Statistical Analysis Plan (SAP) for: VIA Family—a family-based early intervention versus treatment as usual for familial high-risk children.

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Roles and responsibility

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Background

Children of parents with mental illness (COPMI) have an increased lifetime risk for developing a mental illness themselves (Rasic et al. 2014). Already during childhood COPMI have an increased risk for experiencing pediatric psychopathology and they have lower levels of functioning in their everyday life compared to children without parental mental illness (Ellersgaard et al. 2018). Children who are born to and grow up with parents who experience a severe mental illness (SMI) have a twofold risk: an enhanced genetic and a psychosocial risk.

There is a need for early interventions and preventive strategies in order to help children with current their problems while also enhancing resilience in the families and thus, hopefully prevent the development of mental illness in the children later in life.

Objectives and Trial design:

The VIA Family study aims to investigate the effect of an early intervention for families with parental SMI on children's level of functioning and psychological wellbeing.

The trial is a randomized controlled trial in a two-armed parallel group design. The study aims to test for superiority of the VIA Family Intervention (VFI) compared to treatment as usual (TAU).

The participating families were randomly assigned to VFI or TAU. The allocation ratio was 1:1. Randomization was stratified by parental inclusion diagnosis. Randomization was performed through the randomization module within the electronic database REDCap (Harris et al. 2009).

For more information see study protocol (Müller et al. 2019)

Sample size

The power calculation of the sample size on the primary outcome of the study, the Children's Global Assessment Scale (CGAS), detected that the study needed to include 37 children in each group to show a high effect size of a change of 10 points on the CGAS, a scale from 1-100. For further details on sample size calculation see study protocol (Müller et al. 2019).

Trial population

All participants were screened for eligibility criteria before randomization.

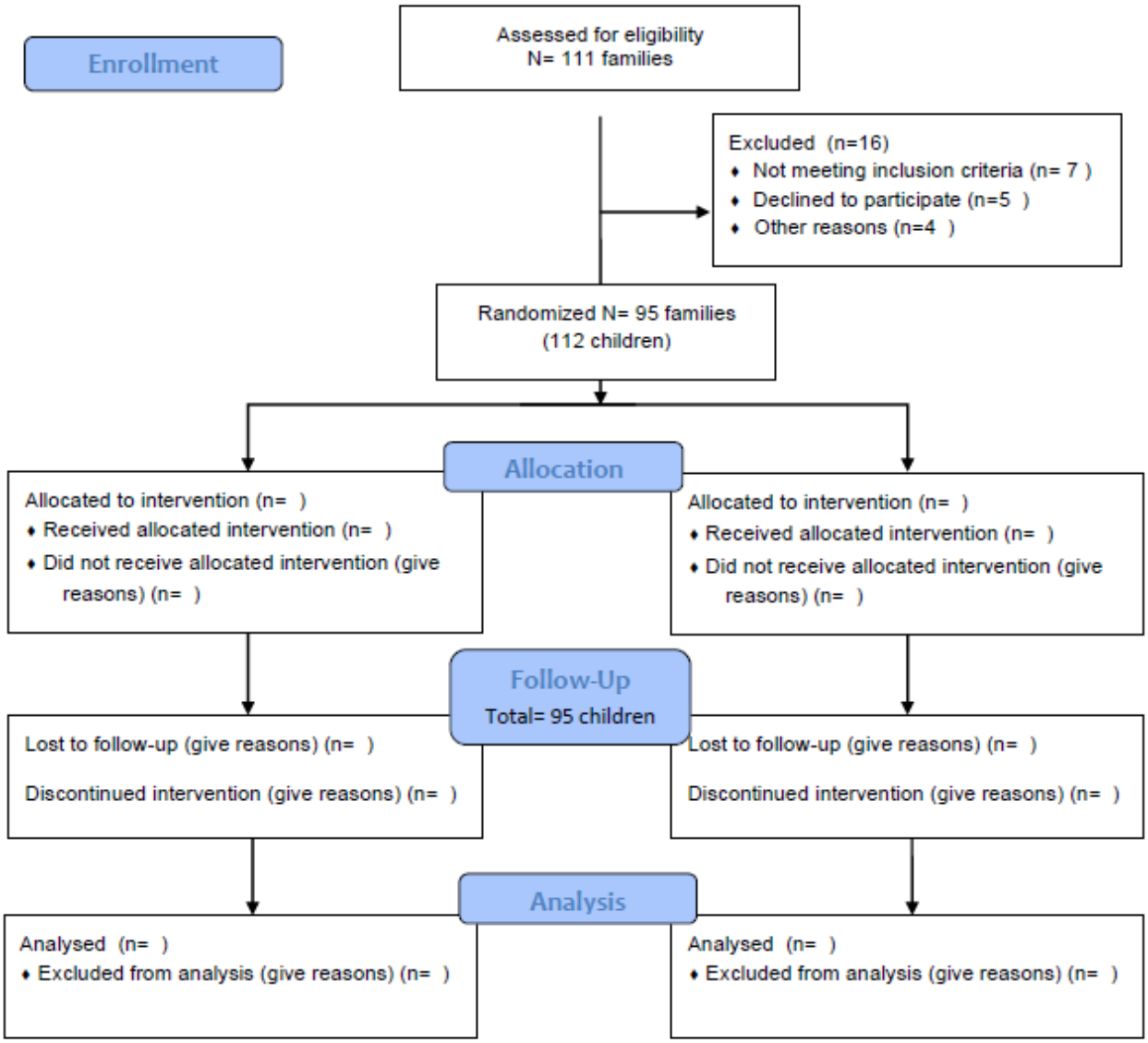
Eligibility criteria were: Having (at least) one child between age 6-12. Living in the municipalities of Frederiksberg or Copenhagen (Denmark). The parent has been registered in the Danish registers as having been diagnosed with one of the following psychiatric diagnoses: Schizophrenia Spectrum Disorder, Bipolar Disorder, Recurrent severe or moderate depression, within child's life. Comorbid disorders were allowed.

Exclusion criteria were: Parent with insufficient Danish language skills to be able to engage in treatment. Having received intensive family treatment in primary sector within the last 26 weeks before study participation.

For more detailed information see study protocol (Müller et al. 2019).

See CONSORT flow-diagram for screening, inclusion process and follow-up (Fig. 1)

Fig. 1 CONSORT 2010 Flow Diagram



Withdrawal/ Follow-up

Baseline characteristics of the study population will be presented in a descriptive table, presenting any possible differences between the two groups and the level of statistical significance.

Withdrawal from the study will be registered and reason for lost to follow up will be registered if possible. All participants who are missing at random will be included in the ITT analyses, see CONSORT diagram for drop out.

Statistical Analyses

Primary outcome

The primary outcome of the study is the change in CGAS. More precisely, the analysis will compare mean changes between baseline and 18 months in the CGAS to the VFI group.

The CGAS is a clinician rated scale from 1-100 (the higher the better) indicating the worst level of child's functioning within the last month. The CGAS will be used as a continuous outcome measure in the analysis.

The research question for the primary outcome is: Do children in the VFI group increase significantly more in CGAS at postintervention, when compared to the TAU group?

Primary Analysis: Intention-To-Treat

The primary analysis will be performed based on intention-to-treat (ITT) principles, meaning that the ITT population includes all randomized participants irrespective of their dropout status.

All outcome data will be analyzed collectively after the last participant has finished post intervention assessment. We will conduct an analysis of the primary outcome of the study followed by sensitivity analysis for the primary outcome. Further secondary analysis will be performed. See study protocol for an elaboration of primary and secondary outcomes (Müller et al, 2019).

The statistical analyses will be performed after follow-up data collection is completed. The statistical software R will be used for data analyses (Team 2010). Significance of results will be reported using two-tailed tests with a significance level of 5%. 95% confidence intervals will be reported for all estimates. The assumption that the data follows a normal distribution will be visually inspected using residual- and qq-plots, and if the data is not found to be normally distributed, log-scaling will be applied.

The primary outcome is the change in CGAS between 18-month follow-up and baseline. A linear mixed model will be used to model the data. Familiarity will be used as random nested factor in the analysis to accommodate for the non-independence that occurs between siblings that are part of the same family. Age, gender and variables with significant baseline differences between the groups will be used as covariates in the analysis. We report the mean difference in change between the VFI group and the TAU group effect and 95% confidence interval for this effect size.

Secondary Analyses:

Planned analyses for secondary outcomes: Change in mean scores on Child Behavior Checklist (CBCL) , Teacher Report Form (TRF) and days of absence from school (≥ 15 %). Parent and family related outcome measures: Family Assessment Device (FAD) and Home Observation Measurement of the Environment (HOME).

Planned analyses for exploratory analysis: Change in mean scores on child related outcome measures: Child Affective Lability Scale (CALS), Behavior Rating Inventory of Executive Function (BRIEF) and Emotion Regulation Questionnaire (ERQ). Child Self-report on: self-esteem (This Is me), health-related quality of life (KIDSCREEN) and resiliency (Child and Youth Resilience Measure -CYRM). Parent and Family related outcomes: Parental Stress Scale (PSS) and Personal and Social Performance Scale (PSP).

For more information on secondary and exploratory outcome measures see study protocol (Müller et al. 2019).

Deviations from the intervention protocol will be handled in the sensitivity analysis. Adherences to intervention protocol have been pre-defined and are explained in detail in the study protocol (Müller et al. 2019)

There has not been planned any interim analysis before data collection has been finished at 18-months post intervention.

Missing Data

In the ITT analysis, assuming normality of the data and that data is "missing at random" (MAR), missing data will be handled through multiple imputations based on maximum likelihood inference of parameters and imputation of missing data from a linear regression model. The analysis will be based on 100 imputations and iterations until convergence. See table 1 for variables that will be included in the imputations.

Table 1: Variables for imputation on missing data. If not otherwise specified data from baseline and follow-up will be included

Child	**Parent/family**	**Teacher**	**other**
Clinician rated interview	*Clinician rated interview*	*Surveys about the child*	Group allocation (experimental/control)
CGAS score	PSP, Primary Caregiver, total score	TRF, total score	
KSADS, any diagnoses (binary: yes/no)	HOME, total score	BRIEF, total sore	
		SRS, total score (baseline)	
Cognitive tests	*Surveys about the child*		
RIST – total score	CBCL, total score		
TOMAL-II total score	BRIEF, total score		
RCFT - total score	SRS, total score (baseline)		
Self-report surveys:	*Self-report surveys:*		
KIDSCREEN, total score	PSS Primary Caregiver, total score		

Sensitivity Analysis

To validate results, the following sensitivity analyses will be performed after ITT analysis:

1. Impact of outliers (analyses without outliers)
2. Per protocol (analyses without protocol violations)
3. Attendance (analyses on participants with ≥50% attendance of intended personal meetings in treatment groups)
4. Adjusting for covariates (analyses without adjustments)
5. For outcome of school absenteeism, a different cut-off will be used for analysis.
6. CGAS change for one child per family (for families with multiple children in the study mean change from all children in one family will be used)

Results from the sensitivity analyses will only be reported if negative.

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Harris, P. A., R. Taylor, R. Thielke, J. Payne, N. Gonzalez, and J. G. Conde. 2009. 'Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support', *J Biomed Inform*, 42: 377-81.

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