

Supplementary Online Content 1

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Study Protocol

Randomised controlled Trial of Improvisational Music therapy's Effectiveness for children with Autism spectrum disorders (TIME-A) (Researcher project - KLINISKFORSKNING)

Application Number: ES479539 Project Number: 213844

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Randomised controlled Trial of Improvisational Music therapy's Effectiveness for children with Autism spectrum disorders (TIME-A) (Researcher project - KLINISKFORSKNING)

Application Number: ES479539 Project Number: 213844

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Project info

Project title

Project title	Randomised controlled Trial of Improvisational Music therapy's Effectiveness for children with Autism spectrum disorders (TIME-A)
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Primary and secondary objectives of the project

Primary and secondary objectives	<p>The objectives of this study are as follows:</p> <ol style="list-style-type: none"> 1.) To determine whether music therapy is superior to standard care in improving social communicative skills in children with ASD as assessed by independent clinicians at the end of the treatment period. 2.) To determine whether music therapy is superior to standard care in improving social responsiveness in children with ASD as assessed by parents/guardians at the end of the treatment period. 3.) To determine whether the response varies with variation of treatment intensity. 4.) To determine how the development of social communicative skills proceeds until follow-up twelve months after the start of treatment. 5.) To determine the cost-effectiveness of music therapy at two intensity levels.
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Randomised controlled Trial of Improvisational Music therapy's Effectiveness for children with Autism spectrum disorders (TIME-A) (Researcher project - KLINISKFORSKNING)

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Project summary

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Background: Previous research has suggested that music therapy may facilitate skills in areas typically affected by autism spectrum disorders (ASD), such as social interaction and communication. However, generalisability of previous findings has been restricted, as studies were limited in either methodological accuracy or the clinical relevance of their approach. The aim of this study is to determine effects of improvisational music therapy on social communication skills of children with ASD. Additional aims are to examine if variation in dose of treatment (i.e., number of music therapy sessions per week) affects outcome of therapy, and to determine cost-effectiveness.

Methods: Children aged 4;0 to 6;11 years diagnosed with ASD will be randomly assigned to one of three conditions. Parents of all participants will receive three sessions of parent counselling (at 0, 2, and 5 months). In addition, children randomised to the two intervention groups will be offered individual, improvisational music therapy over a period of five months, either one (low-intensity) or three (high-intensity) sessions per week. Generalised effects of music therapy will be measured using standardised scales completed by blinded assessors (Autism Diagnostic Observation Schedule, ADOS) and parents (Social Responsiveness Scale, SRS) before and 2, 5, and 12 months after randomisation. Cost-effectiveness will be calculated as man years. A group sequential design with first interim look at usable N = 235 (randomised N = 300) will ensure sufficient power for a small to medium effect as well as efficiency.

Conclusions: Responding to the need for more rigorously designed trials examining the effectiveness of music therapy in ASD, this pragmatic trial sets out to generate findings that will be well generalisable to clinical practice. Addressing the issue of dose variation, this study's results will also provide information on the relevance of session frequency for therapy outcome.

Funding scheme

Supplementary info from applicant

Programme / activity	KLINISKFORSKNING
Application type	Researcher project
Topics	
Other relevant programmes/ activities/projects	
Discipline(s)	Music therapy

Randomised controlled Trial of Improvisational Music therapy's Effectiveness for children with Autism spectrum disorders (TIME-A)

1. Relevance relative to the call for proposals

The proposed project is a **pragmatic international multicentre RCT** that is **sufficiently powered** to detect an effect on a **clinically relevant primary endpoint**. Core symptoms of autism spectrum disorder (ASD) are very difficult to change with any treatment. In music therapy they are hoped to occur as downstream effects from changes in interaction patterns observed within sessions. This project will **build a collaboration of and recruit patients from seven countries** on five continents (Australia, Austria, Brazil, Israel, Korea, Norway, and USA). Several of our collaborators have previously conducted small-scale RCTs on music therapy for autism. Their knowledge of the scientific as well as practical challenges involved in conducting such studies will contribute to the feasibility of this project. Our own experience with a previous international multicentre RCT on music therapy in adult mental health, as well as our knowledge of the subject area, will ensure that the collaborative and intercultural aspects of the trial are taken care of in a good way. The proposed project will be the first **adequate and well-controlled effectiveness study** and the largest RCT on **non-pharmacological therapy** for autism so far, the first that is comparable in size and power to **Phase III trials** in drug development. It will therefore have potential for publication in a **high-ranked international journal** and will raise the standards by which autism therapies are evaluated. An **economic cost-benefit/cost-effectiveness analysis** will be included to enable an informed evaluation by **health services**. Collaboration with a **regional competence centre in clinical research** (Centre for Clinical Research, Haukeland University Hospital, Bergen) will further improve the quality and impact of the project as well as contributing to **competence and network-building**. Overall, the project will strengthen clinical research on **children**, people with **disabilities**, and **mental disorders**, three prioritised areas. **Ethnic minorities** will also be included.

2. Aspects relating to the research project

2.1. Background and status of knowledge

Impairments or delayed development in skills concerning social interaction and communication are at the core of ASD [1]. The attempts to help children with ASD develop meaningful language and social communication skills cover a wide range of different approaches. Yet, for most of the various intervention methods available and reported within ASD that are designed to improve communication and social interaction, only insufficient evidence of effectiveness exists [2]. In systematic reviews, music therapy has been found one of the few treatment options with promising results that warrant further investigation [2,3]. Due to various methodological quality limitations of previous studies in the field of ASD intervention research [2], further high quality randomised controlled trials on common interventions for ASD are urgently needed. Similarly, in a review of “novel and emerging treatments” for ASD, music therapy was the only non-biological treatment option (together with melatonin, acetylcholinesterase inhibitors, and naltrexone) that reached the highest ranking in an evidence-based grading system [4]. Considering that pharmacological treatments typically target symptoms such as hyperactivity, agitation, or sleep disorders rather

than core symptoms of ASD, and may have adverse effects [2,4], music therapy can be viewed as a promising, but not yet sufficiently evidenced treatment for improving social interaction and communication skills within ASD. Music therapy has a long tradition within ASD [5,6], and there are many clinical reports, case studies, and single group studies [7-10] suggesting that music therapy may enhance skills of social communication such as initiating and responding to communicative acts. In recent years, increased efforts have been made to conduct more rigorous studies in this area. A Cochrane review combining the findings of three small controlled studies [3] concluded that music therapy may have positive effects on the communicative skills of children with ASD, but also noted limited applicability of the studies' results to clinical practice due to very short duration and low flexibility in music therapy techniques applied. The review helped to initiate RCTs that are more applicable to clinical practice [11-13; unpublished report, Thompson, McFerran, and Wigram, 2011]. These recent trials used improvisational, flexible, child-centred methods of music therapy, where a trained therapist reacts musically to the child's initiatives and enters a musical dialogue with them. Instead of practising targeted skills, improvisational music therapy has been noted for its potential to provide a meaningful framework that, similar to early mother-infant interaction, encompasses relevant features of social communication such as being embedded in a shared history of interaction, having a common focus of attention, turn-taking, and musical and emotional attunement [11-14]. Despite improved clinical applicability, these trials were still seriously limited in sample size and test power. A large pragmatic RCT is needed to decide if music therapy improves core symptoms of autism in a generalised setting.

► The objectives are described in the **grant application form**.

2.2. Approaches, hypotheses and choice of method

Participants

The study will include children referred from participating institutions (hospital departments, development centres, parents' support groups) who comply with the following criteria:

Inclusion criteria and baseline assessment

(a) *Aged 4;0 to 6;11*: This age range is appropriate in relation to aims (to enhance basic social communication skills), setting (being able to attend therapy in a one-to-one setting), outcome measures (SRS applicable from age 4, see below), and context (normally before school age).

(b) *Diagnosis of autism spectrum disorder*: Participants must have a diagnosis of an autism spectrum disorder as assessed by a child psychiatrist or clinical psychologist according to ICD-10 criteria. To support the diagnosis of autism, the Autism Diagnostic Observation Schedule (ADOS) [15] will be administered to potential participants. Additionally, the Autism Diagnostic Interview-Revised (ADI-R) [16] will be administered to parents/guardians to acquire data not only on the behaviour displayed during baseline assessment, but also on the history of development of each child, and to avoid loss of specificity [17,18]. The children's level of cognitive ability will be assessed using the Kaufman Assessment Battery for Children (K-ABC) [19,20]. Parents/guardians will be asked to complete the Social Responsiveness Scale (SRS) [21]. In addition, standard demographic parameters (gender, age, first language, family size, parents' educational background), comorbidities, and information on concomitant treatment will be recorded.

Exclusion criteria

(a) *Serious sensory disorder*: Children participating in the study must not be affected by serious sensory disorders such as blindness or deafness as this would alter the aim, course, and implementation of therapy.

(b) Previous experience of music therapy: Children having had music therapy sessions prior to study enrolment will not be included as this would be likely to have a strong influence on the course of therapy.

Non-verbal children as well as those with language skills may be included. Parents/guardians must give informed consent for their children to be enrolled in the study. Participants must be able to attend up to three weekly music therapy sessions.

Interventions

Participants will be randomly assigned to one of the following three conditions:

(1) High-intensity music therapy: Improvisational music therapy sessions (30 minutes each) in an individual setting thrice weekly for five months. Music therapy sessions will be provided by academically trained music therapists (master's level or equivalent) with clinical experience of working with children with ASD. The music therapy approach applied in this study is based on the ideas and principles of improvisational music therapy [22,23], findings from previous music therapy research [9,11-13,24], and developmental psychology [25]. The music played or sung by the therapist is generally attuned to the child's (musical or other) behaviour and expression and includes various improvisational techniques to engage the child and establish contact with the child. To this end, "musical" features of the child's expression (pulse, rhythmic, dynamic or melodic patterns, timbre etc.) may be mirrored, reinforced, or complemented, thus allowing for moments of synchronization between child and therapist and giving the child's expressions a pragmatic meaning within the context. To allow elicitation of specific social communicative behaviours, the therapist may also gently provoke the child e.g. by violating expectations or jointly developed patterns. While engaging in joint musical activities within a shared history of interaction, the child is offered opportunities to develop and enhance skills such as affect sharing, joint attention, imitation, reciprocity, and turn-taking, all of which are associated with later development in language and social competency [26,27]. The duration of five months should be sufficient for detectable developments in children's social communication skills (based on earlier RCTs on music therapy in autism [3,11,12] and a meta-analysis of the dose-effect relationship in music therapy [28]), but not too long to sustain parents'/guardians' motivation to participate in the study.

(2) Low-intensity music therapy: Improvisational music therapy sessions as above, but only once a week for five months.

(3) No music therapy. Standard care, available to all participants, will consist of three sessions of parent counselling (one session at baseline, one after two months, and a third one after five months) and any concomitant treatment outside the trial. Parent counselling sessions will be approximately 60 minutes and will be conducted by a music therapist and/or clinical psychologist experienced in the field of ASD. They will comprise supportive conversations with a focus on current concerns, problems, and difficulties arising from the child's problems, behaviour, and development over time, as well as providing information about autism, child development, and social communication as relevant to the families' everyday life situations. Any concomitant treatment or therapeutic interventions that participating children might receive will be recorded during assessment sessions before randomisation and after 2, 5, and 12 months, specifying the kind and amount or frequency of intervention.

Treatment guide and treatment fidelity

Music therapy and parent counselling sessions will both be provided in accordance with a treatment guide devised for this study in order to specify the treatment procedures and to allow for training of staff. Within this guide, the setting, general goals, and basic principles of the intervention will be described with examples. The guidelines are to be administered flexibly according to the requirements of each individual situation and needs of the client or

parent within the therapy process or counselling session, and have to be applied in combination with and relying on the clinical expertise of the therapist or counsellor. While the manual will help to ensure the trial's validity and replicability, it is also important to retain flexibility and openness to emerging procedures within music therapy in clinical practice [29]. Keeping enough "space" for flexible adaptation within the treatment guide according to the child's spontaneous social behaviours will also ensure that the intervention will be shaped in a way that is tailored to the individual strengths and needs of each child, thus addressing the great variability of developmental profiles present in children on the autistic spectrum. To determine if the treatment is conducted as intended, fidelity will be assessed as follows: After every session, the therapist/counsellor will document significant events, notable child/parent behaviours, and intervention techniques applied. In addition to these self-reports, all therapy sessions will be videotaped to allow for assessment by independent raters [30]. As in a previous music therapy RCT [31], adherence and competence will also be monitored and sustained through clinical supervision, using clinical notes and video recordings as needed.

Study design

The study will be a pragmatic international multicentre single-blind (assessor-blinded) randomised controlled trial with three parallel arms. After informed consent and baseline assessment, participants will be assigned to one of the two music therapy conditions or the standard care condition on an individual basis using a computer generated randomisation list. Allocation ratio to the three groups will be 1:1:2 so that power is maximised for the main comparison of any music therapy versus standard care. Randomisation will be made in blocks with random sequences of block sizes of 4 or 8 respectively (a separate list for each site) to avoid possible guessing of some allocations. When it is confirmed for a participant that eligibility criteria have been met, baseline data are complete, and informed consent has been given, the participant is formally enrolled and the randomisation code is revealed to the site investigator by an administrative person at the central randomisation office who has no contact to participants. An overview of the study design is shown in Figure 1.

Power calculation and sample size

A Cochrane review on music therapy for ASD found effect sizes (standardised mean differences) of $d = 0.50$ and 0.36 for gestural and verbal communicative skills, respectively [3], based on small trials. A larger trial on another behavioural intervention found a effect size of $d = 0.24$ on the ADOS scale [32]. Thus, an effect size in the small ($d = 0.20$) to medium ($d = 0.50$) range may be expected [33], corresponding to a 1 to 2.5 points difference on the ADOS scale with $SD = 5$ [32]. An effect size in this range would be clinically meaningful as the ADOS scale measures the core symptoms of ASD which are difficult to influence with any treatment. In light of the uncertainty around the true effect size and the difficulty of recruiting large samples, a group sequential design (GSD, [34]) will ultimately ensure 80% power (two-sided alpha 0.05) even for a small effect, while avoiding excessively large sample size if there is in fact a medium effect. We used the Lan-DeMets alpha spending function and Pocock boundary to make early stopping likely. Calculations and simulations were made for up to four equally spaced looks, using East 5.4 software by Cytel Inc., 2010. Table 1 shows that if there is a medium effect of music therapy, power at the first interim look (usable $N = 235$) will be 93%. Power will also be acceptable (76%) if the effect is slightly smaller than medium. If there is only a small effect size, power can still be retained by recruiting more participants. An independent data monitoring committee will perform the interim look. In the present project, we will aim to randomise $N = 300$ participants (150 to standard care and 75 to each type of music therapy) to account for possible drop-outs and clustering within sites [35]. The interim look will be taken at a fixed time point (see 2.3).

Table 1. Sample size and power under different scenarios

Raw difference on the ADOS scale (SD = 5)	Standardised effect size (Cohen's d)	Power at first interim look ¹	Test power over all 4 interim looks ²
2.5	0.5 (medium effect)	93%	100%
2	0.4	76%	100%
1.5	0.3	47%	99%
1	0.2 (small effect)	20%	80%

Note. Based on 10000 simulations for each scenario. ¹Usable N = 235 (300 randomised).

²Maximum usable N = 939.

Outcomes

The study will use assessments by blinded clinicians as well as reports by parents/guardians. Outcome variables will be assessed at several time points: after the baseline assessment (before randomisation), and two months (intermediate), five months (end of intervention), and twelve months after randomisation. Thus, close analysis of the mechanism of action (i.e. how long an intervention is required to begin to have an effect) and maintenance of any observed effects over a longer period of time will be possible [2].

Primary outcome: The ADOS is a validated scale widely used in research and clinical practice which has demonstrated inter-rater reliability, test-retest reliability, and internal validity [15]. As a semi-structured, standardised observation instrument, it addresses communication, social interaction, and play or imaginative use of materials through 28 to 31 specific behavioural criteria, depending on the child's expressive language level and chronological age [15]. The primary outcome will be the ADOS social communication algorithm score which has been used as an outcome measure in previous RCTs of interventions for autism [32,36]. To improve sensitivity to change, the scoring procedure will be modified as in an earlier RCT on treatment effects [32], i.e. the module applied to each child will be the same across assessment points to avoid discontinuity of scores, and the full range of scores will be retained [37]. To avoid bias in observation and assessment, assessors administering the instrument will be blinded to group allocation of the children to be assessed. Success of blinding will be verified by asking assessors whether or not they inadvertently found out about the child's allocation. The measure is most appropriate as a primary outcome because it addresses the core problems of the participants [32,38].

Secondary outcomes: To cover a multi-domain perspective, parents/guardians will be asked to complete the SRS [21]. The 65-item rating scale measures the severity of autism spectrum symptoms occurring in natural social settings, assessing social awareness, social information processing, capacity for reciprocal social communication, social anxiety/avoidance, and autistic preoccupations and traits. Defined as suitable for assessing treatment response [39], these five subscales seem appropriate as secondary outcome measures. The scale features high inter-rater and test-retest reliability as well as internal validity rates and may be completed in 15 to 20 minutes [40-42], thus easily applicable during appointments. Cost-effectiveness of music therapy will be compared to standard care. Cost will be measured as real resources used in treatment, in terms of personnel hours of work. Effectiveness is measured by ADOS, and cost-effectiveness ratios and incremental cost-effectiveness ratios for the different alternatives can be calculated. Gains for the general health care sector and society will be more long term, and can hardly be included in this project. However, some consideration will be made as to possible effects on school attainment. Costs can be made comparable across countries using purchasing power parity measures.

Statistical analyses

The primary analysis will be intention-to-treat. 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 the correlation among the repeated observations for each subject [43]. GEE analyses will also be used to examine dose-effect relationships and to explore possible confounding effects of site or relevant subgroups such as age or ASD subtype.

Discussion

The pragmatic nature of the trial and its high clinical applicability are reflected in its broad eligibility criteria, extended treatment duration, flexibility of music therapy interventions (improvisational music therapy conducted by experienced therapists in a typical setting), standard care as a control, and a distal primary endpoint reflecting patient relevance more than proximity to treatment [38,44]. The focus of pragmatic trials of effectiveness is to help users choose between options [44], and the present trial will enable informed evaluation by health services and service users as well as guiding clinical practice.

Findings of the present project will also be relevant for other fields where music therapy is applied, such as adult mental health [6,28], and for basic research into the musical qualities of early mother-infant communication providing a rationale for music therapy [14,25]. Music therapy in general is an intervention that focuses on developing social and emotional abilities, and ASD is a case in point because impairments in these abilities are central for ASD.

Possible extensions and pilot studies

While the overall protocol for the multicentre trial has been streamlined as much as possible to maximise feasibility, extensions are possible for individual sites. Site investigators may for example add proximal measures that allow examining the relationship between proximal and distal outcomes [38]. Specifically, the Korean site may examine joint attention using video recordings of music therapy sessions [11,13], and the Norwegian site may assess reciprocity of face-to-face communication using double video laboratory [45] and neurophysiological measures thought to be relevant in ASD [46] as separate but connected projects.

Pilot/feasibility studies are currently underway in Austria and the USA.

2.3. The project plan, project management, organisation and cooperation

► Project period, progress plan, main activities/milestones – see **grant application form**.

Host institution: The project will be able to draw upon Uni Research's many-faceted expertise in managing research projects. The Grieg Academy Music Therapy Research Centre (GAMUT), affiliated both to Uni Health (Uni Research's unit for health-related research) and the University of Bergen, provides an excellent context for conducting both quantitative and qualitative research. It offers an outstanding international network including established research collaboration with universities world-wide and the publication of two international music therapy journals. Uni Health is specialised in conducting health-related research, with a special focus on high-quality RCTs. It provides a strong infrastructure with its own methodological and statistical experts to support this project. The core team at the host institution will consist of the applicant (CG), a senior researcher (Karin Mössler), a project statistician (Jörg Assmus, also affiliated with the Centre for Clinical Research at Haukeland University Hospital, Bergen), GAMUT's research director (Brynjulf Stige), and a new postdoc or PhD. This team, experienced in music therapy research in general and high-quality RCTs of complex interventions in particular, will be responsible for the overall conduct and integrity of the study. Other departments at the host institution will include Uni Health's

Centre for Child and Adolescent Mental Health, with Maj-Britt Posserud, Gun Iversen, and Hanne Braarud as experts on ASD and assessment, and Uni Rokkan Centre with Jan Erik Askildsen for advice on health economic analyses. GAMUT has a pending application for a Centre of Excellence and if this is successful, the Bergen fMRI Group, with Karsten Specht as an expert on auditory perception, will conduct an extension as described above.

External collaboration partners, national and international: This project requires an international collaboration primarily to achieve the targeted sample size, but this will also enable cross-cultural comparison and generalisation of the results. Each of the seven sites (Australia, Austria, Brazil, Israel, Korea, Norway, USA) will aim to recruit at least 40-50 participants. The project brings together leading thinkers from these countries with top expertise in conducting and supervising clinical music therapy for children with ASD as well as an excellent basis in outcome research. Our partners in Australia, Brazil and Korea have earlier conducted small RCTs on music therapy for children with ASD showing indications of effectiveness. The University of Melbourne has successfully collaborated with us on a previous international multicentre RCT (NCT00137189, Research Council of Norway project no. 186025). All collaborators can draw on a strong network of clinicians to recruit participants and organise competent assessment. – In Norway, our network of collaborators will include a range of organisations, from clinical to research to user organisations. One key person in integrating the study in specialist clinical teams in the Bergen area is Ingvar Bjelland, chief psychiatrist at the Child and Adolescent Psychiatry Department at Haukeland University Hospital, Bergen. We will also attempt to recruit participants from other areas of Norway, especially from the densely populated Oslo area.

Supervisory committees: Three expert panels will be established to aid with the conduct of the trial: A Trial Steering Committee (TSC), consisting of leading members of each site with clinical and scientific expertise, will have regular meetings to closely supervise all aspects of the study, including any protocol amendments, progress of recruitment, and publication plan. The Scientific Advisory Board will function as a resource group of external experts who can, after an initial meeting, be consulted when necessary. The Data Monitoring Committee will have unblinded access to study data and will give recommendations for action to the TSC.

2.4. Budget – see grant application form

3. Key perspectives and compliance with strategic documents

3.1. Compliance with strategic documents

With the establishment of GAMUT in 2006, research relevant to music and health has become a new focus area of Uni Research. High-quality RCTs that can inform health services are the mainstay of Uni Health's research agenda.

3.2. Relevance and benefit to society

The project's societal impact will include increased knowledge on music therapy in a field where other therapies have failed, increased research expertise among the participating institutions and individuals, and in case of positive results new possibilities for improving the health of children with persistent mental health problems and for reducing society's burden related to it. All of these will apply on a local, national and international level.

3.3. Environmental impact – not applicable

3.4. Ethical perspectives

Approval by the responsible ethics committees will be secured before the start of enrolment at each site. Freely given, written informed consent will be obtained from participant's parents/guardians. Random allocation of participants to study groups is considered reasonable as no adverse effects are expected in any of the conditions. Inconveniences caused by the necessity to attend three weekly sessions of music therapy for the families assigned to this study group are considered tolerable in view of the anticipated benefit.

3.5. Gender issues (Recruitment of women, gender balance and gender perspectives)

In terms of participants, both boys and girls with ASD will be included and can be analysed separately because of the large sample size. In terms of researchers, our goal is to have 40-60% females. Presently, one senior researcher and three site investigators are female.

4. Dissemination and communication of results

4.1 Dissemination plan – see grant application form

4.2 Communication with users

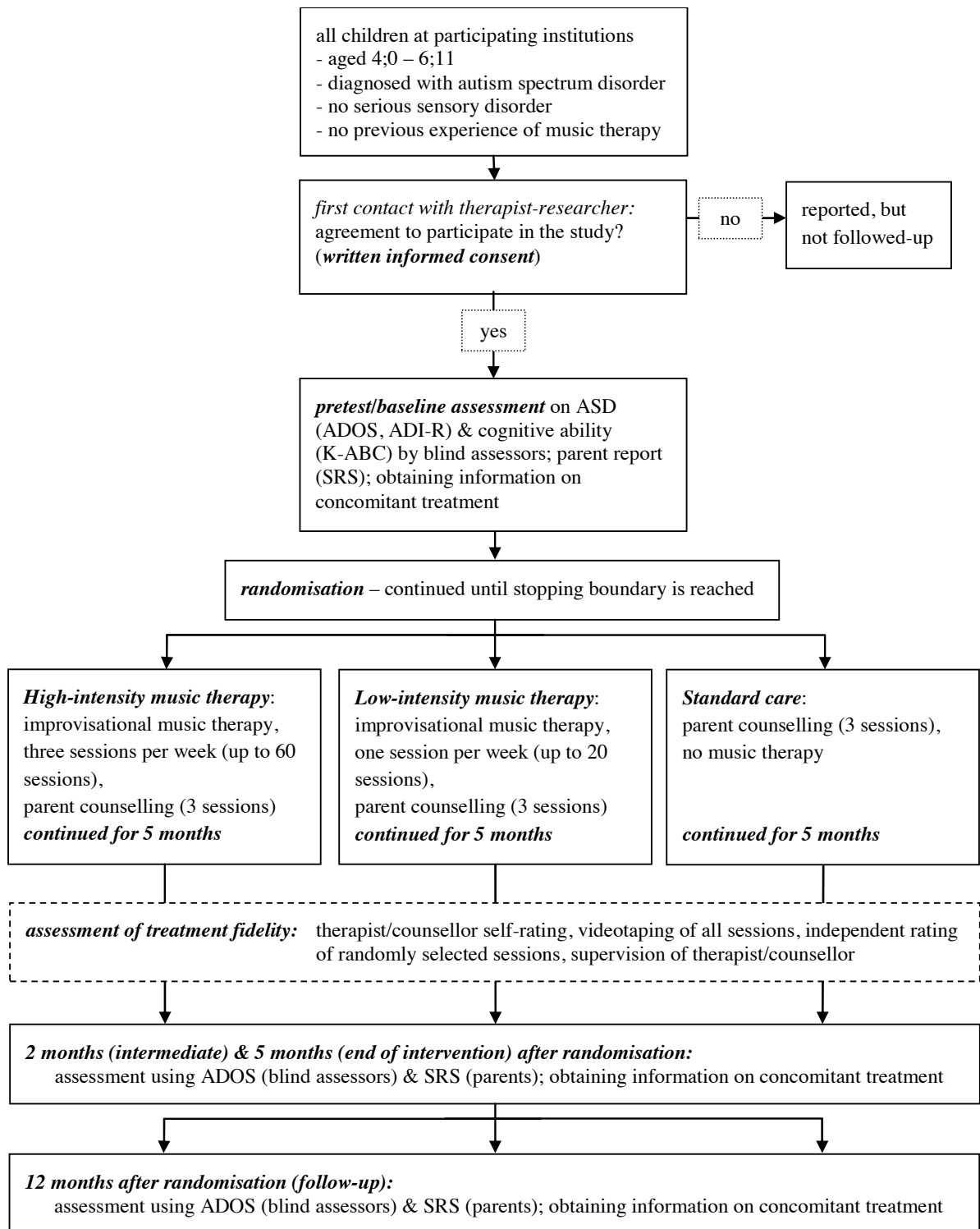
We will aim to include users in the development and conduct of the project as much as possible. The user organisations Autismforeningen in Norway and Österreichische Autistenhilfe in Austria have already been contacted, and we will aim to include similar user organisations in all countries involved. Their involvement will be relevant at all stages and will be vital to contribute to the success of the project as well as to its relevance and impact.

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Figure 1: Flow chart of the study design



Abbreviations: ASD – autism spectrum disorders; ADOS – Autism Diagnostic Observation Schedule; ADI-R – Autism Diagnostic Interview-Revised; K-ABC – Kaufman Assessment Battery for Children; SRS – Social Responsiveness Scale.