Trial Protocol

Internal project No.:

Efficacy of Internet Based Parent Management Training in the Treatment of Affective Dysregulation and Coexisting Conditions in Children (ADOPT Online)

Teilprojekt 4: Anpassung und Evaluation eines bestehenden Internet-basierten Elterntrainings für Eltern von Kindern mit affektiver Dysregulation

Version 02 , date 17.04.2018

Sponsor

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Bundesministerium
für Bildung
und Forschung

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List of abbreviations

AD	Affective Dysregulation
ADOPT	Affective Dysregulation in Childhood - Optimizing Prevention and Treatment
ADHD	Attention Deficit Hyperactivity Disorder
ANCOVA	Analysis of Covariance
ARH1	Heterogeneous first-order autoregressive (covariance structure)
ARI	Affective Reactivity Index
BSCL	German Brief Symptom-Checklist
CATS	German version of the Child and Adolescent Trauma Screening
CBCL 6-18R	Child behavior checklist (parent-rated)
CoCo	Comorbid conditions
CD	Conduct Disorder
DADYS	Diagnostikum für Affektive Dysregulation bei Kindern
DCL-SSV	Diagnosis Checklist for Disruptive Behavior Disorder
DISYPS-III	German Diagnostic System for Mental Disorders in Children and Adolescents
DMC	Data Monitoring Committee
DMDD	data management manual
DRKS	Deutsches Register Klinischer Studien
DSM-5	Diagnostic and statistical manual of mental disorders of the American Psychiatric Association, 5th edition
eCRF	Electronic case report form
ERC	Emotion Regulation Checklist
FAS	full analysis set
FBB-ADHS	Fremdbeurteilungsbogen ADHS (rating scale for ADHD)
FBB-SSV	Fremdbeurteilungsbogen SSV (rating scale for oppositional defiant disorder and conduct disorder)
FPNE	German Questionnaire for Positive and Negative Parenting
GCP	Good clinical practice
GEE	generalized estimating equation
HTML	Hypertext Markup Language
ICH-GCP	International Conference on Harmonization of Good Clinical Practice
ICTRP	International Clinical Trials Search Portal
ID	identification number
ILF-External	Structured interview for externalizing symptoms
ILF-Internal	Structured interview for internalizing symptoms
ILF-Kontakt	Structured interview for contact-related symptoms
ILF-SCREEN	Structured screening interview
ITT	intention-to-treat
IMSB	Institute of Medical Statistics and Computational Biology
MMRM	Mixed models for repeated measures
MTA	Multimodal Treatment Study of Children with ADHD
NoAD	No Affective Dysregulation
OCD	Obsessive compulsive disorder
ODD	Oppositional Defiant Disorder
OnPaSH-AD	**On**line **Pa**rent **S**elf-**H**elp of **A**ffective **D**ysregulation
PeMOT-AD	Personalized Modular Outpatient Treatment of Affective Dysregulation and coexisting disorders
PMT	Parent Management Training
PP	per protocol
RCI	reliable changes
RCT	randomized control trial

REDCap	Remote data entry system
ROC	Receiver Operator Characteristics
RDoC	Research Domain Criteria
SAD	screen children for AD
SBB-ADHS	Selbstbeurteilungsbogen ADHS (self-rating scale for ADHD)
SBB-SSV	Selbstbeurteilungsbogen SSV (self-rating scale for oppositional defiant disorder and conduct disorder
SCL-K-9	9-item self-report short version of the Symptom-Checklist
SMART	Sequential, Multiple Assignment, Randomized Trial
SOP	Standard operating procedure
TAU	Treatment as usual
TMF	trial master file

Synopsis

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GRANT	GEFÖRDERT VOM Bundesministerium für Bildung und Forschung
TITLE OF STUDY	Efficacy of Internet Based Parent Management Training in the Treatment of Affective Dysregulation and Coexisting Conditions in Children (ADOPT-online)
BACKGROUND	The term *Affective Dysregulation (AD)* describes a transdiagnostic dimension and characterizes an excessive reactivity to negative emotional stimuli with an affective (anger) and a behavioral component (aggression). AD is a criterion for several DSM-5/ICD-10 diagnoses. Given the overlap of symptoms of AD with the criteria for these diagnoses, it is not surprising that high rates of AD are found in children with ODD/CD, ADHD, anxiety disorders, mood disorders (Nock, Kazdin, Hiripi, & Kessler, 2007), as well as attachment disorder and post-traumatic stress disorders. Effective psychotherapeutic approaches include parent management training (PMT) and/or child-centered cognitive-behavioral therapy and to date mostly focus on proactive aggression rather than on affective dysregulation, irritability or anger.
OBJECTIVES	Primary: To adapt and to determine the efficacy of an online self-help PMT (OnPaSH) in comparison to Treatment as Usual (TAU) in children aged 8;0 to 12;11 yrs. with substantial symptoms of AD. Secondary: (1) to evaluate the feasibility of the implementation in children drawn from a community sample; (2) to evaluate predictors, moderators, mediators and stability of outcome.
OUTCOMES	Primary efficacy measure: Change in AD from T1 to T2 according to a blinded clinician-rated patient and parent interview conducted with the Outcome Measure for AD (DADYS) that is developed in *ADOPT-epidemiology* Key secondary measures: Blinded clinician-rated psychosocial impairment (from DISYPS-III); patient- and parent -rated AD, ADHD and ODD/CD (from DISYPS-III), other comorbid conditions (e.g., anxiety, depression) (CBCL 6-18R; TRF 6-18R; DISYPS-III), psychological well-being (KIDSCREEN) *Predictors/Moderators for treatment outcome*: 1) gender, (2) age, (3) chronicity of AD-Symptoms, (4) severity of AD symptoms, (5) severity of comorbid symptoms, (6) AD-symptoms and other psychopathologyof the mother, (7) public assistance of the family, (8) socioeconomic status of the family, (9) early childhood neglect of the patient, (10) traumatic events experienced by the patient, (11) family

	climate, (12) social support, (13) profile of usage of the online tool (only as predictor in the OnPaSH group) Mediators for treatment outcome: positive and negative parenting practices.
INCLUSION CRITERIA	• Age 8;0 to 12;11 yrs. • Resident with at least one natural parent • Clinician-rated Outcome Measure for AD (DADYS interview, DADYS questionnaire) > cut-off. The cut-off will be determined by a clinical overall rating of AD at the end of the structured clinical parent interview. • Willingness and ability of parents to participate in the online intervention (existence of an informed consent of the guardians and an assent of the child)
EXCLUSION CRITERIA	• Intelligence below average (IQ < 80) • Resident without natural parents (e.g. foster parents, grandparents) • mental disorder other than Coexisting Conditions (CoCo) is primary disorder and main cause of AD (e.g. autism spectrum disorder, OCD) • current or planned intensive behavioral therapy on a weekly/biweekly basis
STUDY TYPE	Randomized controlled parallel group trial, observer blind, Sequential, Multiple Assignment, Randomized Trial (SMART) with subsequent Personalized Modular Outpatient Treatment
LEGAL FOUNDATION	Consultation and approval of study by independent ethics committee according to section 15 of the Medical Association's Professional code of conduct (Berufsordnung)
STATISTICAL ANALYSIS	Efficacy: The primary outcome measure is the change in AD symptoms (DADYS) from T1 to T2 (i.e. following 3 months of treatment). Estimated marginal means are compared between groups. Description of the primary efficacy analysis and population: The full analysis set (FAS) includes all randomized patients with a valid T1 assessment and at least one follow-up measurement (ITT approach). The "change in AD symptoms from T1 to 3 months post randomization (T2)" is evaluated by analysis of covariance (ANCOVA). To assess the impact of up to 20% attrition multiple imputation approaches are taken, accounting for proxy measures and assuming specfic missingness-not-at-random patterns. The details are documented in a statistical analysis plan. Analysis of subjects essentially observed and treated per protocol (PP) is supportive. Effect size assumed for estimation of sample size: 0.356 (Cohen's *d*); 5:1 randomisation. Safety: Adverse events are aggreated by type, seriousness, intensity and relatedness; PAERS ratings are summarized by item (group) and

	treatment arm. Key secondary endpoints: Rating scores are analyzed along the same lines as the primary outcome measure; possibly using linear mixed models for repeated measures (MMRM) over time (ARH1-structured covariance matrix). Subgroup (moderation) analyses are done by gender, age, AD symptoms (chronicity, severity), comorbid symptoms, depression, anxiety, parental stress, public assistance of the family, socioeconomic status of the family, positive and negative parenting practices; interaction with treatment is investigated. All efficacy and safety variables are summarized by time point and treatment arm (mean, standard deviation, percentiles (0, 25, 50, 75, 100); count, percentage).Mediation analyses are done for parental self-efficacy, positive and negative parenting practices and dysfunctional parental attributions.
SAMPLE SIZE	To be allocated to trial (n=560); to be analysed (n=560 ITT; n= 443 PP). Sample size is determined by the subsequent *ADOPT-treatment* trial.
TRIAL DURATION	Time for preparation of the trial: 6 months; Recruitment period: 18 months; First patient in to last patient out (at T4): 39 months; Time for data clearance and analysis: 3 months; Duration of the entire trial: 48 months
PARTICIPATING CENTRES	n=5 centers (Dresden, 2x Köln, Mannheim, Ulm). If needed additional recruitment centers can be added.

1. Introduction and scientific background

1.1. Clinical background

The terms *AD* and *irritability* are largely used synonymous. Most definitions characterize this condition as excessive reactivity to negative emotional stimuli with an affective (anger) and a behavioral component as reflected in externalizing problem behavior like disobeying rules, aggressive, or oppositional behavior. People with AD are overly angry or aggressive in response to provocations. AD or irritability is a criterion for many DSM-5 and ICD-10 diagnoses in children, including mood and anxiety disorders, ADHD, and conduct disorders. AD features are most prominent in oppositional defiant disorder (ODD) (Leibenluft & Stoddard, 2013; Shaw, Stringaris, Nigg, & Leibenluft, 2014). AD fits well within the framework of the recent National Institute of Mental *Health Research Domain Criteria (RDoC)* initiative (Insel et al., 2010) which suggests dimensional constructs that cut across multiple diagnoses and can be examined at multiple levels. The current RDoC include the construct of frustrative nonreward within the negative emotionality domain which encompasses AD (National Institute of Mental Health Research Domain Criteria Project, 2011).

In preventive as well as in psychotherapeutic contexts behavioral PMT is regarded an evidence-based treatment to decrease child externalizing problem behavior (National Institute for Health and Care Excellence, 2013; Sukhodolsky, Kassinove, & Gorman, 2004; Weisz et al., 2013). So far PMT concentrate on the behavioral, but not on the affective component of AD. Preliminary evidence suggests that, to meet the needs of parents with highly irritable children, regular PMT need to be advanced by components focusing on emotion regulation (Waxmonsky et al., 2016). One aim of the trial is to supplement our formerly tested parent interventions (Kierfeld et al., 2013; Ise et al., 2015) by a special component on teaching children how to regulate their emotions. To date no PMT for German speaking families has addressed this issue. As psychosocial risk factors increase the risk for child behavior problems as well as make frequent attendance of parent sessions less likely (National Institute for Health and Care Excellence, 2013), we aim at realizing this advanced parent intervention as a self-help online intervention. No such web-based PMT is yet available, neither nationally nor internationally, for parents of AD children. In general, self-help or online PMT have proven to be effective in reducing child behavior problems. However, they might only be capable of reaching a subpopulation of parents (Kierfeld et al., 2013), e.g. better educated, less burdened, those with less affected children. In the framework of a stepped-care approach self-help interventions can thus serve as a time-and cost-effective first step of intervention that can reduce symptoms in a subpopulation (Tarver et al., 2014; Ng & Weisz, 2015). As evidence is inconsistent with respect to moderators of PMT effects, we aim at analyzing various moderators that can be used to predict intervention efficacy. There is evidence for parental practices as mechanism of change in PMT, although results are not consistent [Forehand et al. 2014]. Therefore we will conduct mediation analyses to examine – among others - the change of parenting practices due to PMT as putative mediator for the change of AD symptoms of the child.

1.1. Current state of science and research

The following search terms combined by ’or‘ were used to define the medical problem: *affective dysregulation, emotional dysregulation, irritability, lability, anger, disruptive mood dysregulation, severe mood dysregulation, intermittent explosive disorder*. Hits were limited by ‚and child’*‘. 8050 hits were found in Medline, 10179 in PsycInfo, 313 in PSYNDEX, 1347 in the Cochrane library, 0 in Deutsches Register Klinischer Studien (DRKS) and 220 in International Clinical Trials Search Portal (ICTRP). These hits were narrowed down by adding combinations of the terms *treatment, training, parent, cognitive-*

behavioral, therapy, prevention, self-help, Internet-based, and *web-based*. Due to the great body of literature on effects of PMT systematic reviews and meta-analysis were considered first, and then supplemented by newly conducted or published trials which had not been identified by the systematic search. For PMT effects specifically on AD children and for effects of online interventions single studies are reported as well as reviews and meta-analysis if available. A total of 85 relevant papers and trial discriptions was selected for further inspection.

As shown by various meta-analyses cognitive-behavioral PMT are effective in reducing child externalizing behavior problems in general (Furlong et al., 2012), in children with ADHD (Daley et al., 2014), and in children with ODD and conduct disorders (National Institue for Health and Care Excellence, 2013). Analysing the data of 13 randomised controlled or quasi-randomised trials Furlong and co-workers (Furlong et al., 2012) reported clinically significant effects of moderate size. Here, long-term outcome could not be determined due to missing follow-up comparisons of intervention and control groups. An older meta-analysis using less rigorous inclusion criteria for 83 PMT studies found similar immediate treatment effects (Lundahl et al., 2006), that decreased to small effect sizes after one year follow-up (21 studies).

Mediation analyses evaluate the conceptual theory of a treatment by testing mechanisms hypothesized to bring about the change (Gottfredson et al., 2015). Analysis of mediating processes in PMT find the reduction of dysfunctional parenting (Hanisch et al., 2014), as well as increases of positive parenting (Gardner et al., 2006) and improvements of parent-child relationship (Zhou et al., 2008) to account for positive treatment effects. Effects of PMT have found to vary based on family as well as on child characteristics (Lundahl et al., 2006). Family adversity, e.g. low socioeconomic status or single parent status are examples for factors that have been reported to undermine PMT effectiveness. Child factors predicting PMT outcome have previously been nature and severity of symptoms (Hautmann et al., 2010) or child gender (Eyberg et al., 2008). The two most recent meta-analysis on PMT come to different conclusions with respect to moderation of interindividual differences in treatment outcome: while the 2006 meta-analysis (Lundahl et al., 2006) finds economically disadvantage to be the most salint moderator, favoring children with less family adversity, the more recent review by Furlong neither found symptom severity nor socioeconomic status to have moderating effects (Furlong et al., 2012).

Effectiveness studies assess intervention outcomes across different real-world practice contexts and can estimate the ecological validity of treatment effects. In their meta-analysis Michelson et al. summarize the effects of 28 effectiveness trials comparing everyday real-world treatment application to waitlist control groups (Michelson et al., 2013). The authors conclude that PMT is effective even when delivered under a variety of everyday practice conditions. There was no consistent relationship between effect sizes and the degree to which the included trials reflected real-world practice criteria.

Cognitive-behavioral PMT can thus be regarded an evidence-based treatment for reducing child disruptive behavior across various populations, subgroups within this populations, and delivery settings. However, little is known on the effectiveness of similar group-based parenting interventions in relation to child emotional problems like irritability (Furlong et al., 2012; Sukhodolsky et al., 2016).

In the MTA study sample children with ADHD and comorbid irritability were treated most effectively with medication or with a combination of parent training and medication. Here, parent training alone was equally effective as community care. Treatment response for children with ADHD and comorbid oppositional and aggressive behavior differed insofar that parent training alone was superior to

community care. Irritability thus seems to be a separable dimension within the ODD construct in children with ADHD calling for specially tailored interventions (Fernandez de al Cruz et al., 2015). Waxmonsky and co-workers conducted the first randomized trial of a psychosocial therapy designed for youths with severe mood dysregulation (Waxmonsky et al., 2016). The experimental treatment (combination of medication and parent and child group sessions integrating components from cognitive-behavioral therapy for mood disorders, parent training for externalizing disorders, and social-cognitive programs for aggression) was superior to the combination of medication and community care in reducing parent-rated irritability. Dosage effects were reported for the reductions in hyperarousal and other mood symptoms. Here, the psychosocial treatment outperformed medication alone, stressing the need for adding interventions specifically targeting AD. Dunsmore and coworkers (2016) found that the presence of high levels of externalizing symptoms predicted reduced efforts by parents to engage in emotion regulation coaching with their child indicating that there might be an especially harming interplay between child temperamental and behavioral characeristics and parenting behavior in AD children with additional externalizing problems. Parents of AD children thus need to be especially trainined in promoting their child‘s emotion regulation.

Despite clear evidence with regard to efficacy and cost-effectiveness of PMT, interventions can be hard to access for families living in rural areas or exhibiting psychosocial adversities (Furlong et al., 2012). Local availability, lack of transportation, or missing childcare are examples of practical factors hindering parents to attend (National Institute for Health and Care Excellence, 2013). Book or Internet-based, telephone assisted self-help PMT seem to be effective and easy to access alternatives to face-to-face PMT (Tarver et al., 2014; Breitenstein & Gross, 2013; Breitenstein, Gross & Christophersen, 2014). In their meta-analysis Tarver and co-workers estimated pooled standard mean difference of eleven trials of self-directed parenting intervention with no face-to-face therapist input resulting in large effect sizes (mean=1.01; 95% CI=0.7 to 1.24) for parent-reported change in child problem behavior. Effects did not uphold (SMD=0.15), however, when observed child behavior was considered. For all outcomes, effect sizes decreased after removal of interventions that involved regular therapist contact via phone or Internet suggesting that this had at least some mediating effect. Tarver studied mostly book or video based self-help programs, three out of eleven combined books with online tools. In Breitenstein’s systematic review on eleven studies nine different digital delivery methods were reported (e.g. Internet, television, DVD; Breitenstein, Gross & Christophersen, 2014). Six of the nine used the Internet as the primary delivery method. The average proportion for intervention completion was 78.3% of sessions outperforming attendence rates of face-to-face PMT by far (Breitenstein, Gross & Christophersen, 2014). Four studies reported parent-rated behavioral outcomes resulting in effect sizes of *d*=0.61 for child, and *d*=0.46 for parent outcomes. In a more recent paper, parents of preschool children with ADHD symptoms completed a self-directed, interactive parent training delivered via the Internet (Franke et al., 2016). In a RCT design, short term effects were found on various mother-reported child and parent outcomes. However, six-month stability was only seen for a reduction in dysfunctional parenting and for increases in mother’s well-being.

After 18-month a 10-week Internet-delivered PMT resulted in decreases of dysfunitional parenting and of conduct problems in an indicated community sample (Högström et al., 2015). Here, total number of homework completed by parents predicted short-term, but not long-term changes in child behavior. Positive parenting, on the other hand, declined during the follow-up period.

The Cologne research group conducted various RCTs on book-based self-administered PMT. Positive treatmemt effects on child externalizing problem behavior upheld one year after the intervention, and

the number of children with externalizing behavior within the clinicial range was decreased (Ise et al., 2015). Comparison of a behavioral with a nondirective guided self-held parent intervention in a clinical sample of children with externalizing disorders suggests that ODD, but not ADHD symptoms declined more in the behavioral intervention group than in the nondirective. An analysis of mediating processes made a change in parents‘ attribution of a less hostile intent responsible for this differential treatment effect (Katzmann et al., 2016) implying that this topic should be covered in OnPaSH-AD as well.

To our knowledge only one evaluation has yet been published of a self-administered PMT formatted for mobile devices (Breitenstein et al,. 2016). The authors examined the use and efficacy of a self-administered, tablet-based PMT in a sample of low-income ethnic minority parents of 2-5-year old children recruited from a pediatric primary care setting. The tablet-based PMT was compared with a face-to-face health promotion group. Treatment completion rate was significantly higher in the tablet-based condition and resulted in greater improvements in parenting warmth. No other significant group differences were found. Authors compared the effects on parenting behavior in the tablet-based version of their parent training with previous findings of their face-to-face parent intervention and found similar or greater effects of the self-administered version. Using a population-based screening procedure Sourander et al. (2016) targeted an indicated preventive preschool sample to compare an Internet version of their PMT to an education control group that was provided access to a website introducing parents to positive parenting strategies, to a 45-minute call from a coach, and to standard care by their physicians. Internet-based PMT resulted in significant improvement in child externalizing symptoms six and 12 months after randomization compared with the education control group. Interestingly, here child emotional problems were assessed as well, and affective and anxiety problems were reduced as well as disrutive behavior problems.

PMT are thus effective when delivered in self-administered, Internet-based formats. No completed or ongoing study could be found that evaluates an extended self-help PMT for AD children covering emotion regulation aside from regular PMT topics.

Summarizing the national and international findings, there is clear evidence for efficacy of PMT for child externalizing behavior problems delivered either with face-to-face therapist contact or online. Treatment components reducing dysfunctional and increasing positive parenting seem to be crucial to reduce disruptive behavior. Preliminary evidence suggests that interventions for children with additional AD need to extend regular PMT by components teaching parents how to support child emotion regulation. As severely affected AD children oftentimes live in families suffering from multiple adversities these specialized treatments should address special needs for this parent population. Easy to assess Internet-based interventions seem to be especially promising for highly burdened parents. Thus, taking these findings as the theoretical basis the aim of ADOPT Online is to develop and evaluate an online training that is tailored to the special needs of parents of children with AD and CoCo.

2. Objectives

The results will inform future guidelines on the treatment of children with AD and CoCo and will help to improve guidelines and to develop usable, potentially more cost-effective, individualized modular treatment in children with AD. The study will specifically convey about the benefit of online self-help for parents compared to standard approaches. These effects will be related to AD symptoms, comorbid symptoms, impairment, and psychological well-being. The main results are on diagnostic instruments and psychotherapeutic interventions. Since AD is an important risk factor for the development of severe mental disorders, results should affect the health status of the pediatric target population in

later periods of life. Therefore, the results of the proposed project will be highly relevant for the assessment and treatment of children with AD and CoCo.

The following principal *research questions* are to be addressed:

(1) What is the overall efficacy of the **On**line **Pa**rent **S**elf-**H**elp of **A**ffective **D**ysregulation and coexisting disorders (OnPaSH-AD) on AD and comorbid conditions, functional impairment and psychological well-being in comparison to Treatment as Usual (TAU) in children aged 8;0 to 12;11? What is the clinical significance of the symptom-change in terms of normalization rates (in comparison to a control group of participants without AD, defined at T1) or reliable changes (RCI, Jacobson & Truax, 1991)?

(2) How feasible is the online treatment and how satisfied are parents with the intervention?

(3) Can specific psychopathological profiles be identified (e. g. AD with high ADHD compared to AD with low ADHD) that moderate/predict treatment outcome?

(4) Which moderators/predictors (e. g. gender, age, parental mental health) can be identified to predict treatment outcome?

(5) What is the stability of the treatment outcome for those with no substantial residual symptoms of AD after the online intervention?

(6) Do the theoretically expected treatment mechanisms work (e. g. change in parenting behavior mediates symptom change in the child)?

3. Study design and trial duration

This is a interventional, multicentre, randomized-controlled study with two parallel treatment arms according to section 15 of the German Medical Association's Professional code of conduct (Berufsordnung).

Overall design of the whole ADOPT Consortium: Sample recruitment for ADOPT *Online* will be performed by ADOPT Epidemiology. Children selected from a community sample via a short screening instrument will be included. At T1 symptoms of AD will be more intensively evaluated by clinician's ratings based on patient and parent interviews conducted with the outcome measure for AD that is developed in ADOPT Epidemiology. Exclusion criteria (IQ < 80; mental disorder other than CoCo is primary disorder and main cause of AD (e.g. autism spectrum disorder, OCD); current or planned intensive behavioral therapy on a weekly/biweekly basis, child is resident without natural parents (e.g. foster parents, grandparents)) will also be assessed at T1.

Design of ADOPT Online as part of the overall design of the ADOPT Consortium: Children selected from a community sample (see ADOPT Epidemiology) will be randomized to TAU or the **On**line **Pa**rent **S**elf-**H**elp of **A**ffective **D**ysregulation and coexisting disorders (OnPaSH-AD). After 3 months with parents' access to OnPaSH-AD children will be reassessed (T2). Parents randomized to TAU will gain access to OnPaSH-AD after T2. First patient in at T1 to last patient out at T2 will take 21 months (18 months recruitment + 3 months OnPaSH-AD + asessment). ADOPT Online will also persue T3 to T4 of those in the No AD group from the beginning as well as those who showed no residual AD at T2. Therefore first candidate in at T1 to last candidate out at T4 takes 38 months. Time for preparation includes finalizing of the online material and will take 6 months, time for data clearance and analysis is caluculated with 3 months; duration of the entire trial thus adds up to 48 months. T3 assessment as follow up has to be conducted with 90 of those successfully finishing online, 64 of the No AD group from T1 and 56 from

the control group (210 children in total). Additionally, at T4 167 are assessed for further follow-up (assuming a further drop-out of 20% from T3).

4. Sample and selection of trial population

In total, n = 560 children will be recruited. There is no gender-specific discrimination concerning inclusion of patients. Boys as well as girls at the age of 8;0 to 12;11 years will be able to participate. Premise of the inclusion is the fulfilment of the inclusion and exclusion criteria, the existence of a signed informed consent of at least one parent/guardian as well as the signed assent of the child.

The community sample is drawn by ADOPT Epidemiology. A Screening Tool for AD in children (SAD) then identifies the AD (n= 650) and the NoAD (n= 100) sample. For ADOPT Online children with AD will be recruited at 5 sites (2x Cologne, Dresden, Mannheim, Ulm) in 3 waves within 18 months. At T1, inclusion and exclusion criteria will be evaluated for the AD sample, resulting in an estimated sample size of n = 560 children. Thus, we expect n = 90 children to be non-eligible at T1. Totally 560 children will be randomized (467 for online, 93 for control = TAU). That is 467:3:5 ≈ 31.1 patients have to be included per wave and site (and additionally 93:3:5=6.2 patients per wave and site are allocated to TAU). The distribution of included patients per study center is not necessarily fixed and only an estimation.

4.1. Inclusion criteria

Patients will be included if they meet following inclusion criteria:

1. age of child: 8;0 to 12;11 years (= completed 8th year of life to completed 13th year of life) at T1
2. resident with at least one natural parent
3. clinician-rated Outcome Measure for AD (DADYS-clinician rated) based on patient and parent interview > cut-off. The cut-off will be determined by a clinical overall rating of AD at the end of the structured clinical parent interview. Additionally, this rating is validated by analyses of the Receiver Operator Characteristics (ROC) curve of the DADYS total score based on T1 data (first wave) of the samples of children with no AD and children with AD (based on the screening instrument SAD)
4. willingness and ability of parents to participate in the online intervention.

4.2. Exclusion criteria

In case of parents' or child's refusal to participate in the assessments or, in case of the OnPaSH-AD group, in the intervention the entire family will be excluded. No further data will be assessed from either parents or child. Following exclusion criteria will be additionally applied:

1. intelligence below average (IQ < 80) in clinical evaluation, patient attends school for intellectual disabilities
2. resident without natural parent or adoptive parent
3. mental disorder other than CoCo is primary disorder and main cause of AD (e.g. autism spectrum disorder).
4. current or planned intensive behavioral therapy on a weekly/biweekly basis

5. Trial conduct

5.1. Operationalisation and definitions

5.1.1 Differentiation between AD/ noAD

In the ADOPT Epidemiology sub-project, a parent-reported tool to screen children for AD (SAD) will be developed from already existing mental health screening questionnaires and will be validated and further improved into a first version of SAD based on data of the first wave of participants of the screening at T0. This version of SAD will be used in the on-going ADOPT-study to screen children for AD at T0. Based on this screening data, groups of children with high vs. low AD will be defined using a cut-off which will be determined by means of a statistical case definition (percentile 5, n=650; expected non-response for self-help or AD not confirmed by DADYS approx. 10%: n=560 at T1). According to this cut-off groups with AD respectively noAD will be defined.

5.1.2 Treatment As Usual (TAU)

The control intervention includes TAU for three months. No treatment condition would be unacceptable on ethical grounds. There is no gold standard in the treatment of AD and therefore an active treatment as a comparator is not feasible. TAU as control condition informs about the additional benefit compared to usual care. Within TAU, all psychosocial, psychotherapeutic and pharmacological interventions will be documented. For pharmacological interventions we will only document the disorder or problem which the medication aims to resolve (e.g. ADHD, affective dysregulation) and not the agent, dose, or duration of the treatment. The TAU group will be offered the participation in the online intervention after T2.

5.1.3 Online Intervention

Intervention: Material will be adapted based on an established web-based ADHD-parent-trainer (Schürmann & Döpfner for AOK-Bundesverband; www.adhs-elterntrainer.de) which is adapted from evidence-based printed parent-self-help-programs to reduce child externalizing behavior problems (Michelson et al., 2013; Sukhodolsky et al., 2016, Breitenstein & Gross, 2013). Content and dosage of the self-help programs were previously evaluated in face-to-face group formats (Hanisch et al, 2010; Hautmann et al., 2008). Similar dosages were used by others for online PMT (Högström et al., 2015). Yet, only one publication is available on a multicomponent intervention for children with severe AD that includes a PMT component (Waxmonsky et al., 2016).

The idea of adressing AD via parent self-help is based on the concept of a multifactorial model for the emergence and maintainance of AD symptoms (Leibenluft & Stoddard, 2013). Intervention thus targets every possible factor that might be meaningful for the development of these symptoms, such as parents' problems (misinformation and dysfunctional attitudes or specific parental burdens), child's difficulties (e.g. specific behavior problems), or their interaction (burdened parent-child relationship). For example, by providing information about AD OnPaSH-AD aims at altering parents' attitudes (Katzmann et al., 2016) argues for parents to reduce their burden in order to be better prepared for difficult situations with AD, provides skills for solving specific behavior problems and strategies for strengthening the parent-child relationship.

OnPaSH-AD warrants parents access to four modules whose contents are interconnected: (1) psychoeducation (AD – What's that?), (2) parental management of feelings (3) strengthening the parent-child relationship, (4) how to solve behavior problemes and coach child's emotion regulation.

The fourth module leads parents to analyze individual problems with their child using videotaped examples of parenting situations (permanently bad mood, homework, chaos in the child's room, use of media, siblings' quarrel;) in seven levels step by step. Effective strategies to change behavior problems are presented ((1)detecting problems: what's wrong?, (2) analyzing problems: vicious circle, emotions of parent and child & changing structures, (3) defining family rules and helping with emotion regulation, (4) effective commands, (5) positive consequences, (6) natural negative consequences, (7) using token-plans). Parents are led to use these strategies on their child and to document the outcome. In cooperation with the company that also developed the existing online-intervention for parents of children with ADHD (frühlingsproduktionen), texts and video clips will be tailored to the needs of parents of children with AD (e.g. psychoeducation on AD, how to handle disruptive mood).

Applicability: The online format is easy to apply, and intensity of use and work on the problems remains parents' choice. This might address motivational aspects and therefor be helpful to reach parents, who avoid taking up contact with traditional ways of help or self-help (Sukhodolsky et al., 2016).

Dosage: We choose a three months duration for OnPaSH-AD to give enough time to reach a satisfying degree of change for those parents, who use the material intensively (Högström et al., 2015). Moreover, those parents who fail to use the material within this period of time will probably not start using it after three months, and for these as well as for those children with residual AD symptoms the next step of the stepped-care approach then needs to be approached.

The material will be available in total from the beginning of the three months intervention period. An optional telephone hotline will be provided to be used by parents in case of problems with the material and instructions. Use of this on-call presence for online-participants will be documented. During the three months period participants will receive reminders and reinforcement via automatically implemented e-mails depending on their usage of the online-material. Information about the use of the online tool will be collected from the system after informed consent of the participating parents. The online-material will be hosted via a professional service bound to datasavety and –security by strict contracts that allow the use of any data produced by the participants only by the study personell.

5.2. Additional Treatments

Treatment status of participating children for mental health (psychological therapy as well as pharmacotherapy) will be enquired and documented at assessment points. Children with psychotropic medication and continued symptoms of AD under medication at pre-treatment assessment (T1) will be included in the study. In children, who receive psychostimulant medication for ADHD and who are randomized to the experimental condition OnPaSH-AD, pharmacological treatment will strictly follow regular guidelines and will not be altered due to the study. If possible, no changes in medication should be made during the 12 week course of intervention. Other intensive psychotherapies (on a weekly / biweekly basis) are not permitted in the experimental condition.

5.3. Enrolment and treatment guidelines

The patient is included in the study if

(1) at initial investigation, all inclusion criteria and no exclusion criteria are fulfilled and

(2) the patient and both parents /guardians have given their assent and informed consent, respectively, for the participation in the study. If one person has full custody, this will be documented.

5.4. Patient Registration and Randomisation

5.4.1 Patient Registration by REDCap

Each patient will receive a consecutive patient identification number (ID) after screening (ADOPT Epidemiology). The ID will be entered in REDCap for the registration of the patient. Contact data of the patient will also be entered in REDCap by ADOPT Epidemiology but will be technically separated from the other data. ADOPT Epidemiology will inform the responsible study center about screening positive cases by submitting the ID (without identifying information). Only one designated staff member per study center (and a representative) will have access to the participants' contact data, linked with the ID, and will coordinate further contact with the family. The family will be invited for t1 assessment and further participation in the ADOPT study.

5.4.2 Central Internet Randomization

Patients fulfilling the eligibility criteria at T1 will be centrally registered and will be randomly assigned to treatment groups (Online or TAU, allocation ratio 5:1) according to permuted blocks of varying length. Randomization is stratified by gender (i.e. 2 strata altogether) and implemented as a central 24-7 Internet service (ALEA, FormsVision BV, Abcoude, NL) operated by local authorized study staff. Treatment assignments will be displayed on screen and delivered by e-mail. The randomization service will be maintained by X.

5.5 Documentation and visits

Individual duration of study per patient is 20 months (ADOPT Online). Measurements will take place according to a specified schedule. The initial investigation (T0) serves as examination of inclusion and exclusion criteria. Immediately after the initial investigation, there will be the first measurement (T1). For parents of patients randomized to the experimental group at T1, OnPaSH-AD in ADOPT Online will then be carried out over a period of three months. Measurement T2 takes place 3 months after t1. Non-responders to OnPaSH-AD (significant symptoms of AD at T2 as rated by the clinician based on patient and parent interview) will subsequently take part in an Personalized Modular Outpatient Treatment of Affective Dysregulation and coexisting disorders (PeMOT-AD, see ADOPT Treatment), which will be carried out over a period of 9 months. T3 takes place 9 months after T2, also depending on whether the planned amount of sessions for patients receiving behavior therapy has already been conducted. The follow-up measurement T4 takes place 8 months after t3. Thus, for all patients in ADOPT-online, there will be 4 study visits (t1-t4). For non-responders to OnPaSH-AD, who continue treatment in ADOPT Treatment, there will be 24 additional study visits (24 behavior therapy sessions including 3 intermediate measurements).

At T1-T4, primary outcome (blinded clinician-rated AD symptomatology based on patient and parent interview) as well as secondary outcomes will be assessed. To ensure blindness of the clinical rating the interviewing of the parents will be videotaped and rated subsequently. Any information in the video material that will disclose the treatment condition or the measurement point (e.g., T2, T3, T4) will be effaced for the rating. In addition, information about the use of the online tool as well as use of on-call presence will be collected after informed consent of participating parents.

6. Primary and secondary objectives

6.1 Primary objective and outcome

Primary efficacy outcome is the blinded clinician-rated AD symptom score of the child, assessed with a newly developed outcome measure for AD (DADYS interview) based on patient and parent interview at T1-T4. DADYS will be developed by another subproject of the ADOPT consortium (ADOPT Epidemiology, in cooperation with ADOPT Treatment) before the start of the trial.

To date, there is a lack of validated measures on AD (Leibenluft & Stoddard, 2013). Therefore, DADYS interview will be developed by another subproject of the ADOPT Consortium (ADOPT Epidemiology, in cooperation with ADOPT Treatment) before the start of the trial, based on a pre-version of DADYS interview (DADYS-Pre interview) which will be psychometrically analysed in a clinical sample. DADYS-Pre interview includes items based on the Emotion Regulation Checklist (ERC; Shields & Cicchetti, 1997), the Diagnosis Checklist for Disruptive Behavior Disorder (DCL-SSV) from the German Diagnostic System for Mental Disorders in Children and Adolescents (DISYPS-III; Döpfner & Görtz-Dorten, 2016), the Affective Reactivity Index (ARI; Stringaris et al., 2012), the Parent Proxy Scale (Varni et al., 2014), and the PROMIS Pediactric Anger Scale (Irwin et al., 2012).

We use blinded clinician ratings based on patient and parent interviews as primary outcome since these ratings may be less biased compared to parent-ratings and self-ratings of the child. The items of the DADYS interview are scored from 0 (not present) to 3 (very strong). These items are added up to a total score, representing the extent of AD symptomatology of the child.

6.2 Secondary objectives and outcomes

The secondary endpoints are also summary scores/scale scores of the respective items. The secondary outcomes listed below will be evaluated at T1-T4, unless otherwise noted.

Secondary outcomes are (1) psychosocial impairment of the child due to AD symptoms based on patient and parent interview (DADYS interview/DADYS questionnaire), (2) patient- and parent-rated AD symptoms of the child (DADYS questionnaire), (3) patient- and parent-rated symptoms of ADHD and ODD/CD (SBB-ADHS/-SSV, FBB-ADHS/-SSV), (4) other comorbid conditions (e.g., anxiety, depression) assessed by parent-ratings (CBCL 6-18R), (5) psychological well-being in patient- and parent-rating (KIDSCREEN-27; KIDSCREEN-10-Index), and (6) parental satisfaction with the treatment.

- Psychosocial impairment of the patient due to AD symptoms will be measured by the functional impairment scale of the new version of the German Diagnostic System for Mental Disorders in children and Adolescents (DISYPS-III). The items are based on the definition of functional impairment in DSM-5 and assess social impairment in relationship towards adults, other children, and impairment in academic functions. The scale has already proven its reliability and validity in German samples (Döpfner & Görtz-Dorten, 2016). The items will be integrated in the clinical interview with patient and parent (DADYS interview) as well as in the questionnaires for patient- and parent-rating (DADYS questionnaires).
- Patient- and parent-rated AD symptoms of the child will be measured by newly developed questionnaires (DADYS questionnaires). They will be developed by another subproject of the ADOPT consortium (ADOPT Epidemiology, in cooperation with ADOPT Treatment) before the start of the trial, based on a pre-version of DADYS questionnaires (DADYS-Pre questionnaire) which will be psychometrically analysed in a clinical sample. DADYS-Pre questionnaires include

items based on the Emotion Regulation Checklist (ERC; Shields & Cicchetti, 1997), the Symptom Checklist for Disruptive Behavior Disorder (FBB-SSV/SBB-SSV) from the German Diagnostic System for Mental Disorders in Children and Adolescents (DISYPS-III; Döpfner & Görtz-Dorten, 2016), the Affective Reactivity Index (ARI; Stringaris et al., 2012), the Parent Proxy Scale (Varni et al., 2014) and the PROMIS Pediactric Anger Scale (Irwin et al., 2012).

- Comorbid sympoms of ADHS and ODD will be assessed in patient- and parent-rating with the respective rating scales (SBB-ADHS/-SSV, FBB-ADHS/-SSV) based on DSM-5 criteria within the German Diagnostic System for Mental Disorders in Children and Adolescents (DISYPS-III) which have already proven their reliability and validity as well their sensitivity to change in German samples (Döpfner & Görtz-Dorten, 2016).
- Further comorbidities will be assessed in parent-rating with the German version of the Child Behaviour Checklist (CBCL/6-18R; Döpfner, Plück, Kinnen, & Arbeitsgruppe Deutsche Child Behavior Checklist, 2014). Three subscales (Anxious/depressed, Attention problems, Aggressive behaviour) will be used.
- Child Symptoms of Attachment Disorders/Posttraumatic Stress Disorders will be assessed at T1-T4 in parent-rating with the respective scales (FBB-BIST/FBB-TBS) based on DSM-5-criteria within the DISYPS-III (Döpfner & Görtz-Dorten, 2016).
- The KIDSCREEN Scales (The KIDSCREEN Group Europe, 2006) measure subjective health and well-being of children and adolescents in patient- (KIDSCREEN-10-Index) and parent-rating (KIDSCREEN-27).
- For the assessment of satisfaction with the treatment at T2, specific parent satisfaction rating scales will be developed.

6.3 Predictors/moderators for treatment outcome on AD symptoms and impairment

As *predictors/moderators for treatment outcome on AD symptoms and impairment* the following variables will be analyzed: (1) gender, (2) age, (3) chronicity of AD-Symptoms, (4) severity of AD symptoms, (5) severity of comorbid symptoms, (6) AD-symptoms and other psychopathology of the mother, (7) positive and negative parenting practices, (8) public assistance of the family, (9) socio-economic status of the family, and (10) early childhood neglect of the patient. These parameters are assessed at T1, as well as potential risk and protective factors (social support [11], family climate [12], personal resources [13]). Additionally, (14) profile of usage of the online tool will be assessed.

- Sociodemographic variables (e.g., gender of the patient, age of patients and parents, public assistance of the family, socio-economic status of the family) will be assessed via a parent-reported interview at T1.
- Chronicity of AD symptoms of the child will be assessed with DADYS interview (see above) at T1.
- Severity of AD symptoms will be assessed at T1 in blinded clinical rating as well as patient-, parent- and teacher-rating with DADYS interview/questionnaires (see above).
- At T1, comorbid sympoms will be assessed in clinical rating, based on parent interview before the intervention with a structured screening interview which is part of the comprehensive Structured Interview for Children and Adolescents according to ICD-10 and DSM-5 from DISYPS-III (DISYPS-III-ILF; (Görtz-Dorten & Döpfner, 2008). ILF-SCREEN is a semi-structured interview that is used to screen core symptoms of ADHD, ODD, anxiety disorders, depression,

autism and problems in contact behavior in children. For the use in ADOPT, items concerning developmental and excretion disorders will be excluded. If ILF-SCREEN gives evidence for comorbid symptoms, additional scales from the DISYPS-III clinical interviews, corresponding to these symptoms, will be conducted (ILF-External, ILF-Internal, ILF-Kontakt; Görtz-Dorten & Döpfner, 2018).

- AD-symptoms of the mother/parent participating in the intervention will be measured at T1 via self-rating with the Aggression/Hostility subscale from the German Brief Symptom-Checklist (BSCL; Franke, 2017). The scale consists of 5 items that are rated by the mother/participating parent.
- Parental psychopathology will be assessed at T1 with the 9-item self-report short version of the Symptom-Checklist (SCL-K-9; Klaghofer & Brähler, 2001).
- Positive and negative parenting practices will be assessed at T1-T4 via rating of the participating parent with the German Questionnaire for Positive and Negative Parenting (FPNE; Imort et al., 2014), that measures positive parenting (e. g. reinforcing and supportive) and negative parenting (e. g. harsh and inconsistent discipline).
- Early childhood neglect and traumatic events of the patient will be assessed at T1 via parent questionnaire with modified version of the Symptom Checklist for Attachment Disorders from the DISYPS-III (Döpfner & Görtz-Dorten, 2016), and the Sympom Checklist for Posttraumatic Disorders from the DISYPS-III (Döpfner & Görtz-Dorten, 2016).
- Family climate will be assessed at T1 in patient rating with the Family Climate Scale (Schneewind, Beckmann, & Hecht-Jackl, 1985).
- Social support will be assessed at T1 in patient rating with the Social Support Scale (SSS) – Short Version (Sherbourne & Stewart, 1991).
- Personal resources of the child will be assessed with 3 items of the Self efficacy Scale (Schwarzer & Jerusalem, 1999), 1 item of the Berner Questionnaire for Assessment of Wellbeing (Grob A, Lüthi R, & FG, 1991) and 1 item of the Sense of Coherence Scale (Kern, Rasky, & Noack, 1995). The items were modified for the assessment in parent rating.
- The profile of usage will be analysed to identify the frequency and duration of usage and the selection of OnPaSH-modules.

6.4 Mediators of change

As potential *mediator*, parent-reported positive and negative parenting practices measured with the FPNE (Imort et al., 2014) will be assessed at T1 and T4. Additionally, strategies to regulate emotions of the child will be assessed at T1-T4 in parent and patient report.

- Strategies to regulate emotions by the child will be assessed in patient and parent report with a modified version of the Questionnaire for Assessment of Emotion Regulation by Childresn and Adolescents (FEEL-KJ; Grob & Smolenski, 2009).
- Strategies to regulate emotions of the child by the parents will be assessed in parent report with a modified version of the Coping with Children's Negative Emotions Scale (CNNES; German Version VEEB; Fabes, Eisenberg, & Bernzweig, 1990).

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6.5 Safety aspects

We expect a significant part of participants to have comorbid ADHD so that psychopharmacological treatment will be indicated. Pharmacological treatment will be carried out by the clinical physicians of the respective participating patient independently of the study. This also includes the evaluation of individual risks and adverse reactions. In the framework of the study, the evaluation of tolerability/safety will be restricted to the occurrence of serious adverse events (SAEs). A serious adverse event is defined as an event that: (1) results in the participant's death, (2) is a suicide attempt; (3) results in hospitalization for non-suicidal self-harm; or (4) results in hospitalization for mental health problems. Clinicians are instructed to report serious adverse events at any stage during therapy within one working day of being aware of the event. All serious adverse events are reported to the independent Data Monitoring Committee (DMC). Moderate adverse events are defined as: (1) hospitalization for any medical reason, other than mental health problems; (2) serious behavioral problem (i.e. suspension or expulsion from school, running away from home, or problems with the police) or, (3) the use of formal respite care. Information on moderate adverse events is recorded when reported during the study and also collected from the parents at follow-up.

7 Quality assurance and monitoring

7.1 Methods agains bias

Selection bias is minimized by randomly assigning patients to treatment groups (see above). *Performance bias* is minimized by carefully following the study protocol and continuous monitoring of adherence. Treatment fidelity will be assured by a stepped activation of OnPaSH-modules. *Attrition bias* is minimized by dedicated follow-up (frequent e-mail reminders, greeting cards for holidays, telephone calls if parents miss treatment sessions), nevertheless, up to 20% attrition are expected due to the specific paediatric setting. Proxy measures (e.g. from parents) are taken into account to alleviate the corresponding risk of bias. *Detection bias* is minimized by blinded assessment of primary and key secondary outcome measures. The structured parent interviews on which the clinical rating of AD and of impairment is based on are videotaped. At the end of the entire trial audiotapes will be rated by clinicians masked regarding assessment point and treatment condition (sequences on the tape which might inform the rater about treatment condition or assessment point will be deleted prior to clinician's rating). Objectivity will be ascertained by interviewer training and the assessment of interrater-reliability (re-coding 10% of the recorded interviews by a second rater). One family will be rated by the same rater to further increase reliability.

7.2 Monitoring

Monitoring will be performed by X in cooperation with the ADOPT *Coordination* subproject. All investigators agree that the monitor is allowed to visit the center before and during the study. The prestudy monitoring visit and all other monitoring visits will be performed by the X in accordance with the trial protocol, established quality management system (SOPs) and ICH-GCP. The results of the pre-study visits will be documented and reported back to the funding agency. The monitoring strategy will be specified within a study specific monitor manual.

7.3 Source data

Source data is all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents which comprise clinical documentation, data and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, patients´diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments and data and records arising from other departments such as the pharmacy, laboratory and medico-technical departments).

Clinical documentation relevant to the study includes all records in any form (including, but not limited to, written and electronic) that describe or record the methods, conduct and/or results of the study, the factors affecting the study and the actions taken.

All clinical documentation and data arising from the study are to be kept by the investigator.

7.4 Safety

A Data Monitoring Committee (DMC) will be established. The DMC will be formed by three experts with expertise in conducting clinical trials and specific expertise in a) biostatistics b) Psychotherapy and c) Child and Adolescent Psychiatry. Prior to the implementation of the trial, a DMC charter will be worked out describing goals and the work plan of the board. The function of the DMC is to monitor the course of the study and, if necessary, to give a recommendation to the study administration for discontinuation, modification, or continuation of the study. Furthermore, the board will give scientific advice. The DMC will assess on a regular basis whether the execution of the study is still ethically justified and whether performance is acceptable.

8 Data management

ADOPT Coordination in cooperation with X will provide electronic questionnaires within the framework of a remote data entry system (REDCap; Harris et al., 2009) and administer the data base. REDCap is a proprietary remote data entry system based on HTML forms, which is developed by the Vanderbilt University, Nashville TE. An instance of REDCap is hosted and maintained by the X. The X provides REDCap as a qualified system. Technical specifications of the trial database (e.g. variable names and formats) will be documented in a data base manual. Before any data entry is performed, the trial database and edit checks in REDCap will be validated.

The investigator, or a deputy who is designated by the investigator, will document the trial data in the electronic case report form (eCRF) as promptly as possible. A user manual for the REDCap system will be provided. Each investigator/data entry personnel will get separate access information for the use of the REDCap system. Specific forms for the request of user access will be provided. An audit trail within REDCap provides a data history which data were entered, changed or deleted, by whom and when.

Details of the data management (procedures, responsibilities, timelines, data validation and data corrections) will be described in a data management manual (DMM) prior to trial start. The DMM is a working document that is adapted during the clinical trial and contains a record of all data management processes carried out.

The data will be reviewed for completeness, consistency and plausibility. Data corrections will be entered directly into REDCap by the responsible investigator, or a designated person.

9 Biometry

9.1 Sample size calculation

9.1.1 Proposed sample size / power calculations

As the study design includes a stepped care process sample size is defined by expected effect sizes of the ADOPT Treatment step. Sample size of ADOPT Treatment is set to n=261 with n=174 in the treatment arm and n=87 as control group (see ADOPT Treatment for further details on power calculations). Meta-analysis of self-help PMT report effect sizes between 0.46 and 1.01 (Traver et al., 2014; Dunsmore et al., 2016) with smaller effects for self-help interventions with no therapist contact. It remains unclear whether symptom severity serves as a moderator favoring severely affected children in PMT (Lundahl et al., 2006). Breitenstein reported mean completion rates of about 78 % in their meta-analysis on online PMT. In studies on self-help PMT by Döpfner and co-workers drop-out ranged between 5% and 30% (Kierfeld et al., 2013; Ise et al., 2015). On the other hand online interventions might be harder to successfully complete for highly burdened parents, like our AD sample. Taking this into account and the fact that online PMT without therapist contact already is less effective than telephone assisted self-help interventions small effect size such as 0.356, should be expected for ADOPT Online. Thus, the two-sample *t*-test with allocation ratio 5:1 (online: TAU) requires 373 and 75 patients to attain a power 80% at two-sided signficance level 5%. Further accounting for 20% attrition yields about n=560 [=448/0.8] patients to be randomized (n=467 to online, n=93 to TAU). Based on previous experience we expect 800 patients need to be screened for eligibility (i.e. only about 30% are ineligible). Note, power is further increased by taking a baseline adjusted ANCOVA/mixed model for repeated measures (MMRM) approach for statistical analysis (see below). We expect a male: female ratio of 7:3 (Weisz et al., 2012). Missing data and non-compliance will be dealt with by performing intention-to-treat analysis.

9.1.2 Compliance/Rate of loss to follow-up

In our own pharmacotherapeutic trials as well the trials on behavior therapy for children with ADHD/externalizing behavior problems with similar treatment durations, losses to follow-up were below 15%. Missing data and non-compliance will be dealt with by performing intention-to-treat analysis.

9.1.3 Feasibility of recruitment

The patients will be recruited from community samples in four cities (Cologne, Mannheim, Dresden, Ulm). An estimated total of 300,000 children aged 8–12 years live in these cities. The recruitment will be based on the register of the residents' registration offices in these cities and will be performed by the subproject ADOPT Epidemiology. In studies conducted in Cologne in recent years where community samples drawn from the Cologne residents' registration office were used, the number of returns was about 25–30% (e.g., Hanisch et al., 2009). The screening population of 13,000 children aged 8-12 years should thus be available. The ADOPT-epidemiology study office will contact the potential participants and their parents for all ADOPT-project's study centers in order to inform them about the study and obtain the written informed consent of the parents and the children.

9.2 Definition of populations included in the analyses

The full analysis set (FAS) includes all randomized patients with a valid T1 assessment and at least one follow-up measurement (ITT approach). The primary analysis will be conducted according to the

intention-to-treat (ITT) principle. This means that the patients will be analyzed in the treatment arms to which they were randomized, irrespective of whether they refused or discontinued the treatment (OnPaSH) or whether other protocol violations are revealed.

The per-protocol (PP) population is a subset of the full analysis set (FAS) and is defined as the group of patients who had no major protocol violations, received a predefined minimum dose of the treatment (OnPaSH) and underwent the examinations required for the assessment of the endpoints at relevant, predefined times. The analysis of the PP population will be performed for the purpose of a sensitivity analysis. The PP population has to meet the following criteria in detail:

1) OnPaSH will have to take place within the defined time frame. OnPaSH starts with registration of a patient and lasts 3 months.

2) The visits have to take place in a defined time frame:

T0 Screening/ T1 Baseline	T0/T1 visits have to be conducted within a time period of max. 8 weeks (e.g. max 8 weeks between T0 and registration). Rating scales may be returned later, but must have been completed before the start of the OnPaSH-AD. All data must have been collected before the start of the OnPaSH-AD.
Outcome (T2)	T2 visits should be conducted within a short diagnostic phase (max. 3 weeks after end of OnPaSH). Rating scales may be returned later, but for non-responderes of OnPaSH-AD must have been completed before the start of the intervention in ADOPT Treatment. All data must be collected before the start of the intervention in ADOPT Treatment. For patients randomized to TAU or in the No-AD group after T1, T2 visits should be conducted 3 months after T1, within a short diagnostic phase (max. 3 weeks after the 3-months follow-up interval).
Follow-Up (T3)	T3 visits should be conducted within a short diagnostic phase (max. 3 weeks after end of PeMOT-AD, see ADOPT Treatment). Rating scales may be returned later. For patients randomized to TAU, T3 visits should be conducted 9 months after T2, within a short diagnostic phase (max. 3 weeks after the 9-months follow-up interval).
Follow-Up (T4)	T4 visits should be conducted 8 months after T3, within a short diagnostic phase (max. 3 weeks after the 8-months follow-up interval). Rating scales may be returned later.

3) Patients have to receive a predefined minimum dose of the treatment, e.g. completion of at least 50% of the online material.

9.3 Methods of Analysis

Before the inclusion of the first patient a detailed statistical analysis plan (SAP) will be prepared. This will be completed during the 'blind review' of the data, at the latest. If the SAP contains any changes

to the analyses outlined in the trial protocol, they will be marked as such, and reasons for amendments will be given.

9.3.1 Patient demographics/other baseline characteristics

Demographic and other baseline data (including disease characteristics) will be optained at T1 and will be summarized descriptively using all documented patients.

Continuous data will be summarized by arithmetic mean, standard deviation, minimum, 25% quantile, median, 75% quantile, maximum, and the number of complete and missing observations. If appropriate, continuous variables can also be presented in categories.

Categorical data will be summarized by the total number of patients in each category and the number of missing values. Relative frequencies are displayed as valid % (number of patients divided by the number of patients with non-missing values).

9.3.2 Analysis of primary endpoint

The primary (full) analysis set (FAS) is derived from the intention-to-treat principle (all patients randomized with a valid baseline assessment and at least one follow-up measurement). The primary outcome measure “change in Ad symptoms from T1 to 3 months post randomization (T2)” is evaluated by a analysis of covariance (ANCOVA) with fixed effects baseline, gender and treatment arm and corresponding marginal means and contrast tests (type II sums of squares). The interaction of gender with treatment arm is explored. Multiple imputation approaches are taken to assess the robustness of the results. Specifically, missing values are separately imputed by type assuming mixtures of missingness-not-at-random patterns (White et al., 2011). Imputation data sets are post-processed by multiplication with factors and addition of offsets (tipping point analysis) (van Buuren & Groothuis-Oudshoorn, 2011). Proxy measures are taken into account to ameliorate the effects of attrition.

9.3.3 Analysis of secondary endpoints

Secondary outcomes are analyzed along the same lines, possibly using linear mixed models for repeated measures (MMRM; ARH1-structured covariance matrix over time) or generalized estimating equation (GEE) approaches with corresponding marginal means and contrast tests (“multi-level modelling”). Time-to-drop-out distributions are summarized by the Kaplan-Meier method and compared by the (stratified) log-rank test. Analysis of the set of patients essentially observed and treated per protocol (PP) is supportive. Adverse events are aggregated by type, seriousness, intensity and relatedness; PAERS ratings are summarized by item (group) and treatment arm. All efficacy and safety variables are summarized by time point and treatment arm (mean, standard deviation, percentiles (0, 25, 50, 75, 100); count, percentage). Subgroup analyses are done by study center and gender (expected male to female ratio 7:3, thus meaningful results are expected for boys and girls). Moreover, moderation and conditional process modelling (see Hayes, 2013) is done based on regression and structural equations (interaction, simple slope analysis; direct/indirect effects, kappa square). All the details, particularly regarding how to deal with missing data and attrition, are documented in a statistical analysis plan to be finalized before start of enrollment.

9.3.4. Missing values

It should be emphasised that as little patients as possible should discontinue treatment and that all patients should be followed up and also documented after discontinuation of the treatment in order

to record data required according to the intention-to-treat principle. To assess the impact of up to 20% attrition multiple imputation approaches are taken, accounting for proxy measures and assuming specfic missingness-not-at-random patterns. The details are documented in a statistical analysis plan. Analysis of subjects essentially observed and treated per protocol (PP) is supportive.

9.3.5 Safety

Safety analyses will be performed in the safety population. Patients in the safety population are analyzed as belonging to the treatment arm defined by treatment received (PeMOT-AD or TAU). Patients are included in the respective treatment arm, if treatment was started/if they received at least one dose of trial treatment. Patients that refuse participation in PeMOT-AD will also be part of the safety population.

10 Project management and TMF/ISF

The X will support the poject manager of ADOPT Treatment by preparing study-specific documents and files (trial master file – TMF, as well as investigator site file – ISF). During the project, ADOPT Online will administer the TMF. The ISF will be sent to the centres and managed there. After the trial, the TMF will be sent to the principal investigator for archiving.

11 Data protection and informed consent

Guidelines about data protection (European data protection Directive 95/46/EC and national data protection law) will be complied with. Patients, at least one guardian and teachers, if necessary, will be informed about the scope and the relevance of the study as well as the way of collecting and processing the data in separate information sheets. Entering and processing of data will take place as soon as a signed informed consent is available.

The principal investigator will provide patient information appropriate for the study in accordance with ICH-GCP guidelines. The patient information sheet will be submitted to the responsible ethics committee for consultation. All changes made on the patient information sheet have to be submitted to the responsible ethics committee for consultation before it can be established.

All data relevant for the trial will be typed into an electronic remote data entry system (REDCap) from all centres. X in cooperation with ADOPT Coordination will provide the data entry system. Patient data will be registered pseudonymised.

REDCap uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by individually assigned user identification codes and passwords, made available only to authorized personnel.

Each patient will be identified with a study-specific patient number, which will be allocated as soon as the patient is included in the study. The patient number includes information about the centre (centre-specific numbers will be allocated before trial start) as well as a patient-specific number.

ADOPT Coordination in cooperation with X in cooperation will process data through specifically for the study trained personnel, which will work after the standard operating procedures (SOPs) of the study centres. Legal regulations for data protection will be fulfilled.

12 Legal and ethical foundation

12.1 Legal foundation and inclusion of the ethical committee

Notification to relevant ethics committee will be conducted according to section 15 of the German Medical Association's Professional code of conduct. Before the trial starts, all relevant documents will be submitted to the ethics committee responsible for the participating centre. The primary vote of the study will be obtained by the ethics committee of the medical faculty of the University of Cologne.

The study will be conducted in accordance with the ICH-GCP guidelines and the Declaration of Helsinki.

All changes in the trial protocol have to be reported to the ethics committee. For changes of the trial protocol formally in nature and including relevant changes for trial subjects, the ethics committee has to vote anew. Patients/trial subjects will have to be informed about changes in the conditions of the study if necessary. The ethics committee will have to be informed immediately about complications and severe adverse events during the project.

12.2 Insurance and reimbursement

Insurance of patients for study-related services is not necessary.

For the attendance of measurements, a travel accident insurance is contracted for the patients and parents. The stay at the study centre will also be insured by premium loadings.

At T1, the patients will be insured by a travel accident insurance taken out by ADOPT Epidemiology. For T3 and T4, ADOPT Treatment will take out a travel accident insurance that also includes the patients from ADOPT Online.

Additional payments (e.g. reimbursement of travel expenses of the patients) are not intended in the course of the study.

12.3 Risk-benefit considerations

There are no known risks for the patiens associated with OnPaSH-AD. The intervention will follow accepted guidelines and evidence-based behavioural therapeutic methods. Patients might be able to benefit personally directly from the participation in the study (e.g. the sceening of a community sample allows a preventive and thus earlier access to treatment). The results will inform future guidelines on the treatment of children with AD and CoCo and will help to improve guidelines and to develop usable, potentially more cost-effective, individualized modular treatment in children with AD. The study will specifically convey about the benefit of online self-help for parents compared to standard approaches. These effects will be related to AD symptoms, comorbid symptoms, impairment, and quality-of-life. Thus, the trials will have an impact on relieving the burden of disease and improving children’s health. Overall, the benefits of the study exceed possible risks, so that the conduct of the study is ethical.

12.4 Stopping rules

12.4.1 Stopping rules for an individual patient

One (or more) of the following circumstances will result in an early study termination of single subjects (these trial subjects will be rated as drop-out):

- withdrawal of informed consent of all parents/guardians
- withdrawal of assent of the patient

- unwillingness to further participate in the trial
- need for inpatient treatment or other reasons affecting the patient's well-being in the case of continued trial participation
- need for a different kind of treatment for health reasons according to the judgement of the attending physician

12.4.2 Global stopping rules

One (or more) of the following circumstances will result in an early termination of the entire trial or in closing of a single centre:

- emerging of data leading to a revision of the risk-benefit ratio
- Participating centres will be closed in case of on-going failure of recruitment or repeated violations of the study protocol or standard GCP rules. However, prior to closing a centre due to falling below the expected recruitment rate, compensation by existing centres is intended (if necessary, new study centres will be opened).
- For a decision on the termination of the trial or of closing a centre, agreement between principal investigator, site investigators, DMC members, leading ethical committee and project executing organisation (X) is intended.

A termination of the entire consortium will be executed if both ADOPT Epidemiology and ADOPT *Institution* fail to reach 50% of the planned sample size, despite additional recruiting strategies (recruiting of additional study centers, additional recruiting waves in ADOPT Epidemiology, additional recruiting of outpatient samples in participating study centres). The decision will be made by all principal investigators as well as the principal coordinator.

12.5 Investigator site file and archiving

All trial related correspondence, patient records, consent forms should be archived for at least 15 years in accordance with §13 (10) of the GCP-V (German legal implementation of ICH-GCP regulation). Trial site shall ensure archiving and retention of essential trial documents (e.g., ISF, patient files and source data), after the termination or discontinuation of the trial for at least 15 years unless longer times are foreseen by local regulatory requirements. Study patient identification lists at each study site will be stored separately from study documentation.

12.6 Registration in a WHO primary registry

The trial will be registered in a WHO primary registry in accordance with the requirements of the Declaration of Helsinki (§ 19) before including the first patient.

The registry will be carried out in the German clinical trials register (DRKS).

13 Publications

The study serves a scientific purpose. The results of the trial are supposed to be published. Results of the trial will be published on scientific congresses and in scientific journals. The principal investigator has the right for first publication. The mention and sequence of co-authors will be carried out according to their contribution to the publication and will be clarified before publication.

The participating centres have the right to publicise independently; however, they have to reach consensus with the principal investigator. Independent publications of the participating centres require the written approval of the principal investigator.

14 Literature

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