

Adverse events in cognitive behavioral therapy and relaxation training for children and adolescents with obsessive-compulsive disorder: A mixed methods study and analysis plan for the TECTO trial

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ABSTRACT

Background: Knowledge on adverse events in psychotherapy for youth with OCD is sparse. No official guidelines exist for defining or monitoring adverse events in psychotherapy. Recent recommendations call for more qualitative and quantitative assessment of adverse events in psychotherapy trials. This mixed methods study aims to expand knowledge on adverse events in psychotherapy for youth with OCD.

Methods: This is an analysis plan for a convergent mixed methods study within a randomized clinical trial (the TECTO trial). We include at least 128 youth aged 8–17 years with obsessive-compulsive disorder (OCD). Participants are randomized to either family-based cognitive behavioral therapy (FCBT) or family-based psychoeducation and relaxation training (FPRT). Adverse events are monitored quantitatively with the Negative Effects Questionnaire. Furthermore, we assess psychiatric symptoms, global functioning, quality of life, and family factors to investigate predictors for adverse events. We conduct semi-structured qualitative interviews with all youths and their parents on their experience of adverse events in FCBT or FPRT. For the mixed methods analysis, we will merge 1) a qualitative content analysis with descriptive statistics comparing the types, frequencies, and severity of adverse events; 2) a qualitative content analysis of the perceived causes for adverse events with

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prediction models for adverse events; and 3) a thematic analysis of the participants' treatment evaluation with a correlational analysis of adverse events and OCD severity.

Discussion: The in-depth mixed methods analysis can inform 1) safer and more effective psychotherapy for OCD; 2) instruments and guidelines for monitoring adverse events; and 3) patient information on potential adverse events. The main limitation is risk of missing data.

Trial registration: ClinicalTrials.gov identifier: NCT03595098. Registered on July 23, 2018.

1. Introduction

Obsessive-compulsive disorder (OCD) is a mental illness characterized by repetitive and intrusive thoughts (obsessions) and rituals (compulsions). Between 0.5% and 3% of youth (<18 years) are diagnosed with OCD [1]. OCD is a debilitating disorder that can cause school absence, family conflicts, social withdrawal, and impair basic life functions (e.g. eating, getting dressed, and going to the bathroom) [2]. If OCD is not treated in youth, it may become chronic and continue into adulthood [3]. Cognitive behavioral therapy (CBT) is recommended as first-line treatment over pharmacological interventions for youths with OCD [4]. While the efficacy of CBT is systematically explored, monitoring and reporting of adverse events in psychotherapy are sparse and psychotherapy trials are far less likely to report adverse events compared to pharmacological trials [5–10]. Our systematic review highlighted the dearth of knowledge on adverse events in CBT for youths with OCD [11].

No official guidelines or consensus exist for defining or monitoring adverse events in psychotherapy. Currently, researchers use different terms for and definitions of adverse events in psychotherapy trials [8,9]. Although several instruments exist for monitoring adverse events in psychotherapy, no consensus exists for which domains to include nor which instruments to use [9]. Qualitative interviews have been put forward as a recommendation to obtain knowledge on what patients perceive as adverse events as well as the factors that should be included in a quantitative instrument [9,10]. Also, the recommendations call for different perspectives on adverse events (patient, relative, therapist) and distinguishing adverse effects from malpractice [9]. Finally, they call for quantitative assessment of adverse events to evaluate the psychometric properties, their burden as well as relation to treatment outcome (i.e. quality of life) and to explore if adverse events are transient or enduring [9,10]. Thus, trials that include both quantitative and qualitative assessment to explore adverse events are needed.

Adverse events in CBT are plausible. A central component in CBT for OCD is exposure and response prevention (ERP), which involves exposure to a feared object, situation, or thought and helping the youths to refrain from compulsive behavior [12]. The therapist trains the patient to endure distress to show that the emotion is a false alarm and not a sign of actual danger. In some cases, the distress during ERP may be too challenging and thus trigger adverse events such as new symptoms or worsening of current illness (e.g., anxiety, depression, and suicidality), daily functioning, family conflicts, stigmatization or strains in social relations [13–16]. Youths may be at higher risk of experiencing adverse events in CBT compared to adults since they are seldomly self-referred, struggle more with understanding the treatment rationale, and need guidance and support from family members to complete the exposures at home [17]. A randomized clinical trial on self-guided internet CBT for adolescents with OCD reported adverse events to be mood problems (9%), OCD-related symptoms (6%), anxiety (4%), and sleep problems (1%) [18]. In another randomized clinical trial of CBT for youth with OCD, 64% of participants in dose-based stepped-care CBT reported at least one adverse event versus 67% in in-person CBT. The five most frequently reported adverse events were increased anxiety (29% in stepped-care CBT; 35% for in-person CBT), depressive symptoms (20%; 28%), stress (20%; 6%), increased OCD symptoms (10%; 11%), and sleep problems (4%; 12%) [19]. The two trials found no serious adverse events that were related to CBT [18,19]. Similarly, an anonymous

survey of 277 therapists delivering ERP for OCD reported serious negative consequences to be rare [20]. While adverse events are plausible, the lack of systematically gathered data on potential harm from ERP may cause therapists to be unnecessarily reluctant to deliver ERP [20]. Thus, we need more randomized clinical trials that systematically monitor adverse events in child psychotherapy to reach consensus on the types, frequency, and severity of adverse events.

In ERP for OCD, variability in distress is predictive of better outcomes for youths with OCD [21]. In ERP, the therapist introduces test exposures to determine the individual's anxiety tolerance level to secure optimal learning and minimize unnecessary distress [12]. Even when gradual exposures are implemented properly, some youths may be at risk of experiencing adverse events due to comorbid psychiatric disorders, impaired intelligence, strains in family relations, poor therapeutic alliance, or high baseline anxiety levels [14,15,22,23]. One alternative treatment option is psychoeducation and relaxation training (PRT), which comprises breathing practices and muscle relaxation exercises without ERP [24]. While studies indicate lower response rates for PRT compared to CBT for youths with OCD (PRT: 20%–40%; CBT: 50%–72%) [2,25,26]. However, these studies did not monitor adverse events and were at high risk of bias due to unclear randomization and missing outcome data [11,27]. Thus, we wish to examine whether certain individual characteristics or circumstances are risk factors for experiencing adverse events and if PRT should be considered an alternative treatment option for certain youth with OCD.

1.1. Study aim

The primary aim of this study is to gather knowledge on adverse events in psychotherapy for youth with OCD. The goal is to present recommendations for future development of (1) safer and more effective psychotherapy, (2) guidelines and instruments for monitoring adverse event in youth psychotherapy, and (3) patient information regarding expectations and potential risks in psychotherapeutic treatment for youths with OCD.

2. Methods

2.1. Study design

We implement a convergent mixed methods study within the TECTO trial (ClinicalTrials.gov Identifier: NCT03595098) [28–30]. This study is exploratory and hypothesis-free due to lack of knowledge on adverse events in psychotherapy. Rather, we gather and analyze quantitative and qualitative data on adverse events and integrate the two types of data to generate theory on adverse events in psychotherapy. Following the convergent design, we collect quantitative and qualitative data within the same time frame and analyze the two types of data separately before merging the results [31].

We hold a pragmatic approach to mixed methods research [31,32]. For the mixed methods analysis, we follow an abductive approach, meaning that we work back and forth between the inductive qualitative results and deductive quantitative results [32]. The integration of quantitative and qualitative data allows for new insights into adverse events, since the methods complement the strengths and weaknesses of each other [33]. Rather than testing a predefined hypothesis, we aim to use the quantitative and qualitative data to generate theory and

hypotheses on adverse events in psychotherapy for OCD. When reporting our results, we will follow the CONSORT SPI, the Consolidated Criteria for Reporting Qualitative Research (COREQ) and Good Reporting of A Mixed Methods Study (GRAMMS) [34–37].

We use a questionnaire to assess adverse events at three time points during the psychotherapeutic treatment. The validated questionnaire for monitoring adverse events in psychotherapy is based on reports from adults [38]. Thus, we need qualitative data to explore potential different patterns of adverse events for youths receiving psychotherapy. Also, while youths with OCD may report psychotherapy-related adverse events in questionnaires, we lack insight into how these adverse events relate to FCBT and FPRT and what the adverse events mean for the youths' and parents' evaluation of the respective type of psychotherapy. Thus, we integrate quantitative and qualitative findings on adverse events to expand and enhance our understanding on whether and how adverse events are related to FCBT or FPRT for youth with OCD. See Fig. 1.

2.2. Definition and categorization of adverse events

We follow the good clinical practice guidelines, and define *adverse events* as all untoward occurrences that are temporally associated with but not necessarily causally related to the intervention [39]. Thus, adverse events should be unfavorable or unintended [39]. Temporary increase in anxiety is intended in CBT during ERP to achieve habituation or fear tolerance. Therefore, increased anxiety is not necessarily an adverse event in CBT. However, if the anxiety persists beyond the exposure exercise, or anxiety is elevated in subsequent exposures to the same stimulus, it will be considered an adverse event. Following the Good Clinical Practice (GCP) guidelines [39], we also register 1) serious adverse events (SAE): any untoward occurrence or effect that results in death, is life-threatening, requires hospitalization or prolongs existing hospitalization, or results in persistent or significant disability or incapacity; 2) serious adverse reactions (SAR): any SAE that is considered an adverse reaction to the treatment; and 3) suspected unexpected serious adverse reactions (SUSAR): a SAR where the nature or severity is not consistent with what is already known about the intervention. A causally related non-serious adverse events is called a treatment negative effect (NE) [9]. For an adverse event to be categorized as a SAR or NENE, the causal relationship between the adverse events and the treatment should be at least probable. We classify the causality using a predefined scale from certain to un-assessable/unclassifiable [40]. We also judge whether the adverse events can be categorized as a side effect (SE), which occur despite correct treatment, or as malpractice reactions

(MPR), which are caused by incorrect or improperly applied treatment [9,41]. See Fig. 2.

2.3. Setting

The TECTO trial takes place at the Child and Adolescent Mental Health Centre (CAMHC), The Capital Region of Denmark. TECTO's research group is anchored in the Research Unit at CAMHC and the trial is carried out in close collaboration with the extended leadership, as well as the clinical departments, and the Copenhagen Trial Unit (CTU). The trial interventions are conducted by trained MDs and psychologists from the CAMHC. The TECTO trial has a steering committee, an advisory board, and supervisors for the trial interventions and assessments. For more information on the TECTO trial, see the published protocol [30].

2.4. Participants

We aim for at least 128 youth with OCD aged 8–17 years. Potential participants undergo diagnostic screening [42–44] after which eligible patients who consent to participate are randomized to FCBT versus FPRT. CTU performs the randomization using a computer-generated allocation sequence to secure blinding of the investigators. The youths receive 14 psychotherapy sessions of 75 min over 16 weeks. All included participants take part in both the quantitative and qualitative assessment. The sample size calculation, randomization, blinding procedure, and further design details are described in detail in the TECTO protocol [30].

2.4.1. Inclusion criteria

- Age 8–17 years
- A primary diagnosis of OCD (F42) as defined by the International Classification of Diseases-10 (ICD-10) [45] using the Kiddie-Schedule for Affective Disorders and Schizophrenia – Present and Lifetime Version (K-SADS-PL) [43].
- A score of ≥ 16 on the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) [44].
- Informed consent

2.4.2. Exclusion criteria

- Intelligence quotient < 70 [42,46].
- One or more of the following co-occurring disorders: pervasive developmental disorder not including Asperger's syndrome (ICD-10

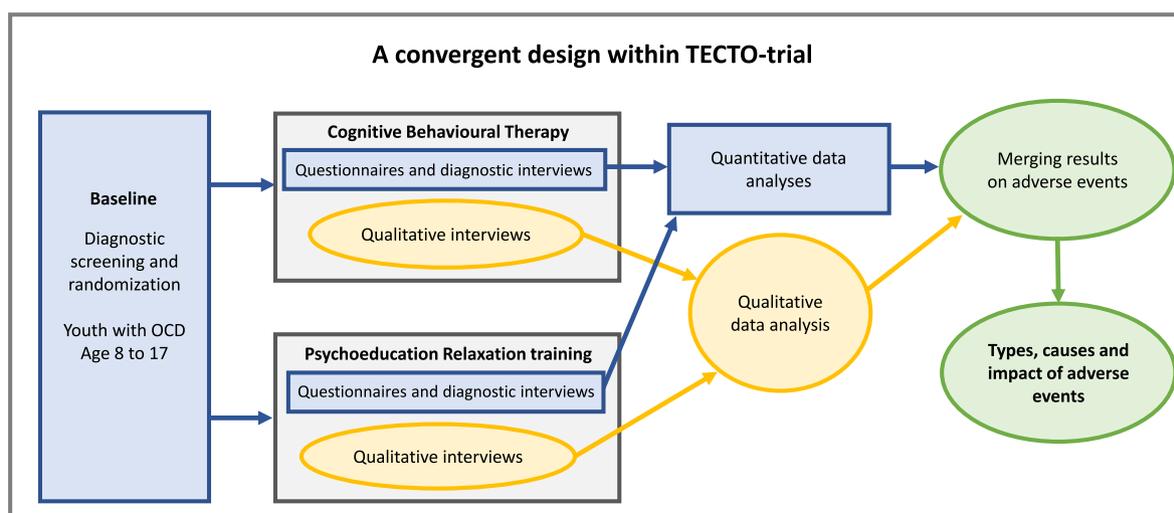


Fig. 1. A convergent mixed methods design within an intervention trial.

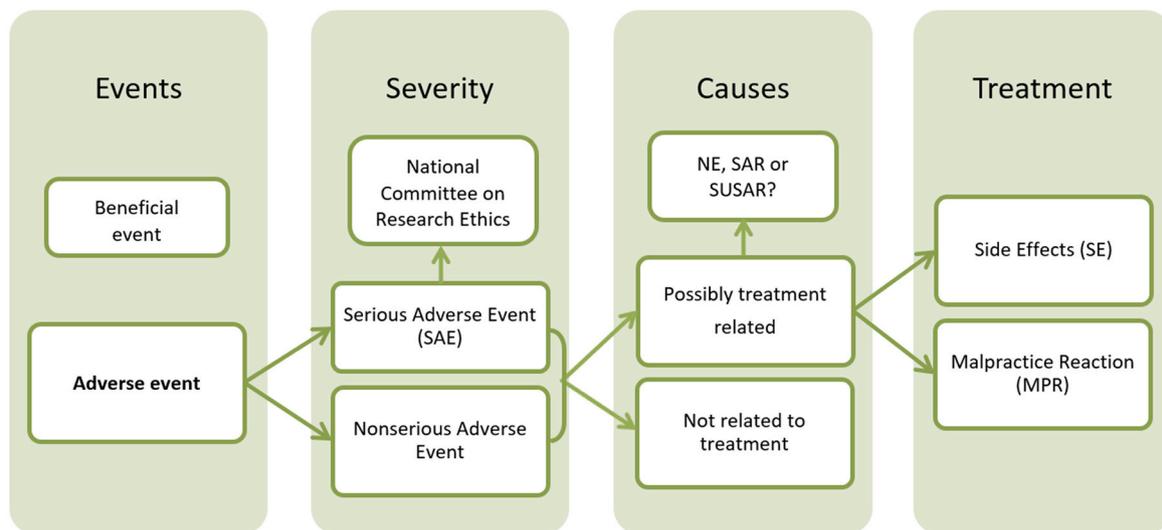


Fig. 2. Categorization of adverse events in TECTO-trial.

F84.0–84.4 + F84.8–84.9), schizophrenia/paranoid psychosis (ICD-10 F20-25 + F28-29), mania or bipolar disorder (ICD-10 F30 and F31), depressive psychotic disorders (F32.3 + F33.3), and/or substance dependence syndrome (ICD-10 F1x.2)

- Treatment with CBT, PRT, antipsychotic medication, or antidepressant medication within the last six months prior to trial entry

2.5. Interventions

The experimental intervention is an FCBT manual developed specifically for youths with OCD [12]. The treatment manual focuses primarily on ERP rather than cognitive restructuring. ERP is believed to be the most effective component in FCBT for OCD [47,48]. The ERP instructions in the manual are based on both habituation (anxiety reduction) and inhibitory learning theory (fear tolerance through non-threat associations) [12,49,50].

The active control intervention is FPRT following a manual developed for youths with OCD [2,24]. The psychoeducation, parental involvement, and the number of exercises correspond to the 14 sessions in the FCBT intervention. Thus, the participants receive the identical number and duration of sessions. In FPRT for OCD, the therapist teaches the youth and parents relaxation techniques (i.e., progressive muscle relaxation, breathing, and imagery) to reduce stress and arousal caused by obsessions and compulsions. ERP is absent in the FPRT manual, which is the primary difference between the two interventions.

The FCBT and FPRT manuals are considered ‘family-based’ due to having parent involvement and a parent specific theme in all sessions as well as a parent participation in five full sessions. See the TECTO-protocol for more information on the interventions [30].

2.6. Therapist training and fidelity

All therapists deliver FCBT and FPRT with weekly supervision. To evaluate whether a treatment related SAE can be categorized as a SE or MPR, we rate therapist fidelity to the therapy manuals using the NordLOTS Treatment Integrity Scale [51,52] and a corresponding fidelity guide for FPRT developed by the TECTO team [30]. We rate two sessions for all participants who experience SAEs or report at least one treatment-related adverse event on the Negative Effects Questionnaire (NEQ) that affected them ‘extremely’. We use the fidelity ratings and registered protocol deviations to categorize treatment-related SAEs or ‘extreme’ adverse events as either an SE or MPR.

3. Outcomes

3.1. Quantitative outcomes

The main quantitative outcome of this sub-study is the NEQ [53]. The NEQ consist of 32 items divided into six factors (symptoms, quality, dependency, stigma, hopelessness, and failure). The item severity is scored on a 0 to 4-point Likert scale and attributed to either the treatment or other circumstances. Both the youths and their parents fill out the NEQ at weeks 4, 8, 16 (end of treatment), and 40 (follow-up). The NEQ is the only instrument in Danish with published psychometric properties to monitor adverse events in psychotherapy [9,38]. Since the NEQ is intended for adults, the tester evaluates whether each patient understands the questionnaire (‘yes’, ‘partly’ or ‘no’).

Furthermore, we collect data on the youths’ quality of life, daily functioning, family psychiatric dispositions, intelligence, family factors, and therapeutic alliance [42,44,54–60]. Also, we monitor treatment compliance in each session as well as motivation and confidence in the treatment on a 7-point Likert scale. See Table 1 for instruments and assessment time points.

3.2. Qualitative outcomes

Since monitoring of adverse events in psychotherapy for youth is unexplored, we include semi-structured interviews investigating the participants’ and their parents’ experience of potential adverse events during and after the psychotherapeutic intervention. We aim to interview all included youths and their parents (see Table 1 for interview time points). We ask the participants and their parents to describe (1) how they experienced the treatment; (2) beneficial and adverse changes and experiences during and after psychotherapy including their duration and impact/severity; (3) what they think caused the changes and experiences; (4) their evaluation of the treatment and suggestions for improvement; and (5) if they experienced an SAE. The youths and parents are instructed to describe positive and negative experiences from the treatment period and the investigators do not provide definitions or examples of adverse events. Furthermore, we conduct one qualitative interview with each psychotherapist and ask them (1) if they experienced unwanted or negative changes in any of the participants; (2) if so, what they think caused the negative change; and (3) how they handled it. Finally, the TECTO team and therapists register adverse events in the participant report form in accordance with Good Clinical Practice (GCP) guidelines [39]. Potential SAEs and reasons for drop-out

Table 1

Measurement timepoints

Negative Effects Questionnaire (NEQ): Self-reported questionnaire to assess adverse events in psychotherapy; **Children’s Yale-Brown Obsessive-Compulsive Scale (CY-BOCS):** Clinician rated semi structured interview to measure the severity of OCD symptoms; **TOCS:** Toronto obsessive-compulsive scale; **Child Obsessive Compulsive Disorder Impact Scale (COIS):** Self-report questionnaire assessing the impact of OCD symptoms on psychosocial functioning; **Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS):** Clinician rated semi structured diagnostic interview to measure current and past psychiatric symptoms in children from 6 to 18 years; **KIDSCREEN:** Self-reported questionnaire measuring subjective health and well-being; **The Clinical Global Impression – Severity scale (CGI-S/I):** Clinician administered rating scale to measure symptom severity and treatment response of patients with psychiatric disorders; **The Children’s Global Assessment Scale (CGAS):** Clinician rated scale from 0 to 100 indicating level of functioning in youths under age 18; **The Wechsler Intelligence Scale for Children/Adults (WISC-V/WAIS-IV):** Administered intelligence test; **Comorbidity:** registration of psychiatric and somatic disorders as well as Z codes. **Family Accommodation Scale (FAS):** Self-reported questionnaire; **Family Environment Scale (FES):** Self-report measure to assess the social climate in a family; **Parental Stress Scale (PSS):** Self-reported questionnaire to assess the level of stress associated with parenting; **Motivation for Treatment:** Self-reported 7-point likert scale measuring motivation for the psychotherapeutic treatment; **Confidence in treatment:** Self-reported 7-point likert scale measuring belief in the efficacy of the treatment; **Treatment Compliance:** Therapist registration of participation in the therapy sessions; **Therapeutic Alliance Scale for Children (TASC-R):** Self-reported and therapist reported questionnaire assessing the therapeutic alliance.

* Planned predictors

** Planned confounding variables.

Week	0	1	2	3	4	5-7	8	9-14	15	16	40
Intervention											
Adverse events											
NEQ					●		●			●	●
Child understanding of the NEQ					●		●			●	●
Qualitative interviews										●	●
Phenomenology											
CY-BOCS*	●				●		●			●	●
TOCS*	●	●									
COIS*	●	●									
K-SADS	●									●	
KIDSCREEN*	●	●									
CGI-S*	●				●		●			●	●
CGI-I					●		●			●	●
CGAS*	●									●	
Family psychiatric disp.*	●										
WISC/WAIS*	●										
Comorbidity*	●									●	
Family Factors											
FAS*	●										
FES*	●	●									
PSS*	●				●		●			●	
Treatment Factors											
Confidence in treatment**		●	●								
Motivation for treatment* + **	●	●	●		●		●		●	●	
Treatment Compliance**		●	●	●	●	●	●	●		●	
TASC-R**		●	●		●		●			●	●

● Scientist ● Therapist ● Patient ● Parents

are registered in the participant’s medical record.

4. Research questions

Below we present three different mixed methods research questions. We approach the mixed methods questions by merging the results from the respective quantitative and qualitative research question.

- Mixed methods research question:** Which adverse events emerge during and after FCBT compared with FPRT for OCD? Which adverse events are treatment-related? And how frequent and severe are they?
 - Quantitative research question:** What are the types and what is the frequency and severity of adverse events during and after FCBT compared with FPRT assessed with the NEQ?

- Qualitative research question:** What do youths with OCD and their parents experience as adverse events during and following FCBT versus FPRT? How do they experience the severity, duration, and impact of potential adverse events?
- Mixed methods research question:** How can FCBT or FPRT for OCD elicit adverse events?
 - Quantitative research question:** What are the best predictors of the number and severity of adverse events for youths with OCD during and after FCBT versus FPRT?
 - Qualitative research question:** What do youths with OCD and their parents believe to have caused adverse events during FCBT or FPRT?
- Mixed methods research question:** What do adverse events signify for the outcome of FCBT and FPRT? And how can the following

qualitative and quantitative results inform safety and improvement of psychotherapy for youths with OCD?

3.1. Quantitative research question: What is the association between the type, frequency, and severity of adverse events, treatment response, and drop-out of treatment?

3.2. Qualitative research question: What do adverse events signify for the youth's and parent's experience and evaluation of the psychotherapeutic treatment? And what do they think would improve psychotherapy for OCD?

5. Mixed methods analysis

5.1. Quantitative analysis

For the first quantitative research question, we will use descriptive statistics (mean, median, and standard deviation) to present the types, frequencies, and severities of adverse events. We use linear mixed models to investigate whether the number and severity of reported 'symptoms' on the NEQ changes over time in the FCBT versus the FPRT arm. For the second quantitative research question, we will employ logistic regression to test the effect of specific baseline characteristics on experiencing adverse events and SAEs. To find the best prediction model for adverse events, we compare a ridge and lasso regression through bootstrap validation (see predictors in Table 1) [61]. For the third quantitative research question, we use Pearson or Spearman correlations [62] to assess the relationship between adverse events (frequency, severity, and types) and treatment drop-out (discontinuation with <10 treatment sessions), as well as treatment response on the CY-BOCS at end of treatment (see planned confounding variables in Table 1). NEQ questionnaires registered as 'not understood', will be excluded from the statistical analysis. All statistical analysis will be performed in R [63].

5.1.1. Handling of missing data

For the primary analyses, we will use complete case analysis to handle missing data. For the sensitivity analysis, we will use two-level imputations: 1) imputations of questionnaires where specific items are missing using questions from week 4 and 8 as covariates, and 2) imputations of full missing questionnaires using both week 4 and 8 data as covariates [64].

5.2. Qualitative analysis

We transcribe and analyze all interviews in which the youth or parent describes an adverse event. For research questions 1.2 and 2.2., we will perform an inductive qualitative content analysis [65]. For research question 3.2 we will perform reflexive thematic analysis [66]. See Fig. 3 for the phases in reflexive thematic analysis [66]. The aim of the qualitative analysis is to identify 1) type, frequency, and severity of adverse events experienced by the youth and parents; 2) their perception of what elicited the adverse events; and 3) what the adverse events mean for their experience of FCBT and FPRT. We report the number and percentage of youths and parents who report at least one adverse event in the qualitative interviews. To establish intercoder reliability for the coding of adverse events and their perceived causes, two independent coders will analyze at least 10% of the interviews and calculate Cohen's kappa coefficient using NVivo [67,68].

5.3. Data integration

This is an abductive, equivalently driven mixed methods study, meaning that we give equal weight to the quantitative and the qualitative data [31]. Through a simultaneous bidirectional framework [31], we merge 1) descriptive statistics with a qualitative content analysis comparing the type, frequency, and severity of adverse events; 2) a prediction model for adverse events with a qualitative content analysis of the perceived causes for adverse events; and 3) a correlational

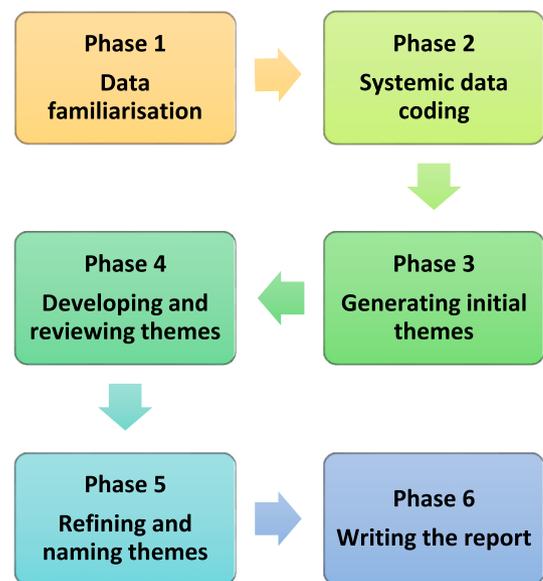


Fig. 3. Six-phase process for reflexive thematic analysis.

analysis (of adverse events and drop-outs/OCD-severity at end of treatment) with a thematic analysis of youths' and parents' treatment evaluation. We aim to expand the knowledge about what types of adverse events occurred in the trial (including their severity and frequency), why the adverse events occurred, and how adverse events relate to the effect of psychotherapy. We use back and forth analysis [69] and joint displays to explore concordance, discordance, and expansion between the quantitative and qualitative results [70]. Depending on the frequency of adverse events, we may not have sufficient data to perform the statistical tests. In such case, we focus on the qualitative analysis.

6. Ethics and dissemination

6.1. Ethics

Data collection for the mixed methods study received approval from The Ethics Committee of the Capital Region of Denmark (H-18010607) and The Knowledge Centre on Data Protection Compliance in The Capital Region of Denmark (VD-2018-263, I-Suite no.: 6502) as part of the TECTO trial protocol [30]. Participants consent to participate in this sub-study when entering the TECTO trial and can withdraw consent to participate at any time. The primary investigator discontinues youths from the trial intervention if they experience intolerable adverse events or deterioration of their clinical state (defined as a 30% increase on the CY-BOCS total score compared to baseline). If the primary investigator decides to discontinue a participant, the participant is offered standard treatment in the outpatient clinic. If a participant reports suicidal thoughts, we immediately perform a systematic suicide risk assessment at the clinic and inform the primary investigator and the professional responsible for the case management of the participant. In case of acute suicidal risk, we refer the youth to the psychiatric emergency department. When retrieving information from a participant's medical records on a potential SAE, we follow the Danish Data Protection Agency (Danish Health Act, section 43 (1) and the Danish Act on Processing of Personal Data). Since SAE/SAR/SUSAR are unanticipated in psychotherapy, all are reported to the National Committee on Research Ethics.

6.2. Dissemination

When the manuscript on the study results is peer reviewed and published, we aim to develop written information for patients and practitioners on the potential adverse effects from FCBT or FPRT for

OCD. We will present the findings for practitioners at CAMHC and nationally, and at international conferences. Our goal is to help practitioners prevent adverse outcomes and offer suggestions for improvement of FCBT and FPRT for OCD. We also spread knowledge on the results through social media.

7. Discussion

This convergent mixed-methods study is an exploratory and in-depth investigation of adverse events from FCBT and FPRT in TECTO trial. As the knowledge on adverse events in youth psychotherapy is sparse, we investigate new insights through abductive integration of qualitative and quantitative data rather than testing a predefined mixed methods hypothesis. Through this approach, we aim to generate new theory that could not be obtained by each method alone [32].

As adverse events in youth psychotherapy are a relatively new research area without official definitions or guidelines, our study has certain limitations. First, the quantitative results from the NEQ may not cover all adverse events in youth psychotherapy. The NEQ is developed and validated for adult psychotherapy [53] meaning that certain adverse events occurring in psychotherapy for youths with OCD may not be included in the questionnaire. While psychotherapy are believed to include a broader spectrum of adverse events than pharmacological treatments due to negative events in social interactions, this has not been thoroughly investigated [9,71]. The recommended medical treatment for OCD is selective serotonin reuptake inhibitors (SSRI) [4]. The most common adverse events from antidepressants in youth is nausea, vomiting, extrapyramidal symptoms, weight gain, diarrhea, sedation, anorexia, headache, and discontinuation of treatment due to side effects [72]. We aim to use the qualitative data to explore the nature of adverse events from psychotherapy, whether they may differ from medical adverse events and potential adverse events that were not included in the NEQ. Second, we expect missing data to be higher for youths who experience significant clinical worsening or intolerable adverse events [73]. To increase transparency from potential underrepresentation of patients who experience adverse events, we systematically register reasons for discontinuations from the trial interventions and ask if they want to continue quantitative and qualitative assessments.

The main strength of this study is the in-depth mixed methods analysis of adverse events in a randomized clinical trial. First, results from the mixed methods analysis can increase understanding of the types of adverse events that occur, who experience them, and what they signify for the outcome of FCBT and FPRT. By understanding why youths experience adverse events, we can improve CBT for youths with OCD and possibly reduce drop-out and non-response and increase help-seeking. Improved efficacy of psychotherapy may lead to a lower need for psychopharmacological interventions and/or prolonged psychotherapeutic interventions. Second, patients have the right to be informed about benefits as well as potential harms and tolerability of the offered treatments [39]. Our study can help clinicians improve patient information and identify patients at risk of experiencing intolerable adverse events. Third, knowledge from this study can inform national and international guidelines on treatment recommendations for pediatric OCD in youth. To date, only benefits of CBT are mentioned in these recommendations [4]. To make a fair comparison to medical choices for OCD, we need knowledge on potential adverse events in CBT and PRT to give patients balanced and safe treatment recommendation.

Author's contributions

Linea Pretzmann: Term, Conceptualization, Methodology, investigation, writing – Original Draft, Project administration. **Sofie Heidenheim Christensen:** Methodology, Investigation, Writing – Review and editing. **Anne Bryde Christensen:** Methodology, Writing – Review and editing, Project Administration. **Camilla Uhre:** Investigation, Writing – Review and editing. **Valdemar Uhre:** Investigation, Writing –

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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List of abbreviations

CAMHC	Child and Adolescent Mental Health Center
COREQ	Consolidated Criteria for Reporting Qualitative Research
CBT	Cognitive Behavioral Therapy
CTU	Copenhagen Trial Unit
CY-BOCS	Children's Yale-Brown Obsessive-Compulsive Scale
ERP	Exposure and Response Prevention
FCBT	Family-based Cognitive Behavioral Therapy
FPRT	Family-based Psychoeducation Relaxation Training
GCP	Good Clinical Practice
GRAMMS	Good Reporting of A Mixed Methods Study
ICD-10	International Classification of Diseases-10
K-SADS	Kiddie Schedule for Affective Disorders and Schizophrenia
MPR	Malpractice Reaction

NE	Negative Effect
NEQ	Negative Effects Questionnaire (NEQ)
OCD	Obsessive-Compulsive Disorder
PRT	Psychoeducation Relaxation Training (PRT)
SAE	Serious adverse events
SAR	Serious adverse reactions
SE	Side Effect
SUSAR	Suspected Unexpected Serious Adverse Reactions
TECTO	Treatment Effects of Family Based Cognitive Therapy in Children and Adolescents with Obsessive Compulsive Disorder

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