuring that ethical considerations are of prime importance, to report (following each DMEC meeting) to the Trial Steering Committee and to recommend on the continuation of the trial.

4. To consider any requests for release of interim trial data and to make recommendations to the TSC on the advisability of this.

5. In the event of further funding being required, to provide to the TSC and HTA programme appropriate information and advice on the data gathered to date that will not jeopardise the integrity of the study.