Introduction and Statistical Analysis Plan (SAP) for

VIA Family 4-years follow-up

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Roles and responsibility

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Background and Aim

This statistical analysis plan concerns the long-term follow-up (4-2.5 years after baseline assessment) of the VIA Family trial[1]. We conducted the VIA Family trial in Denmark between 2017-2020. The trial aimed to test for superiority of the VIA Family intervention compared with treatment as usual (TAU) in improving children's, parents' and families' functioning and wellbeing [1]. Eligible families had at least one parent with a lifetime severe mental illness diagnosis (SMI) (i.e. recurrent moderate to severe depression, bipolar disorder, or schizophrenia spectrum disorder), at least one child between the age of 6-12 years, and lived within the municipalities of Frederiksberg or Copenhagen (Denmark). The trial had a randomized, two-armed, parallel and controlled design. The participating families were randomly allocated to both groups with an allocation ratio of 1:1. For more information see study protocol[1].

We invited families for the 4-year follow-up assessment who at baseline had been randomized to one of the two treatment arms. Families who had withdrawn their consent for participation or had requested not to be

contacted for future follow-up were not invited for participation. At 4-year follow-up we invited only one parent to participate to represent the primary informant of the child.

The aim of the 4-year follow-up was to study potential long-term effects of the VIA Family intervention.

Methods and Measures

Measurements for the 4-year follow-up study were:

Children's Global Assessment Scale (CGAS)[2]

Strengths and Difficulties Questionnaire (SDQ)[3]

Health-Related Quality of Life Questionnaire: KIDSCREEN[4]

This is Me (TIM)[5]

Home Observation Measurement of the Environment (HOME)[6]

Family Assessment Device (FAD)[7]

Parental Stress Scale (PSS)[8]

Personal and Social Performance Scale (PSP) [9]

Parenting Scale (PS)[10]

Hypotheses

We expect that the experimental intervention VIA Family has positively impacted long term improvements in parenting, home environment, parent- and family functioning and other parental and family-related factors of protection for their children. We therefore expect that we will observe greater improvements in child functioning (CGAS), less signs of mental health (SDQ), improved child quality of life (KIDSSCREEN) and improved self-esteem (TIM) at 4-years follow-up, along improvements in parent and family related outcomes (PS, PSS, HOME, FAD, PSP) in families allocated to VIA Family compared with TAU.

The primary hypothesis is:

- The VIA Family intervention will demonstrate a superior change in SDQ from baseline (timepoint 0) to 4-year follow-up (timepoint 2) compared with TAU.

The secondary hypotheses are:

- The VIA Family intervention will demonstrate superior change in CGAS, KIDSSCREEN, TIM, HOME, FAD, PSS, PS, and PSP, respectively from baseline (timepoint 0) to 4-year follow-up (timepoint 2) compared with TAU.

Statistical Analyses

All analyses will be performed in the intention-to-treat (ITT) population including study participants as randomized regardless of treatment adherence and dropout status. The analyses will be conducted using the statistical software R[11] after the last participant completes the follow-up assessment and after the formulation of the statistical analysis plan. A two-tailed p-value of < 5% will be considered statistically significant.

Descriptive statistics

Baseline clinical and sociodemographic characteristics of children, parents, and families will be reported according to allocation group and drop-out status (see Table 1).

Table 1

Variables	**Instrument**	**Treatment As Usual**		**VIA Family**		**All**
Drop-out status at 4 years follow up		*participating*	*dropout*	*participating*	*dropout*	
Children's characteristics	***n(%)***					
Biological sex, female participants[a]	n (%)					
Age at baseline[a]	mean (SD)					
Global functioning[a]	CGAS, mean (SD)					
Any Current Diagnosis[1,a]	K-SADS-PL, n (%)					
Dimensional psychopathology	CBCL total problem score, T-score (Danish norms), mean (SD)					
High (≥ 15%) absence from school	Data from municipalities or schools, n (%)					
Neurocognition						
Estimate of general intelligence	RIST, scaled scores, mean (SD)					
Processing speed	WISC-IV *coding,* scaled scores (Danish norms), mean (SD)					
Visual Memory	RCFT immediate recall, T-scores (US norms), mean (SD)					
Verbal Memory – immediate	Memory for Stories, immediate recall (TOMAL-2), scaled scores (US norms), mean (SD)					
Verbal Memory- delayed	Memory for Stories, delayed recall (TOMAL-2) scaled scores (US norms), mean (SD)					
General Executive Functioning	BRIEF, T-score (Danish norms), mean (SD)					
Social responsiveness	SRS-2, raw score, mean (SD)					

Family and home characteristics	***n***					
Quality of home environment[2,a]	MC-HOME/EA-HOME, mean (SD)					
Single parent family[3]	*parent-reported,* n (%)					
Having two parents with SMI or/and substance misuse lifetime[4] diagnoses (solely out of families with two caregivers)	SCAN interview / patient journal, n (%)					
Index parent's diagnosis	***n***					
Lifetime[4] SZ[a]	SCAN interview / patient journal, n (%)					
Lifetime[4] BP[a]	SCAN interview / patient journal, n (%)					
Lifetime[4] rMDD[a]	SCAN interview / patient journal, n (%)					
Index parent with comorbid diagnosis [4]	SCAN interview / patient journal, n (%)					
Primary caregiver's characteristics	***n***					
SMI or/and substance misuse lifetime[3] diagnoses	SCAN interview / patient journal, n (%)					
General functioning (higher score better functioning)	PSP, mean (SD)					
Parental Stress (higher score more stress)	PSS, mean (SD)					
Family functioning (lower score better functioning)	FAD, mean (SD)					
Employment status parents						
Currently employed or studying [5]	*Interview,* n (%)					
Educational level parents						
Primary/lower secondary	n (%)					
Upper secondary, vocational, or short-cycle tertiary	n (%)					
Bachelor's degree, equivalent, or higher	n (%)					
Support at baseline (family)	***n***					
Family receiving support from municipalities/MHS six months prior to baseline [6]	Interview / Data from municipalities, n (%)					

1 Current Diagnosis within the last 8 weeks, excl. Elimination Disorder, Simple Phobia, Tics/Tourette's Syndrome
2 For children living 50/50 with mother and father, the HOME interview was done in both homes
3 Child has only one caregiver
4 During child's life (including the prenatal period)
5 Personality disorder, substance abuse, ADHD, PTSD, or eating disorder
6 Any form of employment, no minimum working hours, absence from work due to e.g., illness or maternity leave included as work

ADHD-RS Attention Deficit Hyperactivity Disorder Rating Scale[12]; BRIEF Behavior Rating Inventory of Executive Function[13]; CALS Children's Affective Lability Scale[14]; CBCL Child Behavior Checklist[15]; CGAS Children's Global Assessment Scale[2]; CTS Childhood Trauma Screener[16]; FAD Family Assessment Device[7], HOME Home Observation for Measurement of the Environment[6]; K-SADS-PL Kiddie Schedule for Affective Disorders and Schizophrenia - Present and Lifetime[17]; PSP Personal and Social performance Scale[9]; PSS Parental Stress Scale[8]; RCFT Rey Complex Figure Test[18]; RIST Reynolds Intellectual Screening Test[19] ; SCAN Schedules for Clinical Assessment in Neuropsychiatry[20]; SRS-2 Social Responsiveness Scale- Version 2[21]; TOMAL-II Test of Memory and Learning, 2nd Edition[22]; WISC-IV Wechsler Intelligence Scale for Children, 4th Edition[23]

Primary and secondary analyses Changes in child-specific outcomes (CGAS, SDQ, KIDSSCREEN, TIM, HOME, PS) will be analyzed using a linear mixed model including allocation group, baseline measurement, child age,

and sex (registered at birth) as fixed effects and a random effect of family to address non-independence among siblings within the same family.

Changes in parent- and family-specific outcomes (FAD, PSP, PSS) including allocation group, baseline measurement, and parental diagnosis as covariates.

Mean differences in change between the VIA Family intervention and TAU groups, along with a 95% confidence interval, will be reported with corresponding p-values.

Model assumptions will be assessed using residual diagnostics. Severely skewed outcomes will be log-transformed prior to analysis.

Handling of missing data

Characteristics of dropouts and completers will be compared between the allocation groups in descriptive tables to identify any possible systematic patterns or reasons for participant discontinuation. Reasons for dropout will be reported.

Missing data in the primary and secondary analyses will be handled by standard multiple imputations using the mice-package[24] and Amelia-package[25] in R. Missing values in each treatment arm separately will be imputed 100-fold including the variables specified in Table 2 below. Convergence will be assessed by traceplots.

Table 2: *Variables for imputation on missing data.*

Unless specified otherwise, data from baseline, 18 months follow-up, and 50 months follow-up will be included.

Child	Parent/family	Teacher	
Covariates	*Covariates*		
Age [a]	Age [a]		
Sex at birth [a]	Parental SMI diagnosis [a]		
Out-of-home placement [b,c]	Parents living together		
Clinician-rated interview	*Clinician rated interview*	*Surveys about the child*	
CGAS score	PSP, Index parent, total score	TRF, total score [a,b]	
KSADS, any diagnoses (binary: yes/no)[a,b]	PSP, other parent, total score	BRIEF, total sore [a,b]	
	HOME , total score	SRS, total score [a]	
Cognitive tests	*Surveys about the child*		
RIST – total score [a]	CBCL, total score [a,b]		
TOMAL-II total score [a]	BRIEF, total score [a,b]		
Coding (WISC) total score [a]	SRS, total score [a]		
RCFT - total score [a]	SDQ, total score		
Self-report questionnaires	*Self-report questionnaires*		
This Is Me, total score	PSS Index, total score		
KIDSCREEN, total score	PSS, other parent, total score		
[a] Baseline data			

[b] *18 months follow up data (end-of-intervention)* [c] *50 months follow up data*			

Sensitivity analyses

The primary and secondary analyses will be repeated:

a. Excluding outliers
b. In the per protocol population, defined as: Participants needed to attend a minimum of eight physical meetings, incorporating elements from the initial sessions (the family-centered lifeline, resilience and vulnerability mapping, and family-centered psychoeducation about emotions or diagnosis). Additionally, adhering to the intervention protocol required participants to engage in at least two other intervention components from the VIA Family intervention.
c. Without adjustment for baseline covariates
d. In case of differential drop out: with further adjustment for potential post randomization confounders.

Results from the sensitivity analyses will only be reported if they differ from the main analyses.

Subgroup analyses

To explore whether the intervention's effects vary among different demographic or clinical subgroups, the primary analysis will be repeated within the following subgroups:

a. Children without neurodevelopmental disorders (ASD, ADHD) compared with children with neurodevelopmental disorders at baseline and at end-of-intervention (1.5 years follow-up).
b. Families with young children, i.e., 6-9 years at baseline compared with families with older children, i.e., 10-12 years at baseline.
c. Families with low functioning at baseline (characterized by the 35% lowest combined scores in CGAS, HOME and PSP).
d. Families where all family members (parents and all children) have been participating in at least the introductory sessions of VIA Family compared with families were not all family members participated.
e. Families whose primary motivation to participate at baseline was to receive support compared with families whose primary motivation was to support a scientific project.

Estimated treatment differences from the subgroups will be reported in forest plots.

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