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Efficacy of Parent- mediated communication-focused treatment in toddlers with autism (PACT) delivered via videoconferencing: a randomised controlled trial study protocol

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Abstract

Intervention in the preschool period is currently recommended for Autism Spectrum Disorder (ASD). Therapies delivered by parents are particularly suitable for young children. PACT (Preschool Autism Communication Trial) is the only parent-mediated therapy that has shown a significant and sustained impact on autism symptom reduction. However, the access to such evidence-based therapies for families is limited due to autism centers located in large urban area. Using videoconferencing to deliver PACT training to parent may improve accessibility for families living in underserved areas.

This single-blind randomized controlled trial, involving six sites in France, will investigate the efficacy of a videoconferencing-based, parent-mediated PACT therapy on autism symptoms, over a 12 months period. It will compare PACT with treatment as usual (TAU) with TAU only in a cohort of 238 toddlers (119 per group) aged 18 to 36 months at inclusion and living with their families more than 40 min away from the specialist centres for autism. Primary outcome will be the change of overall autism score on the Autism Diagnostic Observation Scale (ADOS) at 12 months. Secondary outcomes will measure change in child skills, child functioning, impact on parents (stress, health, priorities) and implementation characteristics.

Repeated measures analysis will be used to test the effect of PACT intervention on the overall ADOS module 1 score over the 12-month study period. Linear mixed models will be used with time, treatment allocation and the interaction between treatment and time as fixed effects and individual variation as random effect.

Article Summary

Strengths and limitations of this study

- Large multicentre RCT in children with ASD under 3 years old
- Assessment partially done by videoconferencing and based on video material sent by parents
- Recruitment targeted to children living in underserved area
- Short term effect of the intervention will be assessed at 12 months (end of the intervention)
- Owing to the nature of the intervention, parents of the children and PACT therapists cannot be blind to the allocation group.

Keys Words: Early intervention, Autism spectrum Disorder, PACT, videoconferencing, parent-mediated therapy, video-feedback, Health Services Accessibility

Trial registration: ClinicalTrials.gov Identifier: NCT04244721

Introduction

Rationale & background

Autism Spectrum disorder (ASD) is a common neurodevelopmental disorder with a population prevalence of 1-1.5% that can cause significant lifelong disability [1–3] and burden for families and caregivers [4]. Diagnosis is possible as early as 18 months years old [5]. Current evidence suggests that interventions delivered in the early developmental period before the age of 3 years have the potential for maximal impact on autism symptom severity[6–8].

Therapies can be delivered by therapists, teachers and parents [9]. For preschool children with ASD, parent-mediated therapies can empower parents to face challenging social interaction with their children [8,10]. Among the different parent-mediated therapies, PACT (Pre-school Autism Communication therapy) is the only therapy to have shown a significant short and long-term effect in children aged from 2 to 9 years in a large UK cohort (N=152)[9,11,12]. In PACT, parents are guided by a therapist via video feedback to optimize their interactive behaviours in order to enhance parent-child dyadic interaction, which in turn will impact on child language, communication and autism symptoms (PACT reference) [13]. At 13 months, PACT showed a statistically significant reduction in the severity of symptoms and showed an increase in parental communication synchrony with the child, child communication initiations with parents and for parent-child shared attention [11].The follow-up study demonstrated a reduction in autism symptom severity PACT therapy five years after the PACT intervention [14]. The symptom severity as measured by the Autism diagnostic Observation Schedule version 2 (ADOS-2) was significantly reduced between both groups (Effect size=0.55, 95% CI 0.14 to 0.91, p=0·004)[12]. A mechanistic study also confirmed that the distal effect of PACT therapy on autism severity measured by ADOS was mediated by the improvement of child communication initiatives, which in turn was mediated by improved parent-child synchrony [15].

Availability of PACT therapy is limited; even more so in rural setting or in regions away from specialist centres. Training parents to PACT via videoconferencing conducted by trained therapists may be a viable alternative to make such therapies available to families living far from autism centers. Previous studies have shown that it is possible to successfully provide parent-mediated therapy in autism by videoconference [16,17]. The team who developed the PACT therapy has a positive experience of parent guidance by videoconferencing (personal communication). Indeed, remote PACT was partly used, during some session, in a recent RCT [18]. However, PACT has never been evaluated when exclusively delivered by videoconference. The barriers and facilitators of videoconferencing therapy are not sufficiently well known, and hence it is also essential to address them properly [19,20].

The proposed protocol is for a large RCT in children under 3 years with ASD to evaluate the effectiveness of PACT therapy delivered to parents by videoconference. A significant effect would justify and facilitate the routine use of videoconferencing therapy in early intervention and improve the dissemination of this evidence-based practice.

The hypothesis is that PACT intervention + TAU (Treatment As Usual) will have a superior efficacy on child autism symptom severity as compared to TAU alone.

Objectives

Our primary objective will be to test the efficacy of a parent-mediated PACT therapy, in which professionals guide parents via videoconferencing, over a 12-months period, on overall autistic symptoms measured with a standardized measure, the Autism Diagnostic Observation Schedule (ADOS), in children with ASD aged from 18 to 36 months at inclusion, living in undeserved area.

Our secondary objectives, at the child level, will be to evaluate the development of socio-communicative interactions in naturalistic environment, language, initiatives in the communication and daily adaptive behaviour. At the parent level, we will evaluate the intervention effects on stress, health and family priorities.

The implementation of the therapy will be evaluated through the adherence of the professionals and of the parents to the PACT, and through parents and professionals' acceptability and feasibility of the PACT sessions.

Method

Study design (see figure 1 flow-chart of the study)

Our study is a multicentre, prospective, 2 parallel groups, 1:1 ratio, single blind Randomised controlled trial (RCT) comparing PACT intervention + Treatment As Usual (TAU) to TAU alone. Evaluation is based on a mixed-method approach combining quantitative and qualitative studies [21,22].

A qualitative study will be conducted to capture further experience of the implementation of the intervention and causal pathway of effectiveness or ineffectiveness according to the therapists and the parents.

Setting

We will run this trial in six academic centres in France. These centres are located in child and adolescent public hospitals. All centres have a unit for ASD diagnosis and assessment and a distinct unit for intervention where therapists have been trained in PACT and can provide PACT via videoconferencing. Children they care for come from a French-speaking population including socioeconomically disadvantaged groups.

Population

Inclusion criteria

Children will be included if they meet the following criteria:
i) aged between 18-36 months old at inclusion
ii) meet criteria for autism spectrum disorder using the two gold standard instruments ADOS-2 (Autism diagnostic Observation Schedule -2) and ADI-R (Autism Diagnostic Interview-Revised) [23–25]. For inclusion into the study, the severity score comparison (CSS) on ADOS-2 will have to be greater or equal to 4. The score on the ADI-R algorithm for toddlers will have to be greater or equal to 11 [26]. The

diagnosis will be confirmed by a multidisciplinary team specialised in Autism Spectrum Disorder diagnostic and assessment based in the academic department of hospital.
iii) have a non-verbal age equal or above 12 months on the Mullen Scale of Early learning (MSEL) [27].
iiii) live more than 40 minutes away from a Center for Resources in Autism (regional center)

Referent parents will be included if they meet the following criteria:
ii) speak French with their children
iii) are able to do videoconferencing with therapists from the center (assessed through the conduct of the Vineland Assessment Behavioral Scale by videoconferencing)

Exclusion criteria

Exclusion criteria will be as follows for the child:
i)a twin brother or sister with ASD or a brother or sister having already been included in the study
ii) diagnosed with epilepsy requiring medication
iii) have a severe hearing or visual impairment
iv) an identification of a genetic anomaly which may impact on their ability to participate in the intervention or on data validity (determined by the principal investigator on a case-by-case basis).

Exclusion criteria will be as follows for the referent parents (at least one parent with):
i) severe hearing or visual impairment
ii) severe psychiatric disorder
iii) unstable somatic disorders preventing participation in the intervention
iv) lack of internet provision
v) not available for regular intervention and follow-up
vi) opposition of one parent to the child's participation in the study

Intervention conducted in the experimental group

Eligibility criteria for PACT therapist and adherence

Therapists may include will be speech language pathologists, Occupational therapists, Clinical nurse, psychologists or child and adolescent psychiatrist, all specialised in autism. The therapists have already received formal training and supervision in PACT with the team who developed this training [11,28]. The lead therapist will organize regular meeting between therapists of all centers, with scoring and feedback of videotaped therapy session of the study, in order to maintain a high fidelity to the therapy.

PACT treatment principles

As previously described [18], parents will be trained, via video-feedback, to identify and set up key strategies facilitating the socio-communicative interactions between their child and themselves. Parent will also be encouraged to use PACT every day outside the training session at least half an hour per day. The therapy follows a six-staged approach based on child developmental progression and strategies for setting up fundamental skills for the socio-communicative development as shared

attention. The 2 first stages aim to increase parent's identification of child focus and interest, synchrony, responsiveness and sensitivity to the child interest and communication. The third and 4th stages are targeted towards developing expression and comprehension of the child by commenting and modelling with a language adapted to the child's one. The child initiative in communication is also improved through the means of different strategies such as anticipation and routine. The 2 last stages aim to develop conversation and expansion of language for verbal children. Progression from one stage to the other depends on predefined criteria.

Based on the protocol of the first PACT RCT, parents will receive 18 sessions of training in PACT with the therapist over the 12 months (Green, 2010; Pickles, 2016): 1 hour session every fortnight during 6 months to learn PACT strategies then, 1 hour session per month over the last 6 months to maintain the capacity of parents to deliver the strategies.

Therapist will train only one parent per family and maintain fidelity to the therapy manual. The "referent parent" will have to be designated before the randomisation of the child. If the referent become unavailable, the therapy will stop or will continue with the other parent if possible and will be reported.

Parent training session with the professional via videoconferencing

Before each session, parent will be asked to send a10 minute video of an interaction with his/ her child, to the therapist via a secure cloud link. During the videoconferencing session (as in face to face), referent parent will begin with a 5 minutes discussion about progress since the last session. The therapist will then share his/her screen and watch together with the parent the home-based 10 minutes video. They will identify, review and discuss specific clips that demonstrate accomplishment of therapy goals for each stage of the programme. The therapist's role will be to guide parents to identify their successful strategies and responses (i.e episodes of engagement and/ or mutual sharing with their child). Parents will be helped to reflect on their role in enhancing interaction and to identify new intervention goals.

Parent PACT implementation in daily life outside the therapy session

At the end of each session, the therapist will support the parent in setting 2-3 goals, based on the strategies identified during the session. The therapist will encourage the parents to practice the strategies for the next session and will discuss opportunities to achieve these goals in daily routine at home for at least ½ hours per day. Parents will be guided to embed PACT strategies in diverse everyday routines in different contexts. As therapy progresses, parents will be asked to send 10-minutes home videos of short daily routines in different contexts.

Treatment as usual (TAU) and 2 follow-up consultations on ASD and its management

Regardless of group allocation, parents will receive treatment as usual (TAU) consisting in an information about ASD, its management, and educational support for nursery and preschool placement. Parents will be referred to any relevant care available in the community (e.g.: Speech language pathologist (SLP), occupational therapist, educator, behavioural psychologist, psychiatrist). TAU received during the course of the study will be described in both groups.

Regardless of group allocation, a psychiatrist or a psychologist from each autism centers will provide two supplementary 45 minutes follow-up consultations conducted by videoconferencing, at 3 and 6 months after inclusion. They will follow an interview guide. Three thematic areas will be systematically discussed with the parents: ASD information, access to treatment in the community, support for school or nursery. These 2 follow-up consultations will ensure that all parents of both groups have received homogeneous key information on ASD and its management.

Avoidance of contamination

PACT is not disseminated and implement in the community, in particular in underserved area. However, PACT that might be received in the community will be reported (parent-report) [29].

Research assessors will be separate to the therapists and will be located and supervised separately in each center.

Professionals doing the 2-follow-up consultation on ASD and its management will not be trained to the PACT therapy nor be implicated in the research assessment.

Measures

Primary outcome

To assess autism severity

Autism Diagnostic Observation Schedule (ADOS-2) is a semi-structured, researcher-child interaction based, standardized observational assessment, in communication, play, imaginative skills, and repetitive behaviors [30,31]. It is a widely used scale in the field of ASD research with good psychometric properties, recommended for the diagnosis of ASD and assessment of core autistic symptoms [32].

At inclusion and after 12 months, we will use only the module 1, for 18 months old age and older children able to use no or few words.

There is a good Interrater reliability for Module 1 items [33,34] . Internal consistency Cronbach's alpha coefficients was high in original study [32]. This scale has also shown that it can measure change in autism severity [31,35,36].

ADOS-2 is composed of different items scored 0 to 3 or 0 to 2. Item A1 code the level of language, from the severity "the child is using regular use of statements with two or more words" (code 0) to "the child has no spontaneous use of approximate words or words" (code 4). When the language is not enough developed (A1 ≥ 3), the two items measuring the particularity of the language in the algorithm (item A3 speech abnormalities, item A5 stereotyped language) will be scored 3 (worst value) (as already done in Green and collaborators in 2010 [11]). The minimum overall ADOS-2 module 1 raw score will be 0 and the maximum score 42. A higher score means more autistic symptoms.

Our primary outcome will be the change between baseline and 12 month in the overall raw score in reciprocal socio-communicative interactions and repetitive and restrictive behaviors in line with the DSM-V [30,37]

Researcher will be trained to achieve recognized standards. Regular reliability meetings of all researchers with discrepant ratings being addressed to maintain researcher calibration.

Secondary outcomes *(See appendix 1 for more detailed)*

To assess social communication and interaction in the natural setting of parent-child interaction at home :

-*Brief Observation of Social Communication Change (BOSCC)[38]*.

To assess dyadic communication in the natural setting of parent-child interaction at home:

-*Dyadic Communication Measure for Autism (DCMA)* [28].

To assess child cognitive development:

-*Mullen Scales of Early Learning (MSEL) [27]*

To assess child language development:

-"Development of expressive language", (*Development du Language de Production In french_DLPF*)[39].

To assess Adaptative behavior of the child:

-*Vineland Adaptive Behaviors Scales second version (VABS-2)* [40]

To assess Parent's Stress, health, priorities and experience of the family:

-*Autism Family Experience (AFEQ)* [41]

-*ISP (Parental stress index)* [42].

-*General Health Questionnaire (GHQ-28)* [43]

To assess implementation of the intervention:

- *PACT Fidelity Rating Scale*

-Number of training session done

-Quality of videoconferencing during each session

-Parents acceptability of videoconferencing training and implementation of PACT at home (self-report on Likert-scale)

-Number of hours per day using PACT at home at 12 months

-Parent's qualitative PACT adherence coded with DCMA on the 12 minutes home child-parent interaction

Participants timeline (see also figure 1)

Toddlers will be addressed by health professionals for suspected ASD and possibility to be enrolled in this study. We will receive the family, complete the ADI-R during the first meeting, and check the criteria for eligibility. We will then propose the complementary assessments ADOS, Mullen with the child and Vineland by videoconferencing with the parent, to complete the criteria for eligibility. When toddlers and families meet the criteria for participation, parents will be informed in detail about the study and possibility of an intervention with PACT or TAU only according to the randomisation. They will be asked to sign written informed consent if they agree to participate to the study after one week of reflection.

The "referent parent" will be decided before the randomisation. Children will be subsequently randomised into intervention or control group. Parents will be informed of the result of the randomisation and complete the assessment.

Assignment of intervention

Allocation sequence generation and randomisation

All eligible toddlers, with parental consent, will be assigned to the 2 study groups in a 1:1 ratio using the minimization method with the following stratification factors: the centre, the children's age, level of language (according to the ADOS2 scale) and gender. To ensure allocation concealment, a minimization algorithm with a .90 random element will be used and known only by the statistician (AD). The randomisation is centralized.

Blinding

Owing to the nature of the intervention, parents and PACT therapists cannot be blind to the allocation group. PACT therapists will not be involved in the diagnosis or assessment. An assessor blind to the allocation group will administer every assessment. Data manager and biostatistician will be blinded to the allocation groups.

Data collection and management

Data collection

Data will be collected through standardized observations done by a researcher blind of the allocation and questionnaires and interviews completed by parents. We will be particularly vigilant about the measurement accuracy of the first criterion of judgement as described in the paragraph on ADOS-2.

Participation retention and follow-up

Children of both groups will benefit from early diagnosis and assessment and will have the same follow-up evaluations over the 1-year study period in the diagnostic units. That would promote participant retention and complete follow-up. Any discontinuation of study participation will be collected with the reason.

Data Management

The study data will be collected on a secure electronic case report form (eCRF) that will be available at each centre through an internet portal. No personal identifying information will be mentioned on the eCRF. Each subject included in the study will be assigned a unique identification number.

All study data will be stored securely in the Academic Hospital of Lyon. All electronic data will be secured on a password-protected laptop. Paper-based study documents will be stored in a secure filing cabinet at each centre. Access to these files will be limited to research staff involved in the study.

The eCRF will only include the data necessary for the analysis to be reported in a scientific publication.

Statistical analysis

Simple size calculation

On the basis of the findings of PACT Trial (Green, 2010), we have powered the study to be able to detect a difference in change overall ADOS score of 2 points. The group difference in mean change between baseline and month 12 was -1 point for ADOS social affect score (mean change=2.9, SD=3.9 in TAU group and mean change=-3.9, SD=4.7 in PACT+TAU group) and -0.5 points for ADOS restricted and repetitive behaviors score (mean change=2.9, SD=3.9 in TAU group and mean change=-3.9, SD=4.7 in PACT+TAU group). The pre and post measures were correlated at 0.67. Therefore, the most conservative values were fixed for ADOS standard deviation and for correlation among the repeated measures from a single participant. A target of 238 subjects (119 subjects per treatment arm) was planned to be randomized in the trial. Assuming a 2-point difference in favor of the PACT+TAU compared with TAU, a standard deviation of 5, a correlation between subsequent visits of 0.5, a drop-out rate of 20%, and a two-sided significance level of 0.05, the planned sample size would provide about 80% power for the study.

Feasibility of recruitment

A strong partnership with ASD orientation platforms, recently implanted in France, a broad communication (meeting, mail, flyers) to healthcare professionals (Speech pathologist, Occupational therapist, therapist, paediatrician, general practitioner) family associations and other stakeholders will allow to reach the sample size over 2 years.

Statistical analysis

A full statistical analysis plan will be finalized prior to database lock. Statistical analysis and results will be reported at 12 months endpoint in accordance with the CONSORT 2010 statement. No interim analysis will be scheduled. All the statistical analysis will be carried out according the intention to treat principle using SAS statistical software (SAS Institute Inc., Cary, NC, USA).

Baseline characteristics will be presented in each group.

Summary statistics will be presented for process variables (number of PACT sessions, quality of videoconferencing per session, acceptability and satisfaction of PACT intervention, number of hours declared to be realized with the child) to show the feasibility and acceptability of PACT implementation in the intervention group.

The pattern of missing data will be investigated (number and mechanism of missingness). Missing data strategies can be applied and sensitivity analysis of different strategies (simple or multiple imputation) will be conducted.

A repeated measures analysis will be used to test the effect of PACT intervention on overall ADOS module 1 score over the 12-month study period. A linear mixed model will be run with the overall ADOS score as the dependent variable and including time (baseline, month 12), treatment (TAU or TAU+PACT) and the interaction between treatment and time as fixed effects and patient as random effect. Model will be adjusted for stratification factors (centre, age, level of language (item A1 ADOS-2) and gender) and baseline variables that showed evidence of treatment group imbalance. Time will be represented by dummy variable. Model assumption will be verified according to residual analysis. If most of assumptions are not met other alternative such as transformation for ADOS overall raw score can be examined. Sensitivity analyses like complete case and per-protocol analysis can be performed to assess the robustness of the results to protocol deviations. In complete case analysis, only patient with primary outcome documented will be analyzed. In per-protocol participants who violate the protocol will be excluded from the analysis.

All the secondary outcomes (Overall total score of the BOSCC, Initiative of communication and synchrony measured with the DCMA, overall raw score of the MSEL in receptive and expressive language, overall score in expressive language of the DLFP, overall raw score, Communicative and social raw score at the VABS, Parental Stress Indice, Parent General Health score, AFEQ score) will be analyzed in a similar way using when appropriate linear or generalized linear mixed models. Tobit models should be used to address potential floor effects.

We will finally explore the parent's and children's characteristics, moderating the implementation and efficacy of this therapy. We will also test the previously found mediators implicated in the efficacy of this therapy (Pickles, 2017).

Qualitative analysis of barriers and facilitators of implementation

Based on the speech of the parents and of the therapists we will describe the facilitators and barriers of the implementation of video-conferencing PACT.

The data will be collected through semi-structured interview and will be analysed with the classical technique of Interpretative Phenomenological Analysis (IPA) [44] Population selection will follow the rules of the purposive sampling and will allow a maximal variation of the sample [45]. An estimation of 30-60 parents will be necessary to reach data saturation based on previous studies [46–48]. The total number of therapists (around 7-8) will be interviewed. During the 40-60 minutes interview, we will explore different area in links with barriers and obstacles about learning and implementing PACT by videoconferencing. A guide for the interview will be elaborated in the initial phase of the project

based on first interviews. Interview will be recorded, and the verbatim will be transcribed to analysis the entirely communication of the participant.

Data from the quantitative and qualitative sources in the process evaluation will analysed separately. Then, the results of the qualitative study will be integrated with the quantitative results to optimize the findings [49].

Monitoring

Dr Marie-Maude Geoffray (IP) Investigators associated, methodologists, statistician, parent representatives and associate researcher composed the trial steering committee (TSC). The TSC is independent of sponsor and funders and have no competing interests. The TSC has developed the study protocol and is responsible for data collection, management, publications and the final data set.

The coordinating center is independent from the centers for investigation.

According to the French law, the study required a formal data monitoring who will be done by the sponsor. Annual report to the funders will be also ensured.

Adverse effect

No specific suffer harm from trial participation is anticipated.

However, as required by the French law, adverse events will be collected all along the study and reported in the eCRF section. Description of the event, date of occurrence, intensity, severity, accountability will be reported. Outcomes of this event and action taken after its report will also be concealed.

We anticipate that the early assessment, follow-up consultation on ASD and its management will help and support the both groups during the post-diagnosis period. Hence, no post-trial care is planned.

Trial status

The trial status is currently Recruiting. The study has started the 30th June 30, 2020.

Ethics and *Dissemination:* This study is approved by the French Institutional Review Board (reference No 2018-A02516-49). The results will be disseminated via peer-reviewed journals. It will also disseminate via national and international, general and specialist, meeting and through the parent association (https://Bleunetwork.fr; https://autisme-ambitionavenir.com; desailespourgrandir.org). An individual feedback to the participant will be done through a regular newsletter. We will adhere to defined authorship criteria as per the International Committee of Medical Journal Editors.

Author contribution: MMG and ST, PO, LJ conceived and design the project, and MMG is leading the coordination of the trial. MMG, LJ and PO drafted the protocol and procured the project funding. LJ and MMG are responsible for study implementation, staff training and supervision. PO, ST, AD, AZ contributed to the sample size calculation, the randomisation procedure and the statistical plan, and are responsible for data management, randomisation and statistical analysis. JG contributed to the protocol. ARL contributed to the protocol of the qualitative study. CA and NG to the PACT training and supervision of the team. MMG, MJO, LJ, AA, AJ, AB, CS, TM, TD are responsible for recruitment

and evaluation of children. SG contributed to draft the paper. All authors critically reviewed and approved the final version of the manuscript.

IFPAD Study group: Mrs Pauline Auphan (psychologist), Mrs Laeticia Bouveret (research assistant), Mrs Laurie Herman (research assistant), Dr Anne-Laure Toureille (PACT trainer), Mrs Lucie Jansen (PACT trainer), Dr Sandrine Sonié (CRA Lyon), Pr.Mario Speranza (CHU Versaille), Pr. Bruno Falissard (Paris), Pr Nicolas Georgieff (Lyon), Dr Matias Winter (HCL), Mrs Nadège Alloisio (parent association), Mr Chams-Ddine BELKHAYAT (parent association).

Patient and Public Involvement subsection: Mrs Alloisio (Association AAA https://autisme-ambitionavenir.com) and Mr Belkhayat (association https://bleunetwork.fr/pro) are parent of a child with autism and represents two different association. They are part of the steering committee.

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Data sharing statement: The trial statisticians will have access to the data set for the analysis of trial outcomes. The PI will have access to the data and will take full responsibility for the analysis and publication of the results. Once the main analyses have been undertaken, data will be available to principal and other investigators subject to approval of data analysis plans by the steering committee.

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Figure 1. Flow-chart of the study.

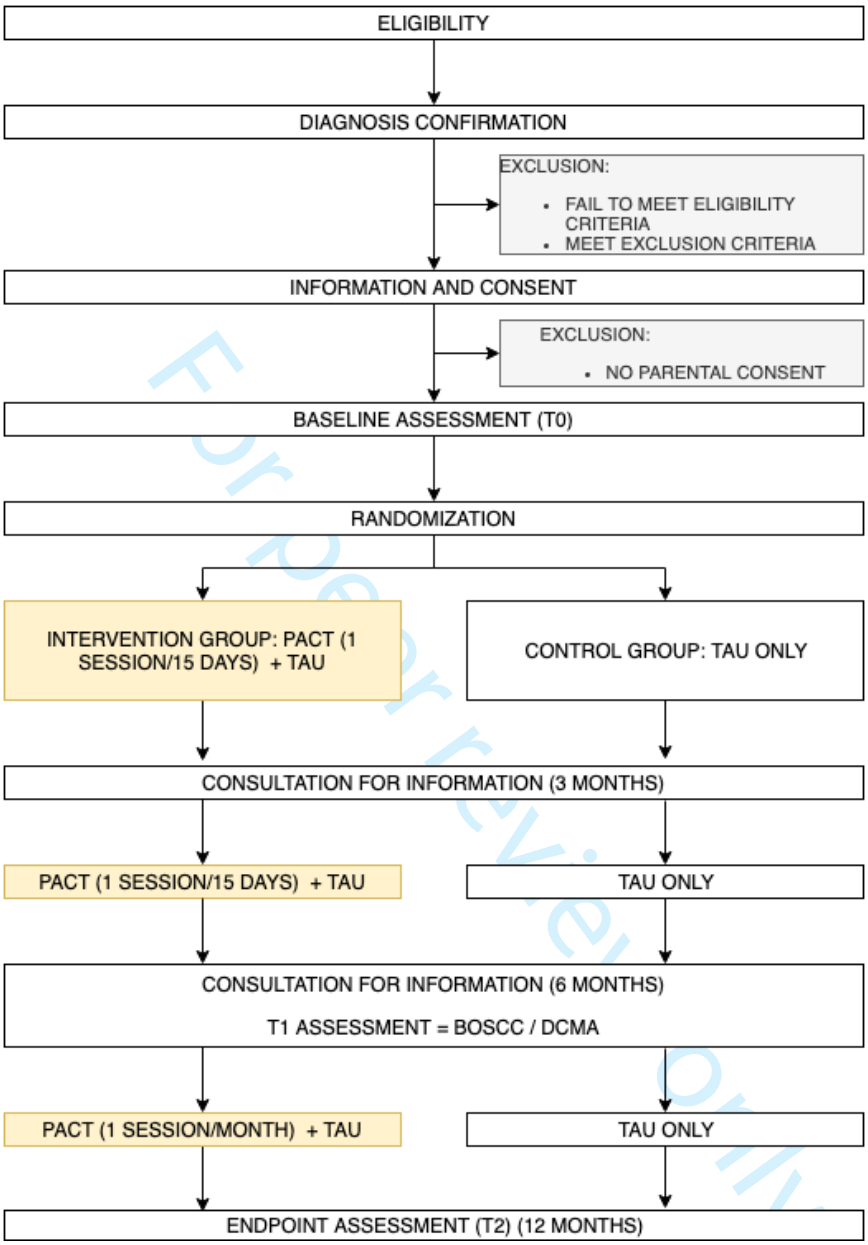

Figure 1. Schedule of enrolment, interventions and assessments (SPIRIT)

Time point	**Enrolment**	**T0 baseline**	**T1 6 months**	**T2 12 months**
Eligibility screen				
DSM-5 criteria	x			
ADOS-2	x			
ADI-R for toddlers	x			
Nonverbal skills MSEL	x			
Adaptative behavioral level : VABS 2 coded based on an interview done by videoconferencing with parents	x			
Informed consent	x			
Allocation		x		
Intervention				
PACT training (1h/15 days during 6 months then 1h/month during 6 months) + daily practice at home		→	→	→
Treatment as usual		→	→	→
Assessment				
Sociodemographic data		x		x
Autistic symptoms: ADOS-2 (primary outcome)		x		x
Change in socio-communicative interactions: BOSCC Played-based interaction between carer and child at home		x	x	x
Communication Synchronization and initiatives: DCMA at home		x	x	x
Expressive and receptive language Mullen scale		x		x
Daily language DLFP		x		x
Adaptative behavioral level: VABS 2 by video-conferencing		x		x
Parental stress index: ISP-short form		x		x
General parents health : GHQ-28		x		x
Parents quality of life and priorities. AFEQ		x		x
Acceptability of PACT intervention and TAU. (Linkert scale)				x
Implementation: Number of PACT training session with the professionnal Mean of quality of videoconferencing collected after each session Number of hours declared by parents using PACT at home				x x x

Qualitative interview (around 35 parents in the PACT intervention group) and all the therapists				x

Figure 3- WHO trial registration data set

Data category	**Information**
Primary registry and trial identifying number	clinicaltrials.gov : NCT04244721
Date of registration in primary registry	January 28, 2020
Secondary identifying numbers	2018-A02516-49
Source of monetary or material support	This study is supported by a grant from the Programme Hospitalier de Recherche Clinique inter-régional Rhône Alpes (PHRCI-15-065) from the AURA region and a grant by the Caisse Nationale de solidarité pour l'autonomie (CNSA) as part of the call for projects launched for IReSP (Institut de Recherche en Santé Publique) in 2016 in collaboration with the Institut national de la santé et de la recherche médicale (Inserm) (IReSP-17-Autisme3-16).
Primary sponsor	Centre Hospitalier Le Vinatier, Bron, France
Secondary sponsor	Not applicable
Contact for public queries	Marie-Maude Geoffray (PI), email: marie-maude.geoffray @ch-le-vinatier.fr Lucie Jurek, email : lucie.jurek@ch-le-vinatier.fr Pauline Occelli, email: pauline.occelli@chu-lyon.fr
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Public title	Efficacy of a parent- mediated communication-focused treatment in toddler with autism (PACT)when parents trained by videoconference: a randomised controlled trial study protocol
Scientific title	Efficacy of a parent- mediated communication-focused treatment in toddler with autism (PACT)when parents trained by videoconference: a randomised controlled trial study protocol
Countries of recruitment	France

Data category	Information
Health condition or problem studied	Autism spectrum disorder (ASD)
Interventions	*Intervention*: PACT for toddlers and young children with ASD *Description*: PACT delivered by the parent trained remotely by therapists 1 hour per 2-weeks during 6 months and 1 hour per month the following 6 months. *Control*: care available in the community, i. e. consultations with a psychologist or child and adolescent psychiatrist, speech and language therapy, occupational therapy, individual or group psychotherapy.
Key inclusion and exclusion criteria	*Age*: between 18 and 36 months *Sex*: male or female *Inclusion criteria*: diagnosis of ASD (Diagnosis and Statistical Manual of Mental Disorders, Fifth Edition, and Autism Diagnosis Observation Schedule), child will have a non-verbal age above 12 months on the Mullen Scale of Early learning, family living further than 40 min away from an ASD specialized center. *Exclusion criteria*: serious neurological or physical condition, family unavailable for a regular follow-up.
Study type	Interventional *Allocation*: randomized 1:1; parallel assignment; blinding: assessor blind
Date of first enrolment	15th July 2020
Target sample size	238
Recruitment Status	Recruiting
Primary outcome	Change in ADOS-2 module 1 standardized score at 12 months
Key secondary outcomes	Child development, child adaptative behavior, child socio-communicative abilities, quality of life of parents, parental stress, obstacle and facilitators of the intervention model.

Appendix 1: Secondary outcomes

The secondary outcomes are measured using standardized coding assessments of naturalistic observational videos (BOSCC, DCMA), performance-based standardized tests (MSEL), and parent-report-based standardized tests (VABS, DLFP, AFEQ, ISP, GHQ).

To assess social communication and interaction in the natural setting of parent-child interaction at home

Brief Observation of Social Communication Change (BOSCC) measures the same construct as the ADOS. It is a researcher coding assessment of autism symptoms based on child-adult interaction. It has good fidelity and results showed good construct validity [1]. The validity to measure the change was analysed in two small populations (N=20-50) and will have to be reanalysed in further trials [36,37]. It has the advantage to allow measure Dyadic interaction across different contexts. It was translated and retro-translated for the purpose of a previous study [2]

The scale is composed of 12 items scored from 0 to 5 according to the BOSCC algorithm. There is an overall score of 0 to 60 measuring core autism symptoms. A higher score indicates more autistic symptoms.

In the current study, a 12 minutes home-video will be recorded by the parents themselves. The parent will be provided with a simple protocol to follow using a standardized set of toys. The standardized set of toys given to the families at each time of assessment will include a cause and effect toy, shape sorter or puzzle, construction toys, miniature pretend play. The protocol includes 10 minutes time of natural play with children with the set of standardized toys and 2 minutes with bubbles play. A first unscored videotape would be done on the center (at T0) to train the parents to video record based on the protocol. In the week following, the parent will videotape at home a child-parent interaction according to the protocol with the standardized set of toys and send the video to the researchers via a secure platform. Professional may make up to two further requests if the video received is judged to not be of adequate quality. If the parent isn't able to send a usable video according to the protocol, the researcher completes a home visit to demonstrate and help the parent to do the video the third time. Two further videos will be done at home at 6 months (T1) and 12 months (T2) in order to assess Social communication interaction in a naturalistic setting.

All the video will be scored by trained researchers.

The same parent called the "referent parent" will be videotaped by a relative at each time of assessment. He/ she will be identified before the randomisation. It will also be the parent who receive PACT therapy if in the group of PACT intervention.

To assess dyadic communication in the natural setting of parent-child interaction at home

The *Dyadic Communication Measure for Autism (DCMA)* is a direct observation instrument of the communication between a parent and a child with autism [3]. It rates parental and child mutual shared attention, child communication (initiation and response) and parental communication style (synchronous/asynchronous).

Independent inter-rated reliability on synchrony has been reported and is good [3]. It was translated and retro-translated for the purpose of a previous study [2]

It can be used to code a number of acts of communication per timepoint. A higher score indicates better communication.

Coding will be done on the same 12 minutes home parent-child video described above in BOSCC.

To assess child cognitive development

The *Mullen Scales of Early Learning (MSEL)* is a direct observation standardized tool from birth to 68 months [4]. It measures verbal and non-verbal skills of the children, according to the success or failure in tasks of the MSEL protocol delivered by a trained researcher. The MSEL has been used extensively as a discriminative and evaluative measure in children with autism spectrum disorder, Fragile X syndrome, and speech delays [5–7]

Internal consistency and concurrent validity are good [4]. It was translated and retro-translated for the purpose of a previous study [2]

Scoring varies by item from 2-point scale (0 = does not meet criteria to 1 = meets criteria) to a 6-point scale. Results for each scale are described by T scores (M = 50, SD = 10), percentile ranks, and age equivalents. An overall score is also measured (M=100, SD=15). A higher score means better skills.

To assess child language development

The "development of expressive language", a standardised French Scale (Development du Language de Production In french_DLPF), is based on a self-administered parent-report [8]. This measure is standardised for age. Only the level 4 of the DLPF will be administered at each assessment to have a continuous score on expressive language.

The DLFP was validated in a study [3].

Score is calculated based on the number of words in the naturalistic environment of the child as reported by the parents. A higher score means better language skills.

It will complete the measure of functional communication with VABS-2 and standardised measure with MSEL.

Adaptative behavior

Vineland Adaptive Behaviors Scales second version (VABS-2) is a parent reported scale to measure the child's daily personal and social skills [9]. This measure will be collected via a parental interview over videoconferencing before the inclusion and at 12 months. This measure will provide an estimate of any assesses functional change in socialization, communication, motor and daily living skills, based on parent observation in the naturalistic settings of the child.

The VABS has well-established psychometric properties [9,10]. It is validated in french.

All of the items are rated on a three-point Likert scale, ranging from '0' (seldom or never present) to '2' (always present). Results for each scale are described by t scores (M = 50, SD = 10). An overall score is described by normalized score (M=100, SD=15). A higher score means better adaptative skills.

To assess Parent's Stress, health, priorities and experience of the family

The psychometry of the following tools are described in the manual of each tool.

Autism Family Experience (AFEQ) [11] is a self-administered parent report about quality of life and priorities for early intervention. It is composed of 4 subscales (experience of being a parent, family life, child development understanding and relationships, child symptoms) and has an overall score. It was translated and retro-translated for the purpose of this study with the author. A higher score means better experience.

ISP (Parental stress index) is a 36-item self-administered parent report to measure the stress in the parent–child system. We will use the short form of the 4th edition. A validated French version exists [12]. A higher score means more stress.

General Health Questionnaire (GHQ-28) is a self-administered parent report, 28 item scaled version, assessing somatic symptoms, anxiety and insomnia, social dysfunction and severe depression. There is an overall score of 60. [13] A higher score means more health problems.

To assess implementation of the intervention

Professional adherence to the treatment:

All therapy training sessions with professionals will be videotaped and will be independently rated by the lead therapist using the PACT Fidelity Rating Scale (of the PACT manual) at regular intervals across the trial period. The PACT Fidelity Rating Scale measures how the therapists follow the PACT manual including the style of training.

Acceptability and feasibility of the PACT session

The therapist will collect the number of the session done with each parent and also the quality of videoconferencing during the session with the professional. Quality of sound and quality of the image will be rated with a 4-points Linkert scale. The number of disconnections along the session will also be collected.

The parents will self-report (likert-scale) the acceptability of videoconferencing training and implementation of PACT at home.

Parent PACT adherence at home

At 12 months, Parents will declare the average number of hours per day using PACT at home outside the PACT session with the therapist.

DCMA, coded on the 12 minutes home child-parent interaction will measure the parent's qualitative adherence of PACT intervention.

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Efficacy of Parent- mediated communication-focused treatment in toddlers with autism (PACT) delivered via videoconferencing: a randomised controlled trial study protocol

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Abstract

Intervention in the preschool period is currently recommended for Autism Spectrum Disorder (ASD). Therapies delivered by parents are particularly suitable for young children. PACT (Preschool Autism Communication Trial) is a parent-mediated therapy that has shown significant and sustained impact on autism symptom reduction. However, the access to such evidence-based therapies for families is limited due to autism centers located in large urban areas. Using videoconferencing to deliver PACT training to parents may improve accessibility for families living in underserved areas.

This single-blind randomized controlled trial, involving six sites in France, will investigate the efficacy of a telehealth, videoconferencing-based, parent-mediated PACT therapy on autism symptoms, over a 12-month period. It will compare PACT plus treatment as usual (TAU) against TAU only in a cohort of 238 toddlers (119 per group) aged 18 to 36 months at inclusion and living with their families more than 40 minutes away from the specialist centres for autism. Primary outcome will be the change of overall autism score on the Autism Diagnostic Observation Scale (ADOS) at 12 months. Secondary outcomes will measure change in child skills, child functioning, impact on parents (stress, health, priorities) and implementation characteristics.

Repeated measures analysis will be used to test the effect of PACT intervention on the overall ADOS module 1 score over the 12-month study period. Linear mixed models will be used with time, treatment allocation and the interaction between treatment and time as fixed effects and individual variation as random effect.

Article Summary

Strengths and limitations of this study

- Large multicentre RCT in children with ASD under 3 years old, testing remote delivery of an evidenced intervention
- Assessment partially done by videoconferencing and based on video material sent by parents
- Recruitment targeted to children living in underserved area
- Short term effect of the intervention will be assessed at 12 months (end of the intervention)
- Owing to the nature of the intervention, parents of the children and PACT therapists will not be blind to the allocation group.

Keys Words: Early intervention, Autism spectrum Disorder, PACT, videoconferencing, parent-mediated therapy, video-feedback, Health Services Accessibility

Trial registration: ClinicalTrials.gov Identifier: NCT04244721

Introduction

Rationale & background

Autism Spectrum disorder (ASD) is a common neurodevelopmental disorder with a population prevalence of at least 1.5% in developed countries and can cause significant lifelong disability [1–3] and burden for families and caregivers [4]. Diagnosis is possible as early as 18 months of age [5]. Current evidence suggests that interventions delivered in the early developmental period before the age of 3 years have the potential for maximal impact on autism symptom severity.

Therapies can be delivered by therapists, teachers and parents [6]. For preschool children with ASD, parent-mediated therapies can empower parents to face challenging social interaction with their children[7,8]. Among the different parent-mediated therapies, PACT (Pre-school Autism Communication Therapy) has shown significant short and long-term efficacy on objectively assessed autism symptoms in children aged from 2 to 10 years in a large UK cohort (N=152); as showed in recent systematic review [9] and meta-analysis [10]. In PACT, parents are guided by a therapist via video feedback to optimize their interactive behaviours in order to enhance parent-child dyadic interaction, which in turn impacts on child language, communication and autism symptoms (PACT reference) [11]. In a trial of PACT intervention compared to regular care, PACT showed a statistically significant effect at 13 month endpoint to reduce of autism symptom severity measured on Autism diagnostic Observation Schedule version 2 (ADOS-2) (effect size 0.64; 95%CI 0.07-1.20); and an increase in parental communication synchrony with the child and child communication initiations with the parent [12]. The follow-up study showed evidence of sustained effect on autism symptom severity six years after intervention end, with a significant overall reduction in symptom severity over the course of trial and follow-up period (effect size=0.55, 95% CI 0.14 to 0.91, p=0·004)[13]. A mechanistic study also confirmed that the distal effect of PACT therapy on autism severity measured by ADOS was mediated by the improvement of child communication initiations, which in turn was mediated by improved parent-child synchrony [14].

Availability of PACT therapy is limited; even more so in rural settings or in regions away from specialist centres. Training parents to PACT via videoconferencing conducted by trained therapists may be a viable alternative to make such therapies available to families living far from autism centers. Previous studies have shown that it is possible to successfully provide parent-mediated therapy in autism by videoconference [15,16]. The team who developed the PACT therapy had a positive experience of parent guidance by videoconferencing (C. Aldred and J. Green, personal communication, June 10, 2020). Indeed, remote PACT was partly used, during some session, in a recent RCT [17]. However, PACT has never been evaluated when exclusively delivered by videoconference. The barriers and facilitators of videoconferencing therapy are not sufficiently well known, and hence it is also essential to address them properly [18,19].

Research question: The proposed protocol is for a large RCT in children under 3 years with ASD to evaluate the effectiveness on autistic symptom severity and other measures of PACT therapy delivered to parents by videoconference.

A significant effect would justify and facilitate the routine use of videoconferencing therapy in early intervention and improve the dissemination of this evidence-based practice.

The hypothesis is that PACT intervention delivered by videoconferencing + TAU (Treatment As Usual) will have a superior efficacy on child autism symptom severity as compared to TAU alone.

Objectives

Our primary objective will be to test the efficacy of a parent-mediated PACT therapy, in which professionals guide parents via videoconferencing over a 12-months period, on overall autistic symptoms measured with a standardized measure, the Autism Diagnostic Observation Schedule 2 (ADOS), in children with ASD aged from 18 to 36 months at inclusion, living in undeserved area.

Our secondary objectives will be to evaluate the development of child socio-communicative interactions, language, communication initiation and daily adaptive behaviour. At the parent level, we will evaluate the intervention effects on stress, health and family priorities.

The implementation of the therapy will be evaluated through the adherence of professionals and parents to PACT, and through parents and professionals' acceptability and feasibility of the PACT sessions.

Method

Study design

Our study is a multicentre, prospective, 2 parallel group, 1:1 ratio, single blind randomised controlled trial (RCT) comparing PACT intervention + Treatment As Usual (TAU) against TAU alone. Evaluation is based on a mixed-method approach combining quantitative and qualitative studies [20,21].

A qualitative study will be conducted to capture further experience of the implementation of the intervention and causal pathway of effectiveness or ineffectiveness according to the therapists' and the parents' experience.

Figure 1 shows consort flow-chart of the study.

Setting

We will run this trial in six academic centres in France. These centres are located in child and adolescent public hospitals. All centres have a unit for ASD diagnosis and assessment and a distinct unit for intervention where therapists have been trained in PACT and can provide PACT via videoconferencing. The Children receiving intervention come from a French-speaking population including socioeconomically disadvantaged groups.

Population

Inclusion criteria

Children will be included if they meet the following criteria:
i) aged between 18-36 months old at referral
ii) meet criteria for autism spectrum disorder using the two gold standard instruments ADOS-2 (Autism diagnostic Observation Schedule -2) and ADI-R (Autism Diagnostic Interview-Revised). For inclusion into the study, the severity score comparison (CSS) on ADOS-2 will have to be greater or equal to 4. The score on the ADI-R algorithm for toddlers will have to be greater or equal to 11 [22]. The diagnosis will be confirmed by a multidisciplinary team specialised in Autism Spectrum Disorder diagnosis and assessment based in the academic departments of the hospitals.
iii) have a non-verbal age equal to or above 12 months on the Mullen Scale of Early learning (MSEL) [23].
iiii) live more than 40 minutes away from a Center for Resources in Autism (regional center)

Referred parents will be included if they meet the following criteria:
ii) speak French with their children
iii) are able to use videoconferencing methods with therapists who will be based at the center (assessed through the conduct of the Vineland Assessment Behavioral Scale by videoconferencing) (see Appendix 1 for details)

Exclusion criteria

Exclusion criteria will be as follows for the child:
i) a twin brother or sister with ASD or a brother or sister having already been included in the study
ii) diagnosed with epilepsy requiring medication
iii) have a severe hearing or visual impairment
iv) an identification of a genetic anomaly which may impact on their ability to participate in the intervention or on data validity (determined by the principal investigator on a case-by-case basis).

Exclusion criteria will be as follows for the referred parents (at least one parent with):
i) severe hearing or visual impairment
ii) severe psychiatric disorder
iii) unstable somatic disorders preventing participation in the intervention
iv) lack of internet provision
v) not available for regular intervention and follow-up
vi) opposition of one parent to the child's participation in the study
vii) currently undertaking PACT therapy

Intervention conducted in the experimental group

Eligibility criteria for PACT therapist and adherence

The therapists included will be speech language pathologists, occupational therapists, clinical nurse, psychologists or child and adolescent psychiatrists, all specialised in autism. The therapists have already received formal training and supervision in PACT with the team who developed this training [12,24]. The lead therapist will organize regular meetings between therapists of all centers, with

scoring and feedback of videotaped therapy session of the study, in order to maintain a high fidelity to the therapy.

PACT treatment principles

As previously described [17], parents will be trained, via video-feedback, to identify and set key strategies facilitating the socio-communicative interactions between their child and themselves. Parents will also be encouraged to use PACT every day outside the training session at least half an hour per day. The therapy follows a six-staged approach based on child developmental progression and strategies for establishing fundamental skills for the socio-communicative development. The first two stages aim to increase parent's identification of child focus and interest, synchrony, responsiveness and sensitivity to the child interest and communication. The third and fourth stages are targeted towards developing expression and comprehension of the child by commenting and modelling language adapted to the child's developmental level. Child communication initiation is also improved in the fifth stage through different strategies such as anticipation and routine. The last stage aims to develop conversation and expansion of language for verbal children. Progression from one stage to the next depends on predefined criteria.

Based on the protocol of the first PACT RCT, parents will receive 18 sessions of training in PACT with the therapist over the 12 months [12,13]: 1-hour sessions every fortnight during 6 months to learn PACT strategies then 1 hour sessions per month over the last 6 months to maintain the capacity of parents to deliver the strategies.

Therapist will train only one parent per family and maintain fidelity to the therapy manual. The "referent parent" will have to be designated before the randomisation of the child. If the referent becomes unavailable, the therapy will stop or will continue with the other parent if possible and this change will be reported.

Parent training session with the professional via videoconferencing

Before each session, the parent will be asked to send a 10-minute video of their interaction with his/her child to the therapist via a secure cloud link. During the videoconferencing session (as in face-to-face intervention), referent parent will begin with a 5-minute discussion about progress since the last session. The therapist will then share his/her screen and watch together with the parent the home-based 10-minute video. They will identify, review and discuss specific clips that demonstrate accomplishment of therapy goals for the relevant stage of the PACT programme. The therapist's role will be to guide parents to identify their successful strategies and responses (i.e. episodes of engagement and/ or mutual sharing with their child). Parents will be helped to reflect on their role in enhancing interaction and to identify new intervention goals.

Parent PACT implementation in daily life outside the therapy session

At the end of each session, the therapist will support the parent in setting 2-3 new goals, based on the strategies identified during the session. The therapist will encourage the parent undertake daily practice the strategies for the next session and will discuss opportunities to achieve these goals in daily routine at home for at least 30 minutes per day. Parents will be guided to embed PACT strategies in

diverse everyday routines in different contexts. As therapy progresses, parents will be asked to send 10-minutes home videos of short daily routines in different contexts.

Treatment as usual (TAU) and 2 follow-up consultations on ASD and its management

Regardless of group allocation, parents will receive treatment as usual (TAU) consisting of information about ASD, management and educational support for nursery and preschool placement. Parents will be referred to any relevant care available in the community (e.g.: Speech language pathologist (SLP), occupational therapist, educator, behavioural psychologist, psychiatrist). TAU received during the course of the study will be described in both groups.

Regardless of group allocation, a psychiatrist or a psychologist from each autism center will provide two supplementary 45 minutes follow-up consultations conducted by videoconferencing at 3 and 6 months after inclusion. They will follow an interview guide. Three thematic areas will be systematically discussed with the parents: ASD information, access to treatment in the community, support for school or nursery. These two follow-up consultations will ensure that all parents of both groups have received homogeneous key information on ASD and its management.

Avoidance of contamination

PACT is not currently widely implemented in the community in France, in particular in the underserved areas. Any families who are currently in receipt of PACT intervention will be excluded from this trial. However, any PACT that might be received in the community will be recorded through parent report as part of TAU [25].

Research assessors will be separate to the therapists and will be located and supervised separately in each center.

Professionals doing the two follow-up consultation on ASD and its management will not be trained to PACT therapy nor be implicated PACT in the research assessment.

Measures

Primary outcome

To assess autism severity

Autism Diagnostic Observation Schedule (ADOS-2) is a semi-structured, researcher-child interaction based, standardized observational assessment, in communication, play, imaginative skills, and repetitive behaviours[26,27]. It is a widely used scale in the field of ASD research with good psychometric properties, recommended for the diagnosis of ASD and assessment of core autistic symptoms [28].

At baseline and follow-up assessment after 12 months, we will use only ADOS-2 module 1, for children who are 18 months of age and older children who use no or few words.

There is a good Interrater reliability for Module 1 [27]. Internal consistency Cronbach's alpha coefficients was high in original study [27]. This scale has also shown that it can measure change in autism severity [13,28].

ADOS-2 is composed of different items scored 0 to 3 or 0 to 2. Item A1 codes the level of language, from the severity for 'the child is using regular use of statements with two or more words' (code 0) to 'the child has no spontaneous use of approximate words or words' (code 4). For children with no or limited language (A1 ≥ 3), the two items measuring language in the algorithm (item A3 speech abnormalities, item A5 stereotyped language) will be scored 3 (worst value) (see Green et al. 2010 [12]). The minimum overall ADOS-2 module 1 raw score will be 0 and the maximum score 42. A higher score means more autistic symptoms.

Our primary outcome will be the change between baseline and 12 months in the overall raw score in reciprocal socio-communicative interactions and repetitive and restrictive behaviours in line with the DSM-V [26,29].

Researchers will be trained to achieve recognized standards. Regular reliability meetings of all researchers will address any discrepant ratings to maintain researcher calibration.

Secondary outcomes

To assess social communication and interaction in the natural setting of parent-child interaction at home:

-*Brief Observation of Social Communication Change (BOSCC)[30]*.

To assess dyadic communication in the natural setting of parent-child interaction at home:

-*Dyadic Communication Measure for Autism (DCMA)* [24].

To assess child cognitive development:

-*Mullen Scales of Early Learning (MSEL) [23]*

To assess child language development:

-Development of Expressive Language, (*Development du Language de Production In french_DLPF*)[31].

To assess Adaptative behavior of the child:

-*Vineland Adaptive Behaviour Scales second version (VABS-2)* [32]

To assess Parent's Stress, health, priorities and experience of the family:

-*Autism Family Experience Questionnaire (AFEQ)* [33]

- *Parental Stress Index* (PSI*)* [34].

-*General Health Questionnaire (GHQ-28)* [35]

To assess implementation of the intervention:

- *PACT Fidelity Rating Scale*

-Number of PACT training sessions undertaken

-Quality of videoconferencing during each session

-Parents acceptability of videoconferencing and implementation of PACT at home (self-report on Likert-scale)

-Number of hours per day using PACT at home at 12 months

-Parent's qualitative PACT adherence coded with DCMA on a 12-minute home child-parent interaction video

Appendix 1 shows more details about assessments.

Figure 2 shows schedule of enrolment, interventions and assessments.

Participants timeline

Toddlers will be seen by health professionals for suspected ASD and possibility to be enrolled in this study. The research recruitment team will receive the family, complete the ADI-R during the first meeting, and check the criteria for eligibility. The complementary assessments, ADOS, MSEL with the child and Vineland will be implemented by videoconferencing with the parent, to complete the criteria for eligibility. When toddlers and families meet the criteria for participation, parents will be informed in detail about the study and possibility of an intervention with PACT or TAU only according to the randomisation. They will be asked to sign written informed consent if they agree to participate in the study after one week of reflection.

The 'referent parent' to take part in the therapy trial will be decided before randomisation. Children will be subsequently randomised into the intervention or TAU group. Parents will be informed of the result of the randomisation and complete the assessment.

Assignment of intervention

Allocation sequence generation and randomisation

All eligible toddlers, with parental consent, will be assigned to the two study groups in a 1:1 ratio using the minimization method with the following stratification factors: the centre, the children's age, level of language (according to the ADOS2 scale) and gender. To ensure allocation concealment, a minimization algorithm with a .90 random element will be used and known only by the statistician (AD). The randomisation is centralized.

Blinding

Owing to the nature of the intervention, parents and PACT therapists cannot be blind to the allocation group. PACT therapists will not be involved in the diagnosis or assessment. An assessor blind to the

allocation group will administer every assessment. Data manager and biostatistician will be blinded to the allocation groups.

Data collection and management

Data collection

Data will be collected through standardized observations done by a researcher blind of the allocation and questionnaires and interviews completed by parents. We will be particularly vigilant about the measurement accuracy of the first criterion of judgement as described in the paragraph on ADOS-2.

Participation retention and follow-up

Children of both groups will benefit from early diagnosis and assessment and will have the same follow-up evaluations over the 1-year study period in the diagnostic units which should promote participant retention and complete follow-up. Any discontinuation of study participation will be collected and recorded with the reasons.

Data Management

The study data will be collected on a secure electronic case report form (eCRF) that will be available at each centre through an internet portal. No personal identifying information will be mentioned on the eCRF. Each subject included in the study will be assigned a unique identification number.

All study data will be stored securely in the Academic Hospital of Lyon. All electronic data will be secured on a password-protected laptop. Paper-based study documents will be stored in a secure filing cabinet at each centre. Access to these files will be limited to research staff involved in the study.

The eCRF will only include the data necessary for the analysis to be reported in a scientific publication.

Statistical analysis

Simple size calculation

On the basis of the findings of the PACT Trial (Green, 2010), we have powered the study to be able to detect a difference in change overall on the ADOS score of 2 points. The group difference in mean change between baseline and month 12 was -1 point for ADOS social affect score (mean change=2.9, SD=3.9 in TAU group and mean change=-3.9, SD=4.7 in PACT+TAU group) and -0.5 points for ADOS restricted and repetitive behaviors score (mean change=2.9, SD=3.9 in TAU group and mean change=-3.9, SD=4.7 in PACT+TAU group). The pre- and post-measures were correlated at 0.67. Therefore, the most conservative values were fixed for ADOS standard deviation and for correlation among the repeated measures from a single participant. A target of 238 subjects (119 subjects per treatment arm) was planned to be randomized in the trial. Assuming a 2-point difference in favor of the PACT+TAU compared with TAU, a standard deviation of 5, a correlation between subsequent visits of 0.5, a drop-out rate of 20%, and a two-sided significance level of 0.05, the planned sample size would provide about 80% power for the study.

Feasibility of recruitment

A strong partnership with ASD orientation platforms recently implemented in France, a broad communication (meeting, mail, flyers) to healthcare professionals (Speech pathologist, Occupational therapist, therapist, paediatrician, general practitioner) family associations and other stakeholders will allow the trial team to reach the sample size over 2 years.

Statistical analysis

A full statistical analysis plan will be finalized prior to database lock. Statistical analysis and results will be reported at the 12-month endpoint in accordance with the CONSORT 2010 statement. No interim analysis will be scheduled. All the statistical analysis will be carried out according the intention to treat principle using SAS statistical software (SAS Institute Inc., Cary, NC, USA).

Baseline characteristics will be presented in each group.

Summary statistics will be presented for process variables (number of PACT sessions, quality of videoconferencing per session, acceptability and satisfaction of PACT intervention, number of hours declared to be realized with the child) to show the feasibility and acceptability of PACT implementation in the intervention group.

The pattern of missing data will be investigated (number and mechanism of missingness). Missing data strategies can be applied and sensitivity analysis of different strategies (simple or multiple imputation) will be conducted.

A repeated measures analysis will be used to test the effect of PACT intervention on overall ADOS module 1 score over the 12-month study period. A linear mixed model will be run with the overall ADOS score as the dependent variable and including time (baseline, month 12), treatment (TAU or TAU+PACT) and the interaction between treatment and time as fixed effects and patient as random effect. Model will be adjusted for stratification factors (centre, age, level of language (item A1 ADOS-2) and gender) and baseline variables that showed evidence of treatment group imbalance. Time will be represented by dummy variable. Model assumption will be verified according to residual analysis. If most of assumptions are not met other alternative such as transformation for ADOS overall raw score can be examined. Sensitivity analyses like complete case and per-protocol analysis can be performed to assess the robustness of the results to protocol deviations. In complete case analysis, only patient with primary outcome documented will be analyzed. In per-protocol participants who violate the protocol will be excluded from the analysis.

All the secondary outcomes, (overall total score of the BOSCC, communication initiation and synchrony measured with the DCMA, overall raw score of the MSEL in receptive and expressive language, overall score in expressive language of the DLFP, overall raw score of communicative and social of the VABS, Parental Stress Index, Parent General Health score, AFEQ score) will be analyzed in a similar way using when appropriate linear or generalized linear mixed models. Tobit models should be used to address potential floor effects.

We will finally explore the parent's and children's characteristics, moderating the implementation and efficacy of this therapy. We will also test the previously found mediators implicated in the efficacy of this therapy [14].

Qualitative analysis of barriers and facilitators of implementation

Based on parents and of the therapists reports we will describe the facilitators and barriers of the implementation of video-conferencing PACT.

The data will be collected through semi-structured interview and will be analysed with the classical technique of Interpretative Phenomenological Analysis (IPA) [36]. Population selection will follow the rules of the purposive sampling and will allow a maximal variation of the sample [37]. An estimation of 30-60 parents will be necessary to reach data saturation based on previous studies [38–40]. The total number of therapists (around 7-8) will be interviewed. During the 40-60 minutes interview, we will explore different area of barriers and obstacles to learning and implementing PACT by videoconferencing. A guide for the interview will be elaborated in the initial phase of the project based on first interviews. Interviews will be recorded, and the verbatim interview will be transcribed to analysis the entirely communication of the participant.

Data from the quantitative and qualitative sources in the process evaluation will be analysed separately. The results of the qualitative study will be integrated with the quantitative results to optimize the findings [41].

Monitoring

Dr Marie-Maude Geoffray (IP) Investigators associated, methodologists, statistician, parent representatives and associate researcher composed the trial steering committee (TSC). The TSC is independent of sponsor and funders and have no competing interests. The TSC has developed the study protocol and is responsible for data collection, management, publications and the final data set.

The coordinating center is independent from the centers for investigation.

According to the French law, the study requires formal data monitoring undertaken by the sponsor. Annual reporting will be completed and submitted to the funders.

Adverse events

Based on results from previous PACT intervention trials, no specific harm from trial participation is anticipated. However, as required by the French law, adverse events will be collected throughout the study and reported in the eCRF section. Description of the event, date of occurrence, intensity, severity, accountability will be reported. Outcomes of this event and action taken after its report will also be concealed.

We anticipate that the early assessment, follow-up consultation on ASD and its management will help and support both groups during the post-diagnosis period. Hence, no post-trial care is planned.

Trial status

The trial status is currently Recruiting. The study has started the 30th June 30, 2020. The anticipated end date will be 30th June, 2023.

Figure 3 shows WHO trial registration data set.

Ethics and *Dissemination:* This study is approved by the French Institutional Review Board (reference No 2018-A02516-49). The results will be disseminated via peer-reviewed journals. It will also disseminate via national and international, general and specialist meeting and through the parent association (https://Bleunetwork.fr; https://autisme-ambitionavenir.com; desailespourgrandir.org). An individual feedback to the participant will be done through a regular newsletter. We will adhere to defined authorship criteria as per the International Committee of Medical Journal Editors.

Author contribution: MMG and ST, PO, LJ conceived and designed the project, and MMG is leading the coordination of the trial. MMG, LJ and PO drafted the protocol and procured the project funding. LJ and MMG are responsible for study implementation, staff training and supervision. PO, ST, AD, AZ contributed to the sample size calculation, the randomisation procedure and the statistical plan, and are responsible for data management, randomisation and statistical analysis. JG contributed to the protocol and paper writing. ARL contributed to the protocol of the qualitative study. CA and NG to the PACT training and supervision of the team. MMG, MJO, LJ, AA, AJ, AB, CS, TM, TD are responsible for recruitment and evaluation of children. SG contributed to draft the paper. All authors critically reviewed and approved the final version of the manuscript.

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Patient and Public Involvement subsection: Mrs Alloisio (Association AAA https://autisme-ambitionavenir.com) and Mr Belkhayat (association https://bleunetwork.fr/pro) are parents of a child with autism and represent two different association. They are part of the steering committee.

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Figure 1 Consort flow-chart of the study.

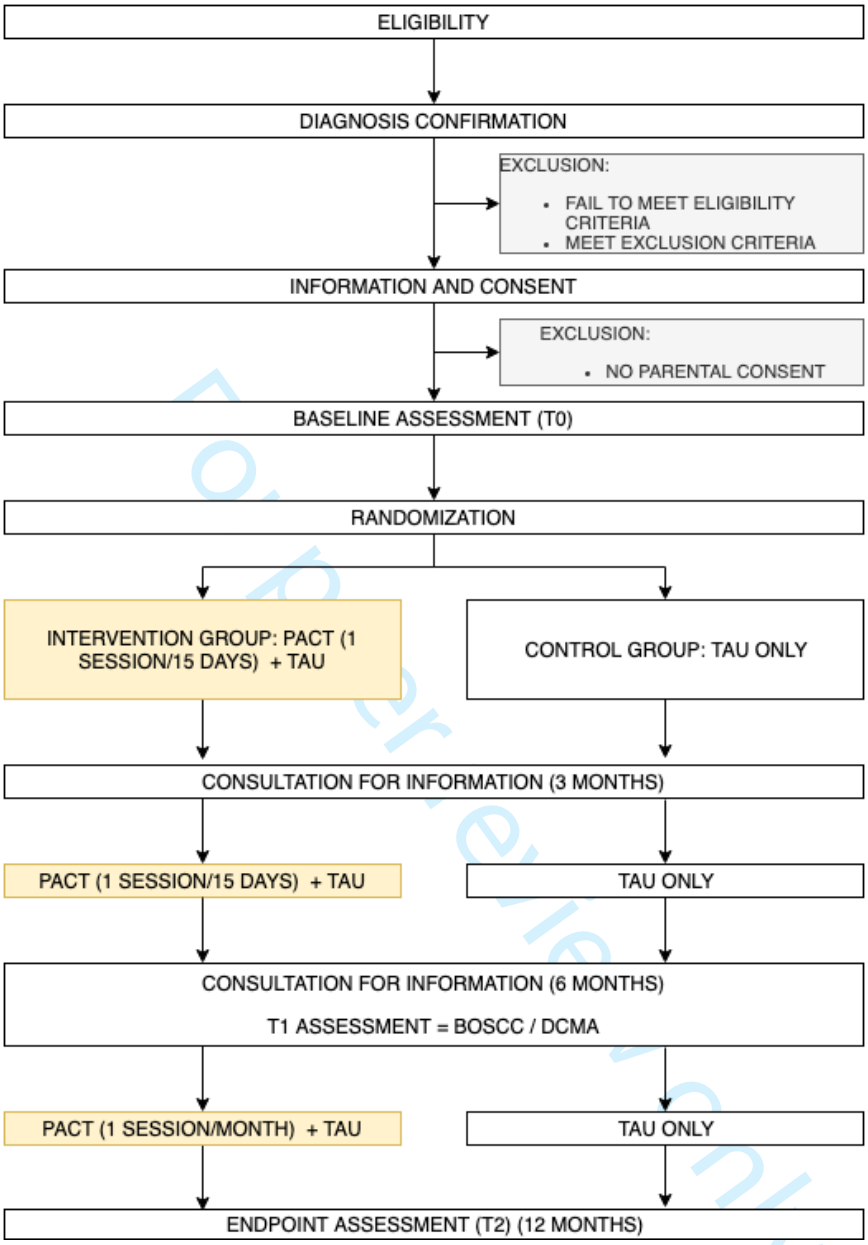

Figure 2. Schedule of enrolment, interventions and assessments (SPIRIT)

Time point	Enrolment	T0 baseline	T1 6 months	T2 12 months
Eligibility screen				
DSM-5 criteria	x			
ADOS-2	x			
ADI-R for toddlers	x			
Nonverbal skills MSEL	x			
Adaptative behavioral level : VABS 2 coded based on an interview done by videoconferencing with parents	x			
Informed consent	x			
Allocation		x		
Intervention				
PACT training (1h/15 days during 6 months then 1h/month during 6 months) + daily practice at home		→	→	→
Treatment as usual		→	→	→
Assessment				
Sociodemographic data		x		x
Autistic symptoms: ADOS-2 (primary outcome)		x		x
Change in socio-communicative interactions: BOSCC Played-based interaction between carer and child at home		x	x	x
Communication Synchronization and initiatives: DCMA at home		x	x	x
Expressive and receptive language Mullen scale		x		x
Daily language DLFP		x		x
Adaptative behavioral level: VABS 2 by video-conferencing		x		x
Parental stress index: ISP-short form		x		x
General parents health : GHQ-28		x		x
Parents quality of life and priorities. AFEQ		x		x
Acceptability of PACT intervention and TAU. (Linkert scale)				x
Implementation: Number of PACT training session Mean of quality of videoconferencing collected after each session Number of hours declared by parents using PACT at home				x x x

Figure 3- WHO trial registration data set

Data category	Information
Primary registry and trial identifying number	clinicaltrials.gov : NCT04244721
Date of registration in primary registry	January 28, 2020
Secondary identifying numbers	2018-A02516-49
Source of monetary or material support	This study is supported by a grant from the Programme Hospitalier de Recherche Clinique inter-régional Rhône Alpes (PHRCI-15-065) from the AURA region and a grant by the Caisse Nationale de solidarité pour l'autonomie (CNSA) as part of the call for projects launched for IReSP (Institut de Recherche en Santé Publique) in 2016 in collaboration with the Institut national de la santé et de la recherche médicale (Inserm) (IReSP-17-Autisme3-16).
Primary sponsor	Centre Hospitalier Le Vinatier, Bron, France
Secondary sponsor	Not applicable
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Public title	Efficacy of a parent- mediated communication-focused treatment in toddler with autism (PACT)when parents trained by videoconference: a randomised controlled trial study protocol
Scientific title	Efficacy of a parent- mediated communication-focused treatment in toddler with autism (PACT)when parents trained by videoconference: a randomised controlled trial study protocol
Countries of recruitment	France
Health condition or problem studied	Autism spectrum disorder (ASD)

Data category	Information
Interventions	*Intervention*: PACT for toddlers and young children with ASD *Description*: PACT delivered by the parent trained remotely by therapists 1 hour per 2-weeks during 6 months and 1 hour per month the following 6 months. *Control*: care available in the community, i. e. consultations with a psychologist or child and adolescent psychiatrist, speech and language therapy, occupational therapy, individual or group psychotherapy.
Key inclusion and exclusion criteria	*Age*: between 18 and 36 months *Sex*: male or female *Inclusion criteria*: diagnosis of ASD (Diagnosis and Statistical Manual of Mental Disorders, Fifth Edition, and Autism Diagnosis Observation Schedule), child will have a non-verbal age above 12 months on the Mullen Scale of Early learning, family living further than 40 min away from an ASD specialized center. *Exclusion criteria*: serious neurological or physical condition, family unavailable for a regular follow-up.
Study type	Interventional *Allocation*: randomized 1:1; parallel assignment; blinding: assessor blind
Date of first enrolment	15th July 2020
Target sample size	238
Recruitment Status	Recruiting
Primary outcome	Change in ADOS-2 module 1 standardized score at 12 months
Key secondary outcomes	Child development, child adaptative behavior, child socio-communicative abilities, quality of life of parents, parental stress, obstacle and facilitators of the intervention model.

Appendix 1: Secondary outcomes

The secondary outcomes are measured using standardized coding assessments of naturalistic observational videos (BOSCC, DCMA), performance-based standardized tests (MSEL), and parent-report-based standardized tests (VABS, DLFP, AFEQ, ISP, GHQ).

To assess social communication and interaction in the natural setting of parent-child interaction at home

Brief Observation of Social Communication Change (BOSCC) measures the same construct as the ADOS. It is a researcher coding assessment of autism symptoms based on child-adult interaction. It has good fidelity and results showed good construct validity [1]. The validity to measure the change was analysed in two small populations (N=20-50) and will have to be reanalysed in further trials [36,37]. It has the advantage to allow measure Dyadic interaction across different contexts. It was translated and retro-translated for the purpose of a previous study [2]

The scale is composed of 12 items scored from 0 to 5 according to the BOSCC algorithm. There is an overall score of 0 to 60 measuring core autism symptoms. A higher score indicates more autistic symptoms.

In the current study, a 12 minutes home-video will be recorded by the parents themselves. The parent will be provided with a simple protocol to follow using a standardized set of toys. The standardized set of toys given to the families at each time of assessment will include a cause and effect toy, shape sorter or puzzle, construction toys, miniature pretend play. The protocol includes 10 minutes time of natural play with children with the set of standardized toys and 2 minutes with bubbles play. A first unscored videotape would be done on the center (at T0) to train the parents to video record based on the protocol. In the week following, the parent will videotape at home a child-parent interaction according to the protocol with the standardized set of toys and send the video to the researchers via a secure platform. Professional may make up to two further requests if the video received is judged to not be of adequate quality. If the parent isn't able to send a usable video according to the protocol, the researcher completes a home visit to demonstrate and help the parent to do the video the third time. Two further videos will be done at home at 6 months (T1) and 12 months (T2) in order to assess Social communication interaction in a naturalistic setting.

All the video will be scored by trained researchers.

The same parent called the "referent parent" will be videotaped by a relative at each time of assessment. He/ she will be identified before the randomisation. It will also be the parent who receive PACT therapy if in the group of PACT intervention.

To assess dyadic communication in the natural setting of parent-child interaction at home

The *Dyadic Communication Measure for Autism (DCMA)* is a direct observation instrument of the communication between a parent and a child with autism [3]. It rates parental and child mutual shared attention, child communication (initiation and response) and parental communication style (synchronous/asynchronous).

Independent inter-rated reliability on synchrony has been reported and is good [3]. It was translated and retro-translated for the purpose of a previous study [2]

It can be used to code a number of acts of communication per timepoint. A higher score indicates better communication.

Coding will be done on the same 12 minutes home parent-child video described above in BOSCC at baseline, 6 months and 12 months.

To assess child cognitive development

The *Mullen Scales of Early Learning (MSEL)* is a direct observation standardized tool from birth to 68 months [4]. It measures verbal and non-verbal skills of the children, according to the success or failure in tasks of the MSEL protocol delivered by a trained researcher. The MSEL has been used extensively as a discriminative and evaluative measure in children with autism spectrum disorder, Fragile X syndrome, and speech delays [5–7]

The MSEL will be assessed on the center before the inclusion and at 12 months.

Internal consistency and concurrent validity are good [4]. It was translated and retro-translated for the purpose of a previous study [2]

The MSEL includes 124 items that measure five specific domains: 1) Gross Motor; 2) Fine Motor; 3) Visual Reception; 4) Expressive Language; and 5) Receptive Language. Scoring varies by item from 2-point scale (0 = does not meet criteria to 1 = meets criteria) to a 6-point scale. Results for each scale are described by T scores (M = 50, SD = 10), percentile ranks, and age equivalents. Four cognitive scales (Visual Reception, Fine Motor, Receptive Language, and Expressive Language) sum to represent an Early Learning Composite Score which measures overall cognitive functioning (M=100, SD=15). A higher score means better skills. This evaluation will be realized before inclusion and at 12 months.

To assess child language development

The “development of expressive language”, a standardised French Scale (Development du Language de Production In french_DLPF), is based on a self-administered parent-report [8]. This measure is standardised for age. Only the level 4 of the DLPF will be administered at each assessment to have a continuous score on expressive language. The DLFP was validated in a study [3]. Score is calculated based on the number of words in the naturalistic environment of the child as reported by the parents. A higher score means better language skills. This questionnaire will be completed by the referent parent at baseline and at 12 months.

It will complete the measure of functional communication with VABS-2 and standardised measure with MSEL.

Adaptative behavior

Vineland Adaptive Behaviors Scales second version (VABS-2) is a parent reported scale to measure the child’s daily personal and social skills [9]. This measure will be collected via a parental interview over videoconferencing before the inclusion and at 12 months. Videoconferencing model has been chosen

in our study to avoid multiples visits on the centre but also to evaluate, before the inclusion, if a long videoconferencing meeting could be done with the family on a technical point of view. A first assessment will be proposed to the parents. In case of technical difficulties during the first meeting, a second, and if necessary, a third meeting will be proposed. Tips to improve videoconferencing will also be provided to the parents. In case of failure of every remote assessment, the family will be considered as not eligible for the study as the remote PACT session require the ability to conduct a videoconferencing meeting.

This measure will provide an estimate of any assesses functional change in socialization, communication, motor and daily living skills, based on parent observation in the naturalistic settings of the child.

The VABS has well-established psychometric properties [9,10]. It is validated in french.

All of the items are rated on a three-point Likert scale, ranging from '0' (seldom or never present) to '2' (always present). Results for each scale are described by t scores (M = 50, SD = 10). An overall score is described by normalized score (M=100, SD=15). The range for each subscale is from 20 to 140. The subscales are summed to compute a total score, ranging from 80 to 560. The higher the scores are, the better adaptive functioning the children achieve.

To assess Parent's Stress, health, priorities and experience of the family

The psychometry of the following tools are described in the manual of each tool.

Autism Family Experience (AFEQ) [11] is a 48-item self-administered parent report about quality of life and priorities for early intervention. It is composed of 4 subscales: experience of being a parent (range 13-65), family life (range 9-45), child development understanding and relationships (14-70), child symptoms (12-60). The sum of all domains gives the total score (range 48 - 240). Each question is assessed using a 5-point Likert scale. Scores range from "always" (1) to "never" (5)". It was translated and retro-translated for the purpose of this study with the author. For the total score and the domain scores a higher score indicates a lower outcome. This questionnaire will be completed by the referent parent at baseline and at 12 months.

ISP (Parental stress index) is a 36-item self-administered parent report to measure the stress in the parent–child system. The PSI consists of three subscales: Parental Distress, Parent–child Dysfunction Interaction, and Difficult Child. Each subscale consists of 12 items rated from 1 (strongly agree) to 5 (strongly disagree), with subscale scores ranging from 12 to 60. The three domains combined form a Total Stress score (with a total score ranges from 36 to 180). We will use the short form of the 4th edition. A validated French version exists [12]. A higher score on the subscales and total stress score indicates increased levels of stress. This questionnaire will be completed by the referent parent at baseline and at 12 months.

General Health Questionnaire (GHQ-28) is a self-administered parent report, 28 item scaled version, assessing somatic symptoms, anxiety and insomnia, social dysfunction and severe depression. Each item is rated according to a Likert score method (1 to 4). The GHQ-28 global score range from 36 to 110 [13]. A higher score means more health problems. This questionnaire will be completed by the referent parent at baseline and at 12 months.

To assess implementation of the intervention

Professional adherence to the treatment:

All therapy training sessions with professionals will be videotaped and will be independently rated by the lead therapist using the PACT Fidelity Rating Scale (of the PACT manual) at regular intervals across the trial period. The PACT Fidelity Rating Scale measures how the therapists follow the PACT manual including the style of training.

Acceptability and feasibility of the PACT session

The therapist will collect the number of the session done with each parent. The quality of videoconferencing during each session with the professional will be rated. Quality of sound and quality of the image will be rated with a 4-points Linkert scale. The number of disconnections along the session will also be collected.

The parents will self-report (likert-scale) the acceptability of videoconferencing training and implementation of PACT at home.

Parent PACT adherence at home

At 12 months, Parents will declare the average number of hours per day using PACT at home outside the PACT session with the therapist.

DCMA, coded on the 12 minutes home child-parent interaction will measure the parent's qualitative adherence of PACT intervention.

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Efficacy of Parent- mediated communication-focused treatment in toddlers with autism (PACT) delivered via videoconferencing: a randomised controlled trial study protocol

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Abstract

Introduction: Intervention in the preschool period is currently recommended for Autism Spectrum Disorder (ASD). Therapies delivered by parents are particularly suitable for young children. PACT (Preschool Autism Communication Trial) is a parent-mediated therapy that has shown a significant and sustained impact on autism symptom reduction. However, access to such evidence-based therapies for families is limited due to autism centers located in large urban areas. Using videoconferencing to deliver PACT training to parents may improve accessibility for families living in underserved areas.

Methods and analysis: This single-blind randomized controlled trial, involving six sites in France, will investigate the efficacy of a telehealth, videoconferencing-based, parent-mediated PACT therapy on autism symptoms, over a 12-month period. It will compare PACT plus treatment as usual (TAU) against TAU only in a cohort of 238 toddlers (119 per group) aged 18 to 36 months at inclusion and living with their families more than 40 minutes away from the specialist centres for autism. Primary outcome will include change of overall autism score on the Autism Diagnostic Observation Scale (ADOS) at 12 months. Secondary outcomes will measure change in child skills, child functioning, impact on parents (stress, health, priorities) and implementation characteristics.

Repeated measures analyses will be used to test the effect of PACT intervention on the overall ADOS module 1 score over the 12-month study period. Linear mixed models will be used with time, treatment allocation and the interaction between treatment and time as fixed effects and individual variation as random effect.

Ethics and dissemination: This protocol (version N°5, date: 10/25/2019) is approved by the French National Review Board (reference No 2018-A02516-49). The results will be disseminated via peer-reviewed journals

Article Summary

Strengths and limitations of this study

- Large multicentre randomised controlled trial (RCT) in children with ASD under 3 years old, testing remote delivery of an evidenced intervention
- Assessment partially done by videoconferencing and based on video material sent by parents
- Recruitment targeted to children living in underserved areas
- Short term effect of the intervention will be assessed at 12 months (end of the intervention)
- Owing to the nature of the intervention, parents of the children and PACT therapists will not be blind to the allocation group.

Keys Words: Early intervention, Autism spectrum Disorder, PACT, videoconferencing, parent-mediated therapy, video-feedback, Health Services Accessibility

Trial registration: ClinicalTrials.gov Identifier: NCT04244721

Introduction

Rationale & background

Autism Spectrum disorder (ASD) is a common neurodevelopmental disorder with a population prevalence of at least 1.5% in developed countries and can cause significant lifelong disability [1–3] and burden for families and caregivers [4]. Diagnosis is possible as early as 18 months of age [5]. Current evidence suggests that interventions delivered in the early developmental period before the age of 3 years has the potential for maximal impact on autism symptom severity.

Therapies can be delivered by therapists, teachers and parents [6]. For preschool children with ASD, parent-mediated therapies can guide parents to face challenging social interaction with their children [7,8]. Among the different parent-mediated therapies, PACT (Pre-school Autism Communication Therapy) has shown significant short and long-term efficacy on objectively assessed autism symptoms in children aged from 2 to 10 years in a large UK cohort (N=152); as showed in a recent systematic review [9] and meta-analysis [10]. In PACT, parents are guided by a therapist via video feedback to optimize parent-child dyadic interaction, which in turn impacts on child language, communication and autism symptoms [11]. In a trial of PACT intervention compared to regular care, PACT showed a statistically significant effect at 13 month endpoint to reduce of autism symptom severity measured on Autism diagnostic Observation Schedule version 2 (ADOS-2) (effect size 0.64; 95%CI 0.07-1.20); and an increase in parental communication synchrony with the child and child communication initiations with the parent [12]. The follow-up study showed evidence of sustained effect on autism symptom severity six years after intervention end, with a significant overall reduction in symptom severity over the course of trial and follow-up period (effect size=0.55, 95% CI 0.14 to 0.91, p=0·004)[13]. A mechanistic study also confirmed that the distal effect of PACT therapy on autism severity measured by ADOS was mediated by the improvement of child communication initiations, which in turn was mediated by improved parent-child synchrony [14].

Availability of PACT therapy is limited; even more so in rural settings or in regions away from specialist centres. Using videoconferencing run by therapists to train parents in PACT, may therefore be a viable alternative to make such therapies available to families living far from autism centers. Previous studies have shown that it is possible to provide parent-mediated therapies in autism by videoconferencing successfully [15,16]. The team who developed the PACT therapy reported positive experiences of parent guidance by videoconferencing (C. Aldred and J. Green, personal communication, June 10, 2020). Indeed, videoconferencing was used to deliver some of the PACT sessions in a recently published RCT [17]. However, PACT has never been evaluated when exclusively delivered by videoconferencing. The barriers and facilitators to delivering such therapies via videoconferencing are not sufficiently well understood, and hence it is essential to investigate and address them adequately [18,19].

Research question: The proposed protocol is for a large RCT in children under 3 years with ASD to evaluate the effectiveness on autistic symptom severity and other measures of PACT therapy delivered to parents by videoconferencing.

A significant effect would justify and facilitate the routine use of videoconferencing therapy in early intervention and improve the dissemination of this evidence-based practice.

The hypothesis is that PACT intervention delivered by videoconferencing + TAU (Treatment As Usual) will have a superior efficacy on child autism symptom severity as compared to TAU alone.

Objectives

Our primary objective will be to test the efficacy of a parent-mediated PACT therapy, delivered by trained therapists to parents living in underserved areas via videoconferencing over a 12-months period, on overall autistic symptoms in children with ASD aged from 18 to 36 months at inclusion, measured using the Autism Diagnostic Observation Schedule 2 (ADOS),

Our secondary objectives will include an evaluation of change in child socio-communicative interactions, language, communication initiation and daily adaptive behaviour. At the parent level, we will evaluate the intervention effects on stress, health and family functioning.

The implementation of the therapy will be evaluated through the adherence of professionals and parents to PACT, and acceptability and feasibility of the PACT sessions to parents and therapists.

Method

Study design

This is a prospective multicentre RCT with 2 parallel group, 1:1 ratio, single blind comparing PACT intervention + Treatment As Usual (TAU) against TAU alone. Evaluation will be carried out using quantitative and qualitative mixed-method approaches [20,21].

Semi-structured interviews with parents and therapists will be conducted to understand the barriers and facilitators of using the videoconferencing approaches to delivering the PACT therapy.

Figure 1 shows consort flow-chart of the study.

Setting

We will run this trial in six academic centres located in child and adolescent public hospitals in France. All centres have a unit for ASD diagnosis and assessment and a distinct unit for intervention where therapists have been trained in PACT and can provide PACT via videoconferencing. The parents receiving intervention come from a French-speaking population including socioeconomically disadvantaged groups.

Patient and Public Involvement

Mrs Alloisio (Association AAA https://autisme-ambitionavenir.com) and Mr Belkhayat (association https://bleunetwork.fr/pro) are parents of a child with autism and represent two different association. They are part of the steering committee.

Population

Inclusion criteria

Children will be included if they meet the following criteria:
i) aged between 18-36 months old at referral
ii) meet criteria for autism spectrum disorder using the two gold standard instruments ADOS-2 (Autism diagnostic Observation Schedule -2) and ADI-R (Autism Diagnostic Interview-Revised). For inclusion into the study, the severity score comparison (CSS) on ADOS-2 will be greater or equal to 4. The score on the ADI-R algorithm for toddlers will be greater or equal to 11 [22]. The diagnosis will be confirmed by a multidisciplinary team trained in ASD assessment and diagnoses based in the academic departments of the hospitals.
iii) have a non-verbal age equal to or above 12 months on the Mullen Scale of Early learning (MSEL) [23].
iv) live more than 40 minutes away from a Center for Resources in Autism (regional center)

Referred parents will be included if they meet the following criteria:
ii) speak French with their children
iii) are able to use videoconferencing methods with therapists who will be based at the center (assessed through the conduct of the Vineland Assessment Behavioral Scale by videoconferencing) (see Appendix 1 for details)

Exclusion criteria

Exclusion criteria for the child will include:
i) a twin brother or sister with ASD or a brother or sister already included in the study
ii) diagnosed with epilepsy requiring medication
iii) severe hearing or visual impairment
iv) an identification of a genetic anomaly which may impact on their ability to participate in the intervention or on data validity (determined by the principal investigator on a case-by-case basis).

Exclusion criteria for the referred parents (at least one parent with) will include:
i) severe hearing or visual impairment
ii) severe psychiatric disorder
iii) unstable somatic disorders preventing participation in the intervention
iv) lack of internet provision
v) not available for regular intervention and follow-up
vi) opposition of one parent to the child's participation in the study
vii) currently undertaking PACT therapy

Intervention conducted in the experimental group

Eligibility criteria for PACT therapist and adherence

Therapists delivering the intervention will include speech language pathologists, occupational therapists, clinical nurses, psychologists or child and adolescent psychiatrists, all specialised in ASD. The therapists have already received formal training and supervision in PACT from the team who developed this training [12,24]. Fidelity to PACT therapy will be maintained by regular meetings between therapists of all centers, with scoring and feedback of videotaped therapy sessions obtained during the study.

PACT treatment principles

As previously described [17], parents will be trained, via video-feedback, to identify and set key strategies facilitating the socio-communicative interactions between their child and themselves. Parents will also be encouraged to use PACT every day outside the training session at least half an hour a day. The therapy follows a six-staged approach based on child developmental progression and strategies for establishing fundamental skills for the socio-communicative development. The first two stages aim to increase parent's identification of child focus and interest, synchrony, responsiveness and sensitivity to the child interest and communication. The third and fourth stages are targeted towards developing expression and comprehension of the child by commenting and modelling language adapted to the child's developmental level. Child communication initiation is also improved in the fifth stage through different strategies such as anticipation and routine. The last stage aims to develop conversation and expansion of language for verbal children. Progression from one stage to the next depends on predefined criteria.

Based on the protocol of the first PACT RCT, parents will receive 18 sessions of training in PACT with the therapist over the 12 months [12,13]: 1-hour session every fortnight for the first 6 months to learn PACT strategies followed by 1 hour session per month over the next 6 months to maintain the capacity of parents to deliver the strategies.

Therapist will train only one parent per family and maintain fidelity to the therapy manual. The "referent parent" will have to be designated before the randomisation of the child. If the referent becomes unavailable, the therapy will stop or will continue with the other parent if possible and this change will be reported.

Parent training session with the professional via videoconferencing

Before each session, the parent will be asked to send a 10-minute video of their interaction with their child to the therapist via a secure cloud link. During the videoconferencing session (as in face-to-face intervention), referent parent will begin with a 5-minute discussion about their progress since the last session. The therapist will then share his/her screen and watch the home-based 10 minutes video together with the parent. Together the parent and therapist will identify, review and discuss specific clips that demonstrate accomplishment of therapy goals for the relevant stage of the PACT programme. The therapist's role will be to guide parents to identify successful strategies and responses (i.e. episodes of engagement and/ or mutual sharing with their child). Parents will be supported to reflect on their role in enhancing interaction and to identify new intervention goals.

Parent PACT implementation in daily life outside the therapy session

At the end of each session, the therapist will support the parent in setting 2-3 new goals, based on the strategies identified during the session. The therapist will encourage the parent to practice the strategies for the next session and discuss opportunities to achieve these goals in daily routine at home for at least 30 minutes per day. Parents will be guided to embed PACT strategies in everyday routines across different contexts. As therapy progresses, parents will be asked to send 10-minutes home videos of daily routines in different contexts.

Treatment as usual (TAU) and 2 follow-up consultations on ASD and its management

Regardless of group allocation, parents will receive treatment as usual (TAU) consisting of psychoeducation about ASD, management and educational support for nursery and preschool placement. Parents will be referred to any relevant care available in the community (e.g.: Speech language pathologist (SLP), occupational therapist, educator, behavioural psychologist, psychiatrist). TAU received during the course of the study will be described in both groups.

Regardless of group allocation, a psychiatrist or a psychologist from each autism center will provide two supplementary 45 minutes follow-up consultations conducted by videoconferencing at 3 and 6 months after inclusion. This consultation will be carried out by following an interview guide. Three thematic areas will be systematically discussed with the parents: ASD information, access to treatment in the community, support for school or nursery. These follow-up consultations will ensure that parents of both groups receive homogeneous information on ASD and its management.

Avoidance of contamination

Currently, PACT is not widely implemented in the community in France, particularly in the rural areas. Any families who are currently in receipt of PACT intervention will be excluded from this trial. However, any PACT that might be received in the community as part of TAU will be recorded .[25].

Research assessors will be separate to the therapists and will be located and supervised separately in each center.

Professionals conducting the follow-up consultations will not be trained in PACT therapy or be part of the research assessments.

Measures

Primary outcome

To assess autism severity

Autism Diagnostic Observation Schedule (ADOS-2) is a semi-structured, researcher-child interaction based, standardized observational assessment, in communication, play, imaginative skills, and repetitive behaviours [26,27]. It is a widely used scale in the field of ASD research with good

psychometric properties, recommended for the diagnosis of ASD and assessment of core autistic symptoms [28].

At baseline and follow-up assessment after 12 months, we will use only ADOS-2 module 1, for children who are 18 months of age and older children who use no or few words.

There is a good Interrater reliability for Module 1 [27]. Internal consistency Cronbach's alpha coefficients was high in original study [27]. This scale has also shown that it can measure change in autism severity [13,28].

ADOS-2 is composed of different items scored 0 to 3 or 0 to 2. Item A1 codes the level of language, from the severity for 'the child is using regular use of statements with two or more words' (code 0) to 'the child has no spontaneous use of approximate words or words' (code 4). For children with no or limited language (A1 ≥ 3), the two items measuring language in the algorithm (item A3 speech abnormalities, item A5 stereotyped language) will be scored 3 (worst value) (see Green et al. 2010 [12]). The minimum overall ADOS-2 module 1 raw score will be 0 and the maximum score 42. A higher score means more autistic symptoms.

Our primary outcome will be the change between baseline and 12 months in the overall raw score in reciprocal socio-communicative interactions and repetitive and restrictive behaviours in line with the DSM-V [26,29]

Researchers will be trained to achieve recognized standards. Regular reliability meetings of all researchers will address any discrepant ratings to maintain researcher calibration.

Secondary outcomes

To assess social communication and interaction in the natural setting of parent-child interaction at home:

-*Brief Observation of Social Communication Change (BOSCC)[30]*.

To assess dyadic communication in the natural setting of parent-child interaction at home:

-*Dyadic Communication Measure for Autism (DCMA)* [24].

To assess child cognitive development:

-*Mullen Scales of Early Learning (MSEL) [23]*

To assess child language development:

-Development of Expressive Language, (*Development du Language de Production In french_DLPF*)[31].

To assess Adaptative behavior of the child:

-*Vineland Adaptive Behaviour Scales second version (VABS-2)* [32]

To assess Parent's Stress, health, priorities and experience of the family:

-*Autism Family Experience Questionnaire (AFEQ)* [33]

- *Parental Stress Index* (PSI*)* [34].

-*General Health Questionnaire (GHQ-28)* [35]

To assess implementation of the intervention:

- *PACT Fidelity Rating Scale*

-Number of PACT training sessions undertaken

-Quality of videoconferencing during each session

-Parent's acceptability of videoconferencing and implementation of PACT at home (self-report on Likert-scale)

-Number of hours per day using PACT at home at 12 months

-Parent's qualitative PACT adherence coded with DCMA on a 12-minute home child-parent interaction video

Figure 2 shows schedule of enrolment, interventions and assessments. Appendix 1 shows more detailed about assessment.

Participant's timeline

Toddlers with a suspected ASD will be approached by health professionals with information about this study. The research recruitment team will meet with the family, complete the ADI-R during the first meeting, and confirm eligibility criteria. Complementary assessments, including ADOS, MSEL with the child and Vineland will be conducted by videoconferencing with the parent, to assess the criteria for eligibility. If toddlers and families meet the criteria for participation, parents will be informed about the study and possibility of an intervention using PACT or TAU based on randomisation. A written informed consent will be obtained if the parent/family agrees to participate in the study after one week of reflection (See Consent form in Appendix 2).

The 'referent parent' used to refer to the parents who will engage with the PACT therapy will be decided before randomisation. Children will be subsequently randomised into the intervention or TAU group. Parents will be informed of the result of the randomisation

Assignment of intervention

Allocation sequence generation and randomisation

All eligible toddlers, with parental consent, will be assigned to the two study groups in a 1:1 ratio using the minimization method with the following stratification factors: the centre, the children's age, level of language (according to the ADOS2 scale) and gender. To ensure allocation concealment, a minimization algorithm with a .90 random element will be used and known only to the statistician (AD). The randomisation will be centralized.

Blinding

Owing to the nature of the intervention, parents and PACT therapists cannot be blind to the allocation group. PACT therapists will not be involved in ASD assessment and diagnosis. An assessor blind to the allocation group will administer every assessment. Data manager and biostatistician will be blinded to the allocation groups.

Data collection and management

Data collection

Data will be collected through standardized observations, parental questionnaires and interviews carried out by a researcher blind to the allocation. We will be particularly vigilant about the measurement accuracy of the first criterion of judgement as described in the paragraph on ADOS-2.

Participation retention and follow-up

Children of both groups will benefit from early diagnosis and assessment and will have the same follow-up evaluations over the 1-year study period in the respective study centres Any discontinuation of study participation will be collected and recorded with the reasons.

Data Management

The study data will be collected on a secure electronic case report form (eCRF) that will be available at each centre through an internet portal. No personal identifying information will be mentioned on the eCRF. Each subject included in the study will be assigned a unique identification number.

All study data will be stored securely in the Academic Hospital of Lyon. All electronic data will be secured on a password-protected laptop. Paper-based study documents will be stored in a secure filing cabinet at each centre. Access to these files will be limited to research staff involved in the study.

The eCRF will only include the data necessary for the analysis to be reported in a scientific publication.

Statistical analysis

Simple size calculation

On the basis of the findings of the PACT Trial (Green, 2010), we have powered the study to be able to detect a difference in overall change on the ADOS score of 2 points. The group difference in mean change between baseline and month 12 was -1 point for ADOS social affect score (mean change=2.9, SD=3.9 in TAU group and mean change=-3.9, SD=4.7 in PACT+TAU group) and -0.5 points for ADOS restricted and repetitive behaviors score (mean change=2.9, SD=3.9 in TAU group and mean change=-3.9, SD=4.7 in PACT+TAU group). The pre- and post-measures were correlated at 0.67. Therefore, the most conservative values were fixed for ADOS standard deviation and for correlation among the repeated measures from a single participant. A target of 238 subjects (119 subjects per treatment arm) was planned to be randomized in the trial. Assuming a 2-point difference in favor of the PACT+TAU compared with TAU, a standard deviation of 5, a correlation between subsequent visits of 0.5, a drop-

out rate of 20%, and a two-sided significance level of 0.05, the planned sample size would provide about 80% power for the study.

Feasibility of recruitment

A strong partnership with ASD orientation platforms recently implemented in France, a broad communication (meeting, mail, flyers) to healthcare professionals (Speech pathologist, Occupational therapist, therapist, paediatrician, general practitioner) family associations and other stakeholders will allow the trial team to reach the sample size within two years.

Statistical analysis

A full statistical analysis plan will be finalized prior to database lock. Statistical analysis and results will be reported at the 12-month endpoint in accordance with the CONSORT 2010 statement. No interim analysis will be scheduled. All the statistical analysis will be carried out according the intention to treat principle using SAS statistical software (SAS Institute Inc., Cary, NC, USA).

Baseline characteristics will be presented in each group.

Summary statistics will be presented for process variables (number of PACT sessions, quality of videoconferencing per session, acceptability and satisfaction of PACT intervention, number of hours declared to be realized with the child) to show the feasibility and acceptability of PACT implementation in the intervention group.

The pattern of missing data will be investigated (number and mechanism of missingness). Missing data strategies can be applied, and sensitivity analysis of different strategies (simple or multiple imputation) will be conducted.

A repeated measures analyses will be used to test the effect of PACT intervention on overall ADOS module 1 score over the 12-month study period. A linear mixed model will be run with the overall ADOS score as the dependent variable and including time (baseline, month 12), treatment (TAU or TAU+PACT) and the interaction between treatment and time as fixed effects and patient as random effect. Model will be adjusted for stratification factors (centre, age, level of language (item A1 ADOS-2) and gender) and baseline variables that show evidence of treatment group imbalance. Time will be represented by dummy variable. Model assumption will be verified according to residual analysis. If most of the assumptions are not met, other alternatives such as transformation of ADOS overall raw score will be examined. Sensitivity analyses like complete case and per-protocol analysis will be performed to assess the robustness of the results to protocol deviations. In complete case analysis, only patient with primary outcome documented will be analyzed. In per-protocol participants who violate the protocol will be excluded from the analysis.

All the secondary outcomes, (overall total score of the BOSCC, communication initiation and synchrony measured with the DCMA, overall raw score of the MSEL in receptive and expressive language, overall score in expressive language of the DLFP, overall raw score of communicative and social of the VABS, Parental Stress Index, Parent General Health score, AFEQ score) will be analyzed in a similar way using

with appropriate linear or generalized linear mixed models. Tobit models will be used to address potential floor effects.

We will finally explore the parent's and children's characteristics, moderating the implementation and efficacy of this therapy. We will also test the previously described mediators implicated in the efficacy of this therapy [14].

Qualitative analysis of barriers and facilitators of implementation

Based on parents and of the therapist's reports, we will describe the facilitators and barriers of the implementation of video-conferencing PACT.

The data will be collected through semi-structured interview and will be analysed with the classical technique of Interpretative Phenomenological Analysis (IPA) [36]. Population selection will follow the rules of the purposive sampling and will allow a maximal variation of the sample [37]. An estimation of 30-60 parents will be necessary to reach data saturation based on previous studies [38–40]. The total number of therapists (around 7-8) will be interviewed. During the 40-60 minutes interview, we will explore the barriers and facilitators to implementing PACT by videoconferencing. A guide for the interview will be elaborated in the initial phase of the project based on first interviews. Interviews will be recorded and transcribed before analyses.

Data from the quantitative and qualitative sources in the process evaluation will be analysed separately. The results of the qualitative study will be integrated with the quantitative results to optimize the findings [41].

Monitoring

Dr Marie-Maude Geoffray (IP) Investigators associated, methodologists, statistician, parent representatives and associate researcher composed the trial steering committee (TSC). The TSC is independent of sponsor and funders and have no competing interests. The TSC has developed the study protocol and is responsible for data collection, management, publications and the final data set.

The coordinating center is independent from the centers for investigation.

According to the French law, the study requires formal data monitoring undertaken by the sponsor. Annual reporting will be completed and submitted to the funders.

Adverse events

Based on results from previous PACT intervention trials, no specific harm from trial participation is anticipated. However, as required by the French law, adverse events will be collected throughout the study and reported in the eCRF section. Description of the event, date of occurrence, intensity, severity, accountability will be reported. Outcomes of this event and action taken after its report will also be concealed.

We anticipate that the early assessment, follow-up consultation on ASD and its management will help and support both groups during the post-diagnosis period. Hence, no post-trial care is planned.

Trial status

The trial status is currently Recruiting. The study has started the 30th June 30, 2020. The anticipated end date will be 30th June 2023.

Figure 3 shows WHO trial registration data set. Figure 4 shows SPIRIT Checklist.

Ethics and ***Dissemination:*** This study (protocol version N°5, date: 10/25/2019) is approved by the French National Review Board (reference No 2018-A02516-49). The results will be disseminated via peer-reviewed journals. It will also disseminate via national and international, general and specialist meeting and through the parent association (https://Bleunetwork.fr; https://autisme-ambitionavenir.com; desailespourgrandir.org). An individual feedback to the participant will be done through a regular newsletter. We will adhere to defined authorship criteria as per the International Committee of Medical Journal Editors.

Author contribution: MMG and ST, PO, LJ conceived and designed the project, and MMG is leading the coordination of the trial. MMG, LJ and PO drafted the protocol and procured the project funding. LJ and MMG are responsible for study implementation, staff training and supervision. PO, ST, AD, AZ contributed to the sample size calculation, the randomisation procedure and the statistical plan, and are responsible for data management, randomisation and statistical analysis. JG contributed to the protocol and paper writing. ARL contributed to the protocol of the qualitative study. CA and NG to the PACT training and supervision of the team. MMG, MJO, LJ, AA, AJ, AB, CS, TM, TD are responsible for recruitment and evaluation of children. SG contributed to draft the paper. All authors critically reviewed and approved the final version of the manuscript.

IFPAD Study group: Mrs Pauline Auphan (psychologist), Mrs Laetitia Bouveret (research assistant), Mrs Laurie Herman (research assistant), Dr Anne-Laure Toureille (PACT trainer), Mrs Lucie Jansen (PACT trainer), Dr Sandrine Sonié (CRA Lyon), Pr.Mario Speranza (CHU Versaille), Pr. Bruno Falissard (Paris), Pr Nicolas Georgieff (Lyon), Dr Matias Winter (HCL), Mrs Nadège Alloisio (parent association), Mr Chams-Ddine BELKHAYAT (parent association).

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Competing interests' statement**:** None declared.

Consent**:** Obtained from both parents of the child (Please find in Appendix 2).

Provenance and peer review: Not commissioned; externally peer reviewed.

Data sharing statement: The trial statisticians will have access to the data set for the analysis of trial outcomes. The PI will have access to the data and will take full responsibility for the analysis and publication of the results. Once the main analyses have been undertaken, data will be available to principal and other investigator subject for approval of data analysis plans by the steering committee.

Figure legends

Figure 1- Consort flow-chart of the study

Figure 2- Schedule of enrolment, interventions and assessments (SPIRIT)

Figure 3- WHO trial registration data set

Figure 4- SPIRIT Checklist

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Figure 1 Consort flow-chart of the study.

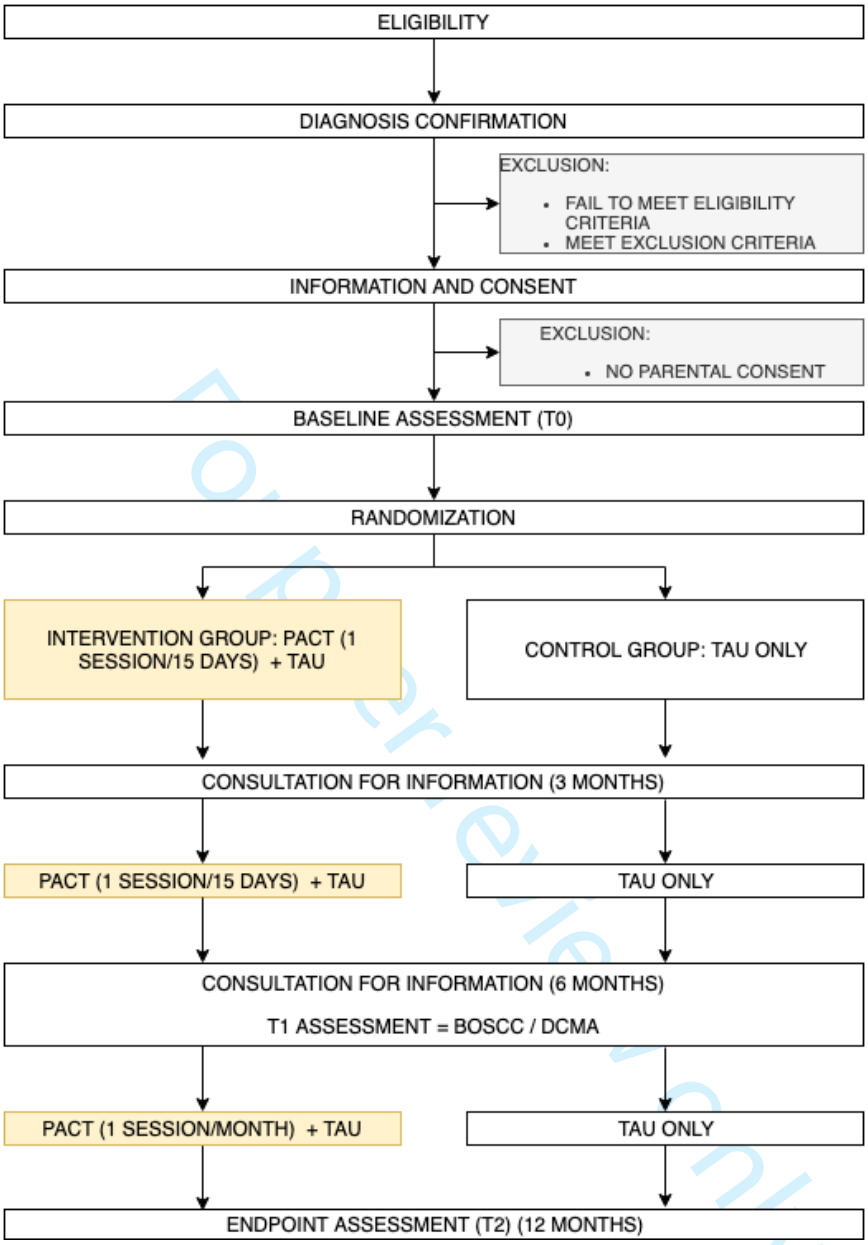

Figure 2. Schedule of enrolment, interventions and assessments (SPIRIT)

Time point	Enrolment	T0 baseline	T1 6 months	T2 12 months
Eligibility screen				
DSM-5 criteria	x			
ADOS-2	x			
ADI-R for toddlers	x			
Nonverbal skills MSEL	x			
Adaptative behavioral level : VABS 2 coded based on an interview done by videoconferencing with parents	x			
Informed consent	x			
Allocation		x		
Intervention				
PACT training (1h/15 days during 6 months then 1h/month during 6 months) + daily practice at home		→	→	→
Treatment as usual		→	→	→
Assessment				
Sociodemographic data		x		x
Autistic symptoms: ADOS-2 (primary outcome)		x		x
Change in socio-communicative interactions: BOSCC Played-based interaction between carer and child at home		x	x	x
Communication Synchronization and initiatives: DCMA at home		x	x	x
Expressive and receptive language Mullen scale		x		x
Daily language DLFP		x		x
Adaptative behavioral level: VABS 2 by video-conferencing		x		x
Parental stress index: ISP-short form		x		x
General parents health : GHQ-28		x		x
Parents quality of life and priorities. AFEQ		x		x
Acceptability of PACT intervention and TAU. (Linkert scale)				x
Implementation: Number of PACT training session Mean of quality of videoconferencing collected after each session Number of hours declared by parents using PACT at home				x x x

Data category	Information
Primary registry and trial identifying number	clinicaltrials.gov : NCT04244721
Date of registration in primary registry	January 28, 2020
Secondary identifying numbers	2018-A02516-49
Source of monetary or material support	This study is supported by a grant from the Programme Hospitalier de Recherche Clinique inter-régional Rhône Alpes (PHRCI-15-065) from the AURA region and a grant by the Caisse Nationale de solidarité pour l'autonomie (CNSA) as part of the call for projects launched for IReSP (Institut de Recherche en Santé Publique) in 2016 in collaboration with the Institut national de la santé et de la recherche médicale (Inserm) (IReSP-17-Autisme3-16).
Primary sponsor	Centre Hospitalier Le Vinatier, Bron, France
Secondary sponsor	Not applicable
Contact for public queries	Marie-Maude Geoffray (PI), email: marie-maude.geoffray @ch-le-vinatier.fr ;Lucie Jurek, email : lucie.jurek@ch-le-vinatier.fr
Contact for scientific queries	Marie-Maude Geoffray (PI), email: marie-maude.geoffray @ch-le-vinatier.fr Sandrine Touzet (scientific contact), email: sandrine.touzet@chu-lyon.fr
Public title	Efficacy of a parent- mediated communication-focused treatment in toddler with autism (PACT)when parents trained by videoconference: a randomised controlled trial study protocol
Scientific tittle	Efficacy of a parent- mediated communication-focused treatment in toddler with autism (PACT)when parents trained by videoconference: a randomised controlled trial study protocol
Countries of recrutement	France
Health condition or problem studied	Autism spectrum disorder (ASD)
Interventions	*Intervention*: PACT for toddlers and young children with ASD *Description*: PACT delivered by the parent trained remotely by therapists 1 hour per 2-weeks during 6 months and 1 hour per month the following 6 months. *Control*: care available in the community, i. e. consultations with a psychologist or child and adolescent psychiatrist, speech and language therapy, occupational therapy, individual or group psychotherapy.
Key inclusion and exclusion criteria	*Age*: between 18 and 36 months *Sex*: male or female *Inclusion criteria*: diagnosis of ASD (Diagnosis and Statistical Manual of Mental Disorders, Fifth Edition, and Autism Diagnosis Observation Schedule), child will have a non-verbal age above 12 months on the Mullen Scale of Early learning, family living further than 40 min away from an ASD specialized center. *Exclusion criteria*: serious neurological or physical condition, family unavailable for a regular follow-up.
Study type	Interventional *Allocation*: randomized 1:1; parallel assignment; blinding: assessor blind
Date of first enrolment	15th July 2020
Target sample size	238
Recrutment status	Recruiting
Primary outcome	Change in ADOS-2 module 1 standardized score at 12 months
Key secondary outcomes	Child development, child adaptative behavior, child socio-communicative abilities, quality of life of parents, parental stress, obstacle and facilitators of the intervention model.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	12 (fig 3)
Protocol version	3	Date and version identifier	13
Funding	4	Sources and types of financial, material, and other support	13
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	13
	5b	Name and contact information for the trial sponsor	13
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
	6b	Explanation for choice of comparators	3
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4

Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	6
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9 (fig 2)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	11
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	12
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	13
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	12
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13
	31b	Authorship eligibility guidelines and any intended use of professional writers	13
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	14

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	App 2
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Appendix 1: Secondary outcomes

The secondary outcomes are measured using standardized coding assessments of naturalistic observational videos (BOSCC, DCMA), performance-based standardized tests (MSEL), and parent-report-based standardized tests (VABS, DLFP, AFEQ, ISP, GHQ).

To assess social communication and interaction in the natural setting of parent-child interaction at home

Brief Observation of Social Communication Change (BOSCC) measures the same construct as the ADOS. It is a researcher coding assessment of autism symptoms based on child-adult interaction. It has good fidelity and results showed good construct validity [1]. The validity to measure the change was analysed in two small populations (N=20-50) and will have to be reanalysed in further trials [36,37]. It has the advantage to allow measure Dyadic interaction across different contexts. It was translated and retro-translated for the purpose of a previous study [2]

The scale is composed of 12 items scored from 0 to 5 according to the BOSCC algorithm. There is an overall score of 0 to 60 measuring core autism symptoms. A higher score indicates more autistic symptoms.

In the current study, a 12 minutes home-video will be recorded by the parents themselves. The parent will be provided with a simple protocol to follow using a standardized set of toys. The standardized set of toys given to the families at each time of assessment will include a cause and effect toy, shape sorter or puzzle, construction toys, miniature pretend play. The protocol includes 10 minutes time of natural play with children with the set of standardized toys and 2 minutes with bubbles play. A first unscored videotape would be done on the center (at T0) to train the parents to video record based on the protocol. In the week following, the parent will videotape at home a child-parent interaction according to the protocol with the standardized set of toys and send the video to the researchers via a secure platform. Professional may make up to two further requests if the video received is judged to not be of adequate quality. If the parent isn't able to send a usable video according to the protocol, the researcher completes a home visit to demonstrate and help the parent to do the video the third time. Two further videos will be done at home at 6 months (T1) and 12 months (T2) in order to assess Social communication interaction in a naturalistic setting.

All the video will be scored by trained researchers.

The same parent called the "referent parent" will be videotaped by a relative at each time of assessment. He/ she will be identified before the randomisation. It will also be the parent who receive PACT therapy if in the group of PACT intervention.

To assess dyadic communication in the natural setting of parent-child interaction at home

The *Dyadic Communication Measure for Autism (DCMA)* is a direct observation instrument of the communication between a parent and a child with autism [3]. It rates parental and child mutual shared attention, child communication (initiation and response) and parental communication style (synchronous/asynchronous).

Independent inter-rated reliability on synchrony has been reported and is good [3]. It was translated and retro-translated for the purpose of a previous study [2]

It can be used to code a number of acts of communication per timepoint. A higher score indicates better communication.

Coding will be done on the same 12 minutes home parent-child video described above in BOSCC at baseline, 6 months and 12 months.

To assess child cognitive development

The *Mullen Scales of Early Learning (MSEL)* is a direct observation standardized tool from birth to 68 months [4]. It measures verbal and non-verbal skills of the children, according to the success or failure in tasks of the MSEL protocol delivered by a trained researcher. The MSEL has been used extensively as a discriminative and evaluative measure in children with autism spectrum disorder, Fragile X syndrome, and speech delays [5–7]

The MSEL will be assessed on the center before the inclusion and at 12 months.

Internal consistency and concurrent validity are good [4]. It was translated and retro-translated for the purpose of a previous study [2]

The MSEL includes 124 items that measure five specific domains: 1) Gross Motor; 2) Fine Motor; 3) Visual Reception; 4) Expressive Language; and 5) Receptive Language. Scoring varies by item from 2-point scale (0 = does not meet criteria to 1 = meets criteria) to a 6-point scale. Results for each scale are described by T scores (M = 50, SD = 10), percentile ranks, and age equivalents. Four cognitive scales (Visual Reception, Fine Motor, Receptive Language, and Expressive Language) sum to represent an Early Learning Composite Score which measures overall cognitive functioning (M=100, SD=15). A higher score means better skills. This evaluation will be realized before inclusion and at 12 months.

To assess child language development

The “development of expressive language”, a standardised French Scale (Development du Language de Production In french_DLPF), is based on a self-administered parent-report [8]. This measure is standardised for age. Only the level 4 of the DLPF will be administered at each assessment to have a continuous score on expressive language. The DLFP was validated in a study [3]. Score is calculated based on the number of words in the naturalistic environment of the child as reported by the parents. A higher score means better language skills. This questionnaire will be completed by the referent parent at baseline and at 12 months.

It will complete the measure of functional communication with VABS-2 and standardised measure with MSEL.

Adaptative behavior

Vineland Adaptive Behaviors Scales second version (VABS-2) is a parent reported scale to measure the child’s daily personal and social skills [9]. This measure will be collected via a parental interview over videoconferencing before the inclusion and at 12 months. Videoconferencing model has been chosen

in our study to avoid multiples visits on the centre but also to evaluate, before the inclusion, if a long videoconferencing meeting could be done with the family on a technical point of view. A first assessment will be proposed to the parents. In case of technical difficulties during the first meeting, a second, and if necessary, a third meeting will be proposed. Tips to improve videoconferencing will also be provided to the parents. In case of failure of every remote assessment, the family will be considered as not eligible for the study as the remote PACT session require the ability to conduct a videoconferencing meeting.

This measure will provide an estimate of any assesses functional change in socialization, communication, motor and daily living skills, based on parent observation in the naturalistic settings of the child.

The VABS has well-established psychometric properties [9,10]. It is validated in french.

All of the items are rated on a three-point Likert scale, ranging from '0' (seldom or never present) to '2' (always present). Results for each scale are described by t scores (M = 50, SD = 10). An overall score is described by normalized score (M=100, SD=15). The range for each subscale is from 20 to 140. The subscales are summed to compute a total score, ranging from 80 to 560. The higher the scores are, the better adaptive functioning the children achieve.

To assess Parent's Stress, health, priorities and experience of the family

The psychometry of the following tools are described in the manual of each tool.

Autism Family Experience (AFEQ) [11] is a 48-item self-administered parent report about quality of life and priorities for early intervention. It is composed of 4 subscales: experience of being a parent (range 13-65), family life (range 9-45), child development understanding and relationships (14-70), child symptoms (12-60). The sum of all domains gives the total score (range 48 - 240). Each question is assessed using a 5-point Likert scale. Scores range from "always" (1) to "never" (5)". It was translated and retro-translated for the purpose of this study with the author. For the total score and the domain scores a higher score indicates a lower outcome. This questionnaire will be completed by the referent parent at baseline and at 12 months.

ISP (Parental stress index) is a 36-item self-administered parent report to measure the stress in the parent–child system. The PSI consists of three subscales: Parental Distress, Parent–child Dysfunction Interaction, and Difficult Child. Each subscale consists of 12 items rated from 1 (strongly agree) to 5 (strongly disagree), with subscale scores ranging from 12 to 60. The three domains combined form a Total Stress score (with a total score ranges from 36 to 180). We will use the short form of the 4th edition. A validated French version exists [12]. A higher score on the subscales and total stress score indicates increased levels of stress. This questionnaire will be completed by the referent parent at baseline and at 12 months.

General Health Questionnaire (GHQ-28) is a self-administered parent report, 28 item scaled version, assessing somatic symptoms, anxiety and insomnia, social dysfunction and severe depression. Each item is rated according to a Likert score method (1 to 4). The GHQ-28 global score range from 36 to 110 [13]. A higher score means more health problems. This questionnaire will be completed by the referent parent at baseline and at 12 months.

To assess implementation of the intervention

Professional adherence to the treatment:

All therapy training sessions with professionals will be videotaped and will be independently rated by the lead therapist using the PACT Fidelity Rating Scale (of the PACT manual) at regular intervals across the trial period. The PACT Fidelity Rating Scale measures how the therapists follow the PACT manual including the style of training.

Acceptability and feasibility of the PACT session

The therapist will collect the number of the session done with each parent. The quality of videoconferencing during each session with the professional will be rated. Quality of sound and quality of the image will be rated with a 4-points Linkert scale. The number of disconnections along the session will also be collected.

The parents will self-report (likert-scale) the acceptability of videoconferencing training and implementation of PACT at home.

Parent PACT adherence at home

At 12 months, Parents will declare the average number of hours per day using PACT at home outside the PACT session with the therapist.

DCMA, coded on the 12 minutes home child-parent interaction will measure the parent's qualitative adherence of PACT intervention.

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Code promoteur : IFPAD

Formulaire de recueil de consentement de participation à une recherche

Titre : Efficacité sur la sévérité des signes autistiques du jeune enfant avec un trouble du spectre autistique d'une intervention développementale conduite par les parents formés par visioconférence (IFPAD).

Investigateur coordonnateur : Dr Marie-Maude GEOFFRAY

Promoteur : *CH Le Vinatier*
95 Boulevard Pinel
69677 BRON CEDEX

Je soussigné représentant légal n°1 : NOM et Prénom : _____ Je soussigné représentant légal n°2 : NOM et Prénom : _____

De l'enfant : NOM et prénom du mineur : _____
Né(e) le : / / à (ville et code postal) : _____
Demeurant : _____

Déclare : que le Dr _____, nous a proposé de faire participer notre enfant à l'étude sus nommée,
-qu'il nous a expliqué en détail le protocole,
-qu'il nous a notamment fait connaître :

- L'objectif, la méthode et la durée de l'étude
- Les contraintes et les risques potentiels encourus
- mon droit de refuser de participer et en cas de désaccord de retirer mon consentement à tout moment
- notre obligation d'inscription à un régime de sécurité sociale pour mon enfant
- que, si nous le souhaitons, à son terme, nous serons informés par le médecin investigateur de ses résultats globaux
- que le comité de Protection des Personnes Sud-est III a émis un avis favorable en date du 30/10/2018 et a accepté l'amendement de la version N° 5 du protocole en date du 25 octobre 2019.
- que l'ANSM a été informée de la mise en place de cette étude
- que dans le cadre de cette étude le promoteur, le CH le Vinatier, a souscrit à une assurance couvrant cette recherche : Assurance SHAM, 18 rue Edouard Rochet, 69372 LYON CEDEX 08

-que nous avons répondu en toute bonne foi aux questions concernant l'état de santé de notre enfant et sa participation à d'autres études.

Les informations relatives à l'étude recueillies par l'investigateur sont traitées confidentiellement. J'accepte que les données enregistrées au cours de l'étude puissent faire l'objet d'un traitement informatisé conformément à la méthodologie MR001 de la Commission Nationale de l'Informatique et des Libertés (CNIL). Nous avons pris connaissance que le Centre Hospitalier Le Vinatier est responsable de nos informations personnelles recueillies dans le cadre de l'étude IFPAD et que ces informations peuvent être conservées pendant 15 ans. Nous avons bien noté que nous disposons d'un droit d'accès et de rectification, d'effacement et d'opposition au traitement des données nous concernant à tout moment de l'étude auprès

du Dr GEOFFRAY, 04.37.91.52.56 ou auprès du responsable de la protection des données du CH Le Vinatier en le contactant à l'adresse mail : fabien.joubert@ch-le-vinatier.fr ou par téléphone au 04.37.91.54.40, dans le respect de la loi « informatique et liberté » (loi du 6 janvier 1978) et du règlement Général à la protection des données (RGPD) entré en vigueur le 25 mai 2018.

Si nous ne sommes pas satisfaits des réponses que nous avons obtenues, nous pouvons nous adresser à la Commission Nationale de l'Informatique et des Libertés (CNIL) en utilisant le lien : https://www.cnil.fr/

Nous pouvons également contacter les médecins suivants : Dr GEOFFRAY, 04.37.91.52.56 en cas d'événement indésirable et pour tout renseignement concernant ma participation à l'étude et en cas de problème médical survenu pendant l'étude.

Après avoir discuté librement et obtenu réponse à toutes nos questions, nous acceptons librement et volontairement de faire participer notre enfant à cette recherche dans les conditions précisées dans le formulaire d'information et de consentement.

Nom et prénom du représentant légal n° 1 Signature précédée de la mention **« lu et compris »** Date : / / Signature :	Nom de l'investigateur : Date : / / Signature :
Nom et prénom du représentant légal n° 2 Signature précédée de la mention **« lu et compris »** Date : / / Signature :	

Document réalisé en 2 exemplaires originaux (dont le premier doit être gardé 15 ans par l'investigateur, et un autre remis aux parents).

Centre Hospitalier le Vinatier – Service de la Recherche - BP 300 39 – 95 bd Pinel
69 678 Bron cedex