PROTOCOL

Project Title:	Trial of Improvisational Music Therapy's Effectiveness for Children with Autism (TIME-A): UK Arm of the Time-A study.
Funder's reference number:	National Institute of for Health Research Health Technology Assessment Programme (HTA): 12/167/95
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This protocol describes the TIME-A UK study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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For general queries, supply of trial documentation, and collection of data, please contact the Trial Coordinating Office.

Clinical queries should be directed to the local Principal Investigator [PI], who will direct the query to the appropriate person.

Sponsoring Institution

Imperial College London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

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1.0 PROJECT TITLE

Trial of Improvisational Music Therapy's Effectiveness for Children with Autism (TIME-A): United Kingdom (UK) arm of the TIME-A study.

2.0 SUMMARY OF RESEARCH

TIME-A is a multi-centre international study of music therapy for children with Autism Spectrum Disorder (ASD) that has been funded by the Research Council of Norway. The international study is a three-arm, parallel group, researcher-blind, randomised trial testing the impact of music therapy plus enhanced treatment as usual versus enhanced treatment as usual alone over a 12 month period. Study participants are children aged from 4:0 to 6:11 years old, who have a clinical diagnosis of ASD, confirmed by independent assessment using validated diagnostic tools (the Autism Diagnostic Observation Schedule [1] and the Autism Diagnostic Interview-Revised [2]). Children who are already receiving music therapy or have done in the past will be excluded from the study, as will children with severe sensory impairment.

Study participants in the UK arm of the trial, which shall be funded by the NIHR HTA, will be recruited from NHS health services at six centres: Cambridge, Essex, Peterborough, and the London Boroughs of Hillingdon, Kensington & Chelsea and Westminster.

In keeping with the international study we will examine the impact of improvisational music therapy. This approach to delivering music therapy was originally developed in the UK [3]. It is the approach that is most widely used to deliver music therapy to children with autism in the NHS and has demonstrated efficacy in small scale trials [4,5]. All those in the trial will also receive enhanced treatment as usual: in addition to usual input from primary and secondary care, parents/ guardians will receive three counselling sessions delivered over a five month period. These sessions will be delivered by experienced clinicians who receive regular supervision and comprise psychoeducation, information about support organisations and support in coping with current problems in keeping with national guidelines [7]. In addition to this, those in one of the two active treatment arms of the trial will be offered either: low-intensity music therapy (weekly sessions for five months), or high-intensity music therapy (sessions three times a week for five months).

All music therapy sessions will last 30 minutes and be delivered by trained music therapists who have experience of working with children with ASD and are registered with the Health Care Professions Council. Therapists will deliver improvisational music therapy in accordance with consensus guidelines which have been developed from practice in previous studies [3-6]. To ensure treatment fidelity, therapists will be asked to document the content of sessions and video-record sessions. Notes from sessions will be used during monthly supervision and video-recordings will be monitored by the lead music therapist in the study.

At baseline eligibility will be established and the child's level of cognitive ability will be assessed using the Kaufman Assessment Battery for Children [10]. The primary outcome measure is the severity of autism symptoms using the social communication algorithm, which is derived from the ADOS [1]. This will be assessed by a trained researcher who is masked to allocation status. The measure has been selected because of its strong psychometric properties, including sensitivity to change [1], and because it has been widely used in other randomised trials of children with autism [11-13].

The main secondary outcomes are the Social Responsiveness Scale [14] - a carer based assessment of the severity of autism spectrum symptoms that has high inter-rater and test-retest reliability [15-16]. In addition to these outcomes which are being used across all centres in the international study, the UK-arm of the trial will include two additional items completed by parents/ guardians of children who take part in the study: the Short-Form

Parenting Stress index, a widely used and validated measure of difficulties in parent-child interactions [17], and the Warwick and Edinburgh Well Being Schedule, a short validated measure of mental well-being [33].

All outcome measures will be assessed 2, 5 and 12 months after randomisation, with the primary end-point being at 5 months.

The main data analysis will be conducted by statisticians based in the main centre in Norway. All primary analyses will be based on intention to treat. Descriptive analysis shall be performed to examine the distribution of each outcome in each group at baseline, at the end of intervention and the end of follow-up and differences in baseline variables between the two main comparison groups (music therapy plus enhanced treatment as usual versus enhanced treatment as usual alone). Following assessment of normality, treatment effects will be analysed using a generalized estimating equations (GEE) approach that allows for analysis of longitudinal data while accounting for correlation among repeated observations for each participant [32]. GEE analyses will also be used to examine dose-effect relationships and to explore effects of covariates including site, age and sub-types of ASD.

3.0 BACKGROUND AND RATIONALE

One in every 100 children in the UK has autism spectrum disorder (ASD) [19]. The core features of the condition are persistent impairment in reciprocal social interaction and social communication together with restricted, repetitive patterns of behaviour, interests or activities [41]. These features occur whether or not the person has intellectual disability and are typically present in early childhood. Developmental disabilities associated with ASD lead to poor health, social exclusion and reduced quality of life [20]. ASD is one of the most important causes of lifelong disability.

The evidence base to inform treatment of children with ASD and their families is weak [31]. Recent guidance from the National Institute for Health and Clinical Excellence concluded that psychotropic medication should not be used to manage its core features and emphasised advice, education and support for parents and efforts to adjust the child's environment to minimise the impact of their disabilities [7].

Over the last decade a number of small scale studies of improvisational music therapy have suggested that it has the potential to improve health and social outcomes of children with ASD. A Cochrane systematic review in 2010 identified three small randomised trials of music therapy and found evidence of improvements in verbal (Standardised Mean Difference = 0.36, 95% CI 0.15 to 0.57) and gestural (Standardised Mean Difference = 0.50, 95% CI 0.22 to 0.79) communication skills. Effects on behavioural problems were not statistically significant. On the basis of these findings the authors concluded that music therapy may help children with autistic spectrum disorder. However they highlighted differences in the approach to delivering music therapy in these trials compared to normal clinical practice. Most children receiving music therapy in clinical practice receive weekly sessions, but the trials tested more intensive, daily, sessions.

Since the publication of this review a number of observational studies have reported improvements in social communication in children with autism who were offered music therapy as it is delivered in the UK [27-30]. This approach involves therapists providing children with a range of musical instruments to play and using a range of techniques including making co-improvised music to engage the child in joint musical activities. During sessions the child is offered opportunities to develop and enhance their communication skills, including affect sharing, imitation, joint attention, and turn-taking, all of which are associated with later development in language and social competency [8,9]. Two subsequent

small-scale trials of weekly improvisational music therapy for children with ASD also found improvements in social communication during therapy [4,5].

With over 500 music therapists in the UK, many of whom work with children with ASD in the NHS, evidence is needed to ensure that this resource is used in the most effective manner. The TIME-A study has been designed to provide this evidence. It is sufficiently powered to generate important information about the clinical effectiveness of improvisational music therapy for children with autism spectrum disorders. A UK arm of this trial would help ensure that the main study achieves the required sample size and help enhance the generalizability of the study findings by including a substantial sub-group of participants who are recruited from NHS services in the UK.

Why this research is needed now?

In 2009 NIHR-Health Technology Appraisal issued a commissioned call for a randomised trial of music therapy for children with autism, however a project was not funded. Since then a number of new small-scale studies have highlighted the potential value of this approach to helping children with ASD [5, 27-30]. A systematic review of music therapy for children with autism, completed in 2010, concluded that 'music therapy may help children with autistic spectrum disorder to improve their communicative skills' and that 'more research is needed to examine whether the effects of music therapy are enduring' [6].

Recent guidance from the National Institute for Health and Clinical Excellence has stressed the importance of psychosocial approaches to helping children with autism and concluded that psychotropic medication should not be used to manage its core features 'because the balance of risks and benefits do not favour their use' [7]. However, the evidence base for psychosocial interventions for autism is weak [31], and a recent high-quality trial of parent-mediated communication skills found little evidence of benefit [11].

Last year a team of researchers in Norway obtained funding to set up a multi-centre international study of improvisational music therapy for children with autism aged between 4 and 7. The 'TIME-A study' will investigate the clinical effectiveness of the approach to music therapy which has been tested so far and is most widely used in the UK [32]. The team received funding to coordinate the study and start recruitment in a number of international sites, and is now looking to recruit participants in the UK.

Music therapy is widely offered to children with autism in the NHS, but the evidence base to support the use of this intervention is not strong enough to be confident that it represents an appropriate use of limited resources. A UK arm of the TIME-A study would help ensure that a high quality evaluation of this promising intervention is successfully completed and enhance the generalizability of the study findings by including a substantial sub-group of participants who are recruited from NHS services in the UK.

4.0 AIMS AND OBJECTIVES

The primary aim is to conduct a UK arm of an international multi-centre trial of music therapy for children with autism to ensure that the main trial recruits sufficient participants to be fully powered and to extend the generalizability of the trial findings to children and parents using NHS services in this country.

The study objectives are:

1) To determine whether improvisational music therapy in addition to enhanced treatment as usual is superior to enhanced treatment as usual alone in improving social communicative skills in children with ASD.

2) To examine whether improvisational music therapy in addition to enhanced treatment as usual is superior to enhanced treatment as usual alone in reducing stress and improving emotional well-being among parents/ guardians of children with ASD.

3) To explore whether any clinical benefits associated with adding improvisational music therapy to enhanced treatment as usual for children with ASD are influenced by the intensity of treatment that is offered.

4.0 STUDY HYPOTHESES

Primary hypothesis: Among children with autism spectrum disorder aged four to seven years old, adding 20 weeks of individual improvisational music therapy to enhanced treatment as usual will improve social communication measured at 5 months using the Autism Diagnostic Observation Schedule.

Secondary hypotheses:

i) Among children with autism spectrum disorder aged four to seven years old, adding 20 weeks of individual improvisational music therapy to enhanced treatment as usual will improve social communication at 12 months measured using the Autism Diagnostic Observation Schedule.

ii) Among children with autism spectrum disorder aged four to seven years old, adding 20 weeks of individual improvisational music therapy to enhanced treatment as usual will improve social communication judged by parents/ guardians and reduce levels of parental stress.

5.0 RESEARCH PLAN

5.1 Study design

A UK arm of a three arm, parallel group, researcher-blind, randomised multi-centre international trial which will examine the impact of adding music therapy to enhanced treatment as usual for children with Autism Spectrum Disorder over a 12-month period.

5.2 Target organisations

NHS services for children with Autism Spectrum Disorder in six areas of London and the south and east of England (Cambridge, Essex, Peterborough, and the London Boroughs of Hillingdon, Kensington & Chelsea and Westminster). NHS services for children in these areas include Child Development Centres and outpatient Child and Adolescent Mental Health Services. Services in these areas are provided by four large NHS Foundation Trusts: Cambridge and Peterborough NHS Foundation Trust, Central and North West London NHS Foundation Trust, Chelsea and Westminster Hospital NHS Foundation Trust and South Essex Partnership NHS Foundation Trust.

5.3 Patient care group

Children with Autism Spectrum Disorder and their parent/ guardians.

5.4 Recruitment

At each study centre information about the trial will be widely publicised among clinical colleagues working in Child Development Centres and outpatient Child and Adolescent Mental Health services. Members of the research team will present plans for the study at local academic and clinical meetings and continue to visit teams on a regular basis to remind

them about the study. Parents or guardians (referred to as parents in the remainder of this proposal) of children aged 4:00 to 6:11 years who have a clinical diagnosis of Autism Spectrum Disorder will be approached by a staff member, given basic information about the study and asked to provide verbal consent to be contacted by a local researcher.

5.5 Obtaining consent

Parents who agree to meet a member of the study team will be invited to a meeting. At this meeting the parent will be provided with written and verbal information about the study including a copy of the Patient Information Sheet. The researcher will encourage parents of potential participants to spend as much time as they want asking questions about the study and considering whether they and their child want to take part. In all instances potential participants will have at least 24 hours before deciding whether they wish to take part in the study. Before any trial specific procedures are performed, the parent will need to sign and date an Informed Consent Form. Following this, the researcher will assess eligibility to participate and collect baseline clinical and demographic data. Those who are ineligible will be thanked for their time and informed of the reason(s) for this. The process of obtaining informed consent will be conducted in accordance with the requirements of Research Ethics Committee guidance and Good Clinical Practice.

5.6 Randomisation

Researchers at each site will enter the results of the baseline assessment on a web-based Case Report Form. Remote web-based randomisation will be undertaken through a fully automated service operated by Uni Research (Norway). The allocation ratio for the study is 2:1:1 such that equal numbers of participants are allocated to enhanced treatment as usual and music therapy and, among those allocated to music therapy, equal numbers will be allocated to high and low-intensity treatment. Randomisation will be made in blocks, with block size randomly assigned to between four and eight. Following randomisation the UK-based trial coordinator will be informed which arm of the trial the participant has been assigned to. Parents and therapists will then be given information about allocation status and arrangements made for delivering parent counselling sessions. For those in one of the two active arms of the trial, arrangements will also be made for delivering music therapy sessions. Study researchers are based in separate departments to those involved in organising treatment, helping to ensure they remain masked to the allocation status of study participants.

5.7 Follow-up

Two months after randomisation, parents will be contacted by the researcher to make arrangements for the first follow-up assessment. Follow-up assessments will take place at a time which is convenient for the parent and their child. A final follow-up interview will be conducted 12 months after randomisation.

Follow-up interviews will be carried out through face-to-face interviews. Any travel costs or other reasonable expenses incurred by the parents will be reimbursed. In addition to these assessments, all study participants will be contacted nine months after randomisation using their preferred method (text, email, letter, phone call), to thank them for their participation, to remind them of the plan for their final follow-up interview and to ask them to let us know of any changes in their contact details.

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6.0 STUDY INTERVENTIONS

6.1 Improvisational music therapy

The TIME-A trial will examine the clinical effectiveness of improvisational music therapy. This form of music therapy was originally developed in Britain in the 1950s by Paul Nordoff and Clive Robbins and was subsequently refined by Professor Tony Wigram and colleagues [3]. It is a child-centred treatment approach which utilises the potential that making music has to enhance social engagement and the expression of emotions [3]. This approach to music therapy is the one most widely used in the NHS for children with autism. Small-scale trials of the intervention have reported positive effects [4-6].

Music therapy sessions in the trial will last for 30 minutes and involve therapists attuning to the child's behaviour through improvisational techniques including making co-improvised music.

Individual sessions will be delivered to the child in local NHS facilities. During sessions music played or sung by the therapist is generally attuned to the child's musical or other behaviours and includes techniques to engage the child and establish a connection with them. To this end the 'musical' features of the child's expression (such as rhythm, melodic patterns, timbre etc) may be mirrored, reinforced or complimented, thus allowing for moments of synchronisation between the child and the therapist and giving the child's expressions a pragmatic meaning within the context of the session. While engaging in joint musical activities the child is offered opportunities to develop and enhance their communication skills, including affect sharing, imitation, joint attention, and turn-taking, all of which are associated with development in language and social competency [8,9].

6.2 Treatment intensity

The TIME-A trial involves two active treatment groups in which music therapy sessions are delivered at two different levels of intensity; once a week (low intensity) or three times a week (high intensity). Over the five month treatment period, those in the low intensity treatment arm will receive up to 20 sessions of music therapy and those in the high intensity treatment arm will receive up to 60 sessions. Previous trials of improvisational music therapy based on both high and low intensity treatment have reported positive effects [4,5]. Low intensity treatment is less costly to deliver and requires less commitment from children and their parents, but some therapists argue that treatment delivered more frequently has a greater impact on a child's communication skills and functioning.

6.3 Enhanced treatment as usual

All parents of study participants will receive enhanced treatment as usual; in addition to usual care from primary and secondary services, parents will receive three counselling sessions delivered over a five month period (at baseline, two months and five months). These sessions will be delivered by experienced clinicians who receive regular supervision and comprise psychoeducation, information about support organisations and support in coping with current problems. This type of support is recommended for parents of children with ASD [7], and will help ensure that all study participants receive a basic level of support across all study centres.

6.4 Treatment fidelity

To determine whether treatment is delivered as intended, therapists will document significant events, notable child behaviours and interventions used after every session. In addition to these self-reports all music therapy and parent counselling sessions will be video-taped to allow for assessment by independent raters. Notes and video-recordings will be used during monthly supervision sessions and video-recordings will be monitored by the lead music therapist in the study. The video recordings shall only be stored for 1 year after the study's results have been published.

7.0 STUDY DESIGN

TIME-A is a three-arm, parallel group, researcher-blind, randomised controlled trial, that will be nested within a larger international study. Using the same basic methods as the TIME-A study [32], the UK arm of the study will involve recruiting 100 participants and following them up five and 12 months after randomisation.

Within the MRC-framework for the evaluation of complex interventions [34], the TIME-A trial is a 'stage 3' pragmatic randomised trial. The interventions are being delivered in the way that they are currently being delivered within the NHS. Outcome measures have been restricted to key outcomes and the main analysis will use the intention to treat principal.

8.0 TARGET POPULATION

The study population is children aged between 4:0 and 6:11 who have autism spectrum disorder and are in contact with NHS services.

9.0 INCLUSION/EXCLUSION CRITERIA

To maximise generalizability of study findings a broad inclusion criteria has been used and number of exclusion criteria have been limited to essential features which are not compatible with using the intervention or participating in the trial. To take part in the study children need to be:

- Aged 4:0 to 6:11 years.
- Have a clinical diagnosis of autism spectrum disorder made by a child psychologist or clinical psychologist according to ICD-10 criteria and confirmed using the Autism Diagnostic Observation Schedule [1], and two of the three domains of the Autism Diagnostic Interview-Revised [2].

Exclusion Criteria

- Received music therapy in the last year.
- Severe sensory disorder: we will exclude children who have severe visual or hearing impairment as this would prevent them from being able to make full use of the intervention we are testing.
- Those who do not have a parent or guardian who is able and willing to provide written informed consent to take part in the trial.

10.0 STUDY SETTING

Study participants will be recruited from NHS healthcare services. These will mainly be Child Development Centres which provide the main point of access for assessment and diagnosis of children with developmental delay, and out-patient clinics provided by child and adolescent mental health services.

Data from community paediatricians in each study site indicate that they receive 80 to 120 referrals of children with ASD each year of whom half are aged 4:0 to 6:11. Child and Adolescent Mental Health Services receive a further 10 to 20 referrals per year of children who would meet study inclusion criteria. The music therapy service in London that covers two of the study sites (Kensington and Westminster) currently receives over 70 referrals a

year of children with ASD, most of whom meet study inclusion criteria. Across the six study centres this equates to referral of over 390 potential participants during the 12 month recruitment phase of the study.

11.0 SAMPLING

11.1 Selection of study sites

The study sites have been selected for the following four reasons:

i. Each site works with sufficient numbers of children with autism spectrum disorders to enable us to recruit the required sample within the available time frame using two full-time researchers (one based in London, the other based in Cambridge/ Essex).

ii. In each area, music therapists are already delivering improvisational music therapy to children with autism spectrum disorders in accordance with the treatment approach being tested in the TIME-A study.

iii. There is strong organisational support for conducting the study among local clinicians and managers.

iv. Recruitment sites cover a range of inner city, urban, suburban and more rural communities, including relatively deprived parts of inner London, more affluent London suburbs and mixed areas of east and central England.

11.2 Selection of study participants

Children aged 4:00 to 6:11 years have been selected because previous research suggests that this intervention is effective when delivered to children in this age range [3-6].

11.3 Sample size calculation for the main trial

A total sample of 300 needs to be recruited in the study as a whole. Previous trials of improvisational music therapy for children with ASD have reported medium effect sizes associated with active intervention. A Cochrane review of music therapy for children with ASD calculated a Standardised Mean Difference of 0.50 for gestural communication skills and 0.36 for verbal communication skills [6].

A sample of 235 patients will provide 90% power to detect a medium effect size of the intervention on the social communication scale of the ADOS score at 12 months with a 5% level of statistical significance [32]. To take account of possible clustering at the level of study therapists and study centres and a drop out we have inflated the total sample required to 300. Loss to follow-up in trials of psychosocial intervention for children with autism spectrum disorder tends to be low. The PACT trial of parent mediated communication focused treatment reported a follow-up rate of 96% at 13 months [11].

11.4 Sample size for the UK arm of the study

To achieve a total sample of 300 participants in the main trial, it has been calculated that 100 participants will need to be recruited in the UK. This sample will also be large enough to provide valuable information about the clinical effectiveness of delivering this intervention in the NHS.

11.5 Rate of recruitment

The aim is to recruit 100 participants over a 12 month period. With the support of Clinical Studies Officers from the Mental Health Research Network, two full-time researchers one covering sites in London, the other covering sites in Cambridge and Essex, will each aim to recruit 50 participants during this period. Previous research among children with autism suggests that meetings need to be arranged with eight parents/ families for every five children that will take part in the trial [11], which means that each researcher will need to meet with an average 1.6 parent/ families each week. Data from recruitment sites indicate that the numbers of children they assess each year who have autism spectrum disorder and are within this age group are well in excess of this (see section 10 above).

12.0 DATA COLLECTION

Data will be collected prior to randomisation (to establish eligibility to participate and assess baseline functioning), and at follow-up: 2, 5 and 12 months after randomisation.

12.1 Data to assess eligibility and covariates

At baseline eligibility will be assessed using the Autism Diagnostic Observation Schedule [1] and the Autism Diagnostic Interview-Revised [2]. In order to minimize inconvenience for parents and children the results of any recent ADOS assessment shall be used in lieu of baseline data (so long as this was completed within six weeks of their entry into the study). To take part in the study potential participants will need to meet criteria for autism spectrum disorder on the ADOS and on two of the three domains of the ADI-R. This combination of data from direct observation and interviews with parents has been used to establish eligibility in previous high quality trials of interventions for children with ASD [11, 13].

In addition to collecting basic demographic data on age, sex, ethnicity, socioeconomic status and education level the child's level of cognitive ability will be assessed using the Kaufman Assessment Battery for Children (K-ABC) [10]. In cases where the application of the K-ABC is not possible due to the child's level of cognitive functioning, researchers will assign the child to one of three categories: no, mild, or moderate/ profound mental retardation, using World Health Organisation (ICD-10) criteria [35].

12.2. Outcome measures

The primary outcome measure is the severity of autism symptoms using the social communication algorithm which is derived from the ADOS [1], which will be assessed by a trained researcher who is masked to allocation status. We have selected this measure because of its strong psychometric properties including sensitivity to change [1], and because it has been widely used in other randomised trials of children with autism [11-13].
Secondary outcomes are:

1) Social Responsiveness Scale [14] - a carer based assessment of the severity of autism spectrum symptoms that has high inter-rater and test-retest reliability [15-16]

2) Questionnaire on Resources and Stress - Friedrich Short Form a widely used measure of parental stress that has been validated among parents of children with autism [17].

3) Warwick and Edinburgh Well Being Schedule, a short validated measure of mental well-being [33].

All outcome measures will be assessed at baseline, 2, 5 and 12 months.

13.0 DATA ANALYSIS

As the study is pragmatic in design, the primary analysis will be by intention to treat. Descriptive analysis will be performed to examine the distribution of each outcome of each group at baseline, at the end of intervention and the end of follow-up, and differences in baseline variables between the two comparison groups. Generalised estimating equations (GEE) shall be used to compare and test changes of the primary and secondary outcomes from baseline to twelve months between the intervention and control group. GEE allows for the analysis of longitudinal data while accounting for correlation among repeated observations for each participant. GEE will also be used to examine dose effect relationships and to explore possible confounding effects of site or relevant subgroups such as age or level of cognitive impairment.

Before carrying out GEE analysis, sensitivity analyses shall be conducted to examine data missing mechanism to decide whether imputation approaches are necessary.

The analytic strategy applies to both primary and secondary outcomes. A detailed analysis plan with templates of statistical tables will be developed for the data monitoring and ethics committee. Statistical software SPSS and MLwiN will be used for the analyses.

14.0 ADVERSE EVENTS

14.1 Adverse Events (AE)

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:

- **Results in death**
- **Is life-threatening** – *refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*
- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

14.2 Reporting Procedures

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

14.2.1 Non serious AEs

All such events, whether expected or not, should be recorded.

14.2.2 Serious AEs

An SAE form should be completed and faxed to the Chief Investigator within 24 hours. However, hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs shall be reported to the [Insert REC Name] and sponsor where in the opinion of the Chief Investigator, the event was:

- 'related', i.e. resulted from the administration of any of the research procedures; and
- 'unexpected', i.e. an event that is not listed in the protocol as an expected occurrence

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Reports of related and unexpected SAEs shall be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies.

Local investigators should use the following contact details when reporting any SAEs:

Please Fax SAE forms to: 0207 386 1216 – FAO: Trial Coordinating Office

15.0 REGULATORY ISSUES

15.1 Ethics Approval

The Chief Investigator has obtained approval from the [Insert REC Name] Research Ethics Committee. The study must be submitted for Site Specific Assessment (SSA) at each participating NHS Trust. The Chief Investigator will require a copy of the Trust R&D approval letter before accepting participants into the study. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

15.2 Consent

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

15.3 Confidentiality

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

15.4 Indemnity

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

15.5 Sponsor

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

15.6 Funder

TIME-UK is funded by the NIHR Health Technology Assessment programme.

15.7 Audits

The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

16.0 DISSEMINATION AND PROJECTED OUTPUTS

The main output from this study will be high quality evidence on the clinical effectiveness of music therapy for children with autism spectrum disorders. By including data from up to 100 children who are using NHS services we will ensure that the findings of the main TIME-A trial are generalisable to the UK. Findings from the TIME-A trial will be used by the National Institute for Health and Clinical Excellence and other bodies when they develop future guidelines for the treatment of children with this condition. Information about the clinical effectiveness of this treatment approach will also be of considerable value to providers of NHS services and help inform choices about investment in music therapy and other psychosocial interventions which are provided in the NHS. Finally data on the impact of music therapy for children with ASD will be of value to parents and guardians of children with ASD as they will be able to make better choices about the interventions and treatments for their child(ren).

16.1 Dissemination of the results of the main trial

The project outputs from the main trial will be co-ordinated by the main trial centre in Norway. This will include: written reports on trial findings and presentations and workshops at a national and international meetings. The consortium of centres participating in the main trial includes teams from North America, Europe, Australasia and East Asia. The international makeup of the team will help ensure that results of the main trial are disseminated internationally and have the potential to have a global impact.

Plans for disseminating the results of the main trial include publishing papers in peer reviewed journals. In addition to the main paper, which will focus on the main study outcomes, papers on the process of delivering improvisational music therapy to children with ASD and papers examining the impact of the intervention in sub-groups of patients will also be published. Study findings will be presented at international conferences including the annual Autism-Europe International Congress and the International Centre for Research into Arts Therapies.

16.2 Dissemination of the results of the UK-arm of the trial

We will prepare a full report to NIHR: HTA that will detail the results of the UK arm of the TIME-A trial and place these in the context of findings from the international study. These findings will provide the basis for a paper on the process and outcomes of the UK arm of the TIME-A study. We will also prepare an English version of the treatment guidelines for improvisational music therapy as used in the main study which will be made freely available to all those working in the NHS.

We will present findings from the UK arm of the trial in the context of the international study at local and national meetings. At a local level we will convene a seminar open to the study team and participants to discuss study findings. At a national level we will present the findings of the study at the National Autistic Society's professional conference and the annual meeting of the British Association of Music Therapists.

16.3 Dissemination to parents of children with ASD

Each parent/ guardian who takes part in the study will be sent a personal letter thanking them for their involvement in the study. This will also include a short summary of the study findings both from the UK arm of the study and the international trial. This will include details of how parents can obtain further information about the project. This summary will be prepared with input from our Project Advisory Group. The group will also help us prepare a lay summary of project findings that will be made available on the internet through the web site of the Mental Health Research Network, and dedicated web pages at Imperial College London.

17.0 PLAN OF INVESTIGATION AND TIMETABLE

17.1 Project milestones

Milestones	Timelines
➢ Start date for project	1st June 2014
Funded set-up phase	
Appoint trial manager and local researchers	June 2014
Publicise study among local clinicians	June 2014 onwards
Train local researchers	June-August 2014
Induct local investigators	June-August 2014
Recruitment and follow-up	
Start participant recruitment	1st September 2014
First follow-up interview	1st November 2014
Complete recruitment	31st August 2015
Complete follow-up	31st August 2016
Analysis and write-up	
Analyze data	September to November 2016
Submit final project report	30th November 2016

18.0 PROJECT MANAGEMENT

The Chief Investigator (Professor Mike Crawford) will have overall responsibility for the research. He will be accountable for achieving project objectives and milestones, and ensure that the research is run in accordance with agreed procedures and protocols. He will direct the Operational Research Team which meet monthly and will consist of Odell-Miller, Maratos, and Oldfield. The purpose will be to review progress and address issues of

implementation. Odell-Miller with have responsibility for supervising the local researcher, overseeing recruitment and follow-up of study participants in Cambridge and Essex. Crawford will hold these responsibilities for London sites.

A Project Management Group (PMG), chaired by Crawford and consisting of co-applicants, will meet on eight occasions over the course of the study. Its purpose will be to oversee the smooth running of the trial, monitor project achievements and weaknesses, review emergent findings at each research phase, and formulate actions required to address significant issues related to project progress.

19.0 APPROVAL BY ETHICS COMMITTEE

Multi-Centre Research Ethics Committee approval will be obtained prior to the start of data collection. Only children whose parent or guardian agrees to provide written informed consent will be included in the study. The parent of each potential participant will be provided with a copy of a Patient Information Sheet that includes a contact number for the study team. The trial will be conducted in accordance with Good Clinical Practice guidelines.

Risks and benefits for trial participants

Each study participant will have the same chance of being allocated to the three trial arms and all parents will be offered the three parent counseling sessions. By taking part in this trial participants and their families will be helping us find out whether music therapy helps children with Autism Spectrum Disorder. If music therapy is effective, this is likely to change the way that children with ASD are treated in the future. If it is not, then the results of the study will help to ensure that fewer children are given ineffective treatments in the future.

Study participants will be asked to give up their time to take part in study interviews and to complete study questionnaires. Baseline assessment takes no longer than 60 minutes observing children and no longer than 120 minutes with parents. Follow-up assessments will require no more than 90 minutes with children and 120 minutes with parents. All parents/ guardians will be offered a £20 honoraria following completion of the 12-month follow-up interview.

As we will collect information on a range of sensitive personal matters such as mental health and behavior we ensure that data is collected and stored carefully. Baseline data will be entered onto a web-based Case Report Form that will not include the patient's name or other information that could identify them. All data will be stored on a secure dedicated web server (based in Norway). Access will be restricted by user identifiers and passwords (encrypted using a one way encryption method). All electronic databases will use a patient identification number rather than the participant's name. Hard copies of data sheets linking the patient identification number to the person's contact details will be kept securely in a locked filing cabinet in a locked office at each participating site, and will only be accessible to a small number of people who are involved in the study.

20.0 PATIENT AND PUBLIC INVOLVEMENT

The views of parents of children with autism helped us develop this proposal and, if our application is successful, will continue to play an important part in helping us conduct the study, oversee study progress and disseminate study findings.

Service user involvement in this project is being led by Morag Maskey and Anna Maratos. Dr Maskey has previous experience of using services for families of children with ASD and previous experience of researching autism and facilitating parent focus groups. Together with Anna Maratos (Head Arts Therapist at CNWL NHS Foundation Trust) she will help

coordinate the Project Advisory Group of parents with children with autism that will help oversee the study, advise us on the design of the Study Information Sheet and help disseminate study findings to parents during the final stage of the study.

Anna Maratos is Head of Arts therapies at CNWL NHS Foundation Trust and has a long track record of working collaboratively with users of NHS services to develop services and test interventions.

20.1 Development of the study protocol

Plans for this study were presented 15 parents of children with ASD from Hillingdon Child Development Centre. Feedback from parents led to changes in the outcome measures we will use and has helped us plan when and where music therapy sessions would be delivered.

20.2 Start-up phase of the study

On agreement of study funding we will set up a Project Advisory Group of service users drawn from clinical services in London. This group will help us develop material for publicising the study and design the Patient Information Sheet that we would use.

20.3 Recruitment and follow-up

Morag Maskey, together with members of the Project Advisory Group, and an independent service user who will be appointed to the Trial Steering Group will help oversee study progress during this phase of the project.

20.4 Disseminating study findings

Members of the Project Advisory Group will be asked to comment on a draft version of the full study report. Each study participant will be offered the option of receiving a summary of study findings at the end of the trial. Members of the Project Advisory Group would take a lead in determining the content of this summary. In addition to this members of the group will be offered an opportunity to make a contribution to other aspects of dissemination strategy including presentations at meetings and workshops.

21. EXPERTISE AND JUSTIFICATION OF SUPPORT REQUIRED

21.1 Expertise

Mike Crawford (Chief Investigator: overall responsibility for the UK arm of the TIME-A study, and supervision of the London-based researcher) is a Professor of Mental Health Research. He has been the Chief Investigator of a number of successful large scale trials of complex interventions.

Christian Gold (Chief Investigator of the main TIME-A trial) is Principal Researcher at Uni Research and Professor of Music Therapy at the University of Bergen, Norway. He has completed a number of randomised trials of music therapy and led the Cochrane review of music therapy for people with autism. He has expertise in music therapy, the treatment of autism, and the evaluation of complex interventions.

Helen Odell-Miller (Principal Investigator – Cambridge and Peterborough site, and supervision of the local researcher) is a Professor of Music Therapy at Anglia Ruskin University. She has completed a number of studies examining the process and outcomes of music therapy and has expertise in the evaluation of complex interventions.

Jorg Assmus (Lead statistician: responsible for overseeing the analysis of trial data) is a senior statistician at GAMUT, Uni Research, Norway. He has led the analysis of data on a number of large scale trials of interventions and has expertise in medical statistics.
Amelia Oldfield (Lead Music Therapist: responsible for overseeing treatment fidelity in the UK arm of the trial) is a Professor in Music Therapy, who has helped develop improvisational music therapy for children with ASD. She has expertise in autism, music therapy and supervising music therapists.

Anna Maratos (Lead Music Therapist for London sites) is Head of Arts Therapies in Central and North West London NHS Foundation Trust and has expertise in Music Therapy, trial management and logistics.

Angela Hassiotis (Collaborator) is Reader in Learning Disability in the Mental Health Sciences Unit at University College London. She is the Chief Investigator on a number of large-scale trials of interventions for people with developmental disorders, and co-chairs the IASSID Special interest Research Group in Challenging Behaviour and Mental Health.

Paul Ramchandani (Collaborator) is a Reader in Child and Adolescent Mental Health and responsible for the community ASD service in Westminster. He has expertise in assessing developmental disabilities and has considerable experience of recruiting children and their families to large-scale clinical studies.

Helen McConachie (Collaborator) is a Professor of Child Clinical Psychology at Newcastle University and is an expert on the assessment and treatment of children with autistic spectrum disorders. She has been PI on a number of early intervention trials.
Dr Maskey (Collaborator) has previous experience of using services for families of children with ASD and previous experience of researching autism and will help lead service user involvement in the study.

21.2 Justification of research costs

As the main costs of the TIME-A study have already been met by the Research Council of Norway, funding for the UK arm of the study would provide an effective and relatively cheap means to generate high quality evidence about the clinical effectiveness of music therapy for children with ASD. Much of the cost associated with trial coordination (randomisation service data management etc.) will be met by the main trial team. We have included costs of a consultancy for the lead health economist and statistician in Norway which will be used to prepare the report of the results of the UK arm of the trial.

As a result most of the costs of the project are those associated with employing a part-time Trial Manager and two full-time researchers who will take a lead on recruiting, assessing and following up study participants. Costs of consultancies for Gold, Assmus and Askilsen have been included for their input into an analysis of UK-only data for the HTA report. Other costs have been kept to a minimum to deliver value for money. We have included part of the salary of the Chief Investigator (5% of his time), and a principal investigator in the Bedfordshire/ Essex region (Professor Helen Odell-Miller - 4%). All other collaborators have been costed at 1-2% of their time for their expert input into the trial management meetings and preparation of study reports.

Honoraria will be offered to all study participants at the end of data collection (£20 per participant). Unwaged service users who are members of the Trial Management Group, Trial Steering Group and Project Advisory Group will be paid £50 per meeting. Costs of travel by researchers and study participants by local public transport have been included. Stationery and photocopying costs associated with data collection have been added. We have also included the cost of computer and printer for each full-time researcher.

22.3 Justification of NHS Support Costs and Excess Treatment

Costs of NHS staff have been agreed with local providers and included in NHS support costs.

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