Statistical Analysis Plan (SAP)

COgnitive REhabilitation in pediatric Acquired Brain Injury (CORE pABI). A randomized controlled study

Section 1: Administrative Information

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Abbreviations

ABI	Acquired brain injury
BADS-C	Behavioral Assessment of the Dysexecutive Syndrome in Children
BRI	The Behavioral Regulation Index
BRIEF	The Behavior Rating Inventory of Executive Function
CONSORT	Consolidated Standards of Reporting Trials
CORE pABI	COgnitive REhabilitation in pediatric Acquired Brain Injury
CPT-III	Conners Continuous Performance Test 3rd edition
CWIT	Color-Word Interference Test
DEX-C	Dysexecutive Questionnaire for Children
D-KEFS	Delis-Kaplan Executive Function System
EF	Executive function
GMT	Goal Management Training
IQ	Intelligence quotient
MI	Metacognition Index
MRI	Magnetic resonance imaging
NTNU	Norwegian University of Science and Technology
OUH-RH	Oslo University Hospital, Rikshospitalet
pABI	Paediatric acquired brain injury
pBHW	Paediatric Brain Health Workshop
pGMT	Paediatric Goal Management Training
PI	Principal Investigator
RCT	Randomized controlled trial
SAP	Statistical Analysis plan
SD	Standard Deviation
SOH	St. Olav`s University Hospital
TBI	Traumatic brain injury
TMT	Trail Making Test
TOL	Tower of London
UNN	University Hospital of North Norway
QoL	Quality of Life
WebCRF	Web Clinical Research Form

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Section 2: Introduction

Background and rationale

Compromised integrity of the brain due to pediatric Acquired Brain Injury (pABI), both traumatic and atraumatic has been associated with cognitive impairment, particularly executive dysfunction, in addition to somatic, behavioural and emotional symptoms [1-9]. Hence, there is a great need for experimentally derived, prospective studies with randomly assigned experimental and control interventions, well-defined samples and investigator-masked outcome measures for children and adolescents with pABI [10, 11].

This statistical analysis plan (SAP) will provide detailed descriptions of the endpoints and the corresponding analyses of a planned randomized controlled trial (RCT). The RCT constitutes a part of a larger project *"COgnitive REhabilitation in pediatric Acquired Brain Injury - CORE pABI – a randomized controlled study"* described in more detail in a recently published paper [12]. The current document concerns the RCT in question and the analyses of planned primary and secondary outcomes. Supplemental analyses of the data collected in the trial, including in-depth-analyses of baseline data and analyses related to additional secondary outcomes will therefore not be described in the current document.

Objectives

The main objective of the present study is to determine the efficacy of a modified and age-adapted version of Goal Management Training© (GMT) for children and adolescents with pABI and executive function (EF) deficits. We have chosen a functional measure; The Behavior Rating Inventory of Executive Function (BRIEF)[13] as primary outcome. The pGMT intervention will be compared to a psychoeducative control intervention (paediatric Brain Health Workshop; pBHW) [14], immediately after the intervention and at 6 months follow-up.

Study hypotheses:

- Primary hypothesis: pGMT will result in a greater improvement in EF in daily life as reported by parents (BRIEF), compared to the active control, pBHW.
- Secondary hypotheses: pGMT will result in greater improvements in EF domains (EF tests and functional EF), as well as other cognitive functions (eg. attention) and academic performance compared to pBHW.

Finally, we want to explore associations between the pGMT effect on these outcomes and patient characteristics such as IQ, age, socioeconomic status and injury variables.

Section 3: Study Methods

Trial design

We have designed a two centre, parallel-randomized controlled trial. Patients are randomized to either paediatric Goal Management Training (pGMT) or the psychoeducative control intervention; paediatric Brain Health Workshop (pBHW)[14]. Function is assessed at three time-points; pre-intervention, immediately after the intervention and at 6 months follow-up.

Randomization and blinding

Participants are randomized to either pGMT or pBWT in a 1:1 ratio, applying block randomisation and stratification by 1) research site (Trondheim or Oslo) and 2) age at the time of intervention (10 - 13 years or 14 - 17 years). The Unit for Applied Clinical Research, Norwegian University of Science and Technology (NTNU) serves as allocator and thus be responsible for the computerized randomisation but will not be involved in determination of participant eligibility, assessment or execution of the interventions. The block randomization is set up in advance by the allocator and hidden from the executer to minimize the possibility of guessing the next allocation. The block size is set to 4 due to the study design of the treatment. Blinding is be applied to reduce systematic bias as a result of knowing the treatment allocations, with the following procedures; i) Families and participants will not be informed about which intervention they have been assigned to (the term "Brain training" will be used consistently in both groups), ii) Test technicians who conduct assessments will be blinded to treatment allocation and are not trained in the interventions; iii) Therapists who administer the two interventions, will be blinded to all test performance and evaluation, iv) The use of the WebCRF system, with data stored anonymously and only biostatistician and research assistant having access, minimizes the likelihood of influence by the investigators, v) The interventions (pGMT and pBHW) will be conducted separately in time on both sites, thus reducing the chance of participants with differing allocations sharing information and experience. Additionally, vi) participants will be explicitly asked not to discuss course content with test technicians assessing them or other potential participants outside of their group.

Analyses will be performed while still blinded for the treatment groups, and treatment allocations will be unfolded only after statistical analyses have been finalized.

Sample size

The proposed study aims at recruiting a total of 80 children and adolescents with pABI. Based on previous studies, the estimated annual incidence of TBI in Norway (aged 0-19 years) is 1400[15]. The prevalence of paediatric brain tumours in Norway is lower, with approximately 40 new cases per year (survival rate is 80%)[16], with a high proportion of patients suffering from cognitive deficits. Incidence rates for childhood stroke vary from 1.3 per 100,000 to 13.0 per 100,000[17], while rates of paediatric encephalitis-related hospitalization range from 3 to 13 admissions per 100,000 children per year (US and Europe) [18]. Thus, the sample size is considered attainable, with reference to the total eligible population. As only one previous single-case study on pGMT in pABI exists to date[19], this represents a challenge in estimating the required sample size in this proposed study. In order to document a clinically relevant effect as experienced by the child/adolescent and their family, we used the Global Executive Composite-scale from the parental report on BRIEF[13] as the main outcome measure in the power analysis. Prior research on the effect of GMT in adults with ABI and spina bifida has reported moderate to large effect sizes. In order to detect an effect size of $d = .70$ with a power = .80 and $\alpha = .05$, 32 patients are needed in each group.

Framework

Based on our study hypothesis, this trial will be testing for superiority on both primary and secondary outcome measures.

Statistical interim analyses and stopping guidance

No interim analyses are planned for in this trial.
Any planned adjustment of the significance level due to interim analysis: Not relevant.
No stop rules are planned for.

Timing of final analysis

Final analysis of the RCT is planned to take place when the 6 months (T3) follow-up has been reached for all intervention groups (November 2019) and when data quality has been assured. All outcomes will be analyzed and reported collectively.

Timing of outcome assessments

The trial will use a repeated-measures design [20] across 3 time-points (pre-intervention (T1), post-intervention (8 weeks after intervention initiation, T2) and 6 months follow-up (T3). Figure 1 illustrates the schedule of study procedures.

Study period							
	Enrollment (n=80)	Allocation	Baseline Assessment	Intervention period		Outcome Assessment	
				Intervention (3 weeks)	Counselling, external cueing (5 weeks)		
Timepoint	>12 months post injury >12 months post treatment		T1			T2 (immediately post intervention)	T3 (6 months post intervention)
Enrollment - Eligibility screening	X						
- Informed consent	X						
- Allocation		X					
Intervention pGMT (n=40)				X	X		
pBHW (n=40)				X	X		
Assessments *Primary outcome measures* (Measures of EF, emotional health, fatigue, social function and quality of life)			X			X	X
Secondary outcome measures (Medical screening, questionnaires of family function, adaptive domains)			X			X (reduced set of tests and quest.)	X

Figure 1 Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) figure. Pediatric Goal Management Training and Pediatric Brain Health Workshop.

Section 4: Statistical Principles

Confidence intervals and P values

The two co-primary endpoints from BRIEF (BRI and MI) will be analyzed using the Hochberg procedure[21] to control the Type I error rate. The global null hypothesis of no difference between groups will be rejected if the test of either endpoint is statistically

significant at the two-sided 0.025 level, or if both tests are significant at the two-sided 0.05 level.
Differences between treatment groups will accordingly be estimated with 95 % confidence intervals. For secondary endpoints, estimates of treatment differences will be presented with 95% confidence intervals, and tests will be performed using a two-sided p-level of 0.05. No adjustment of multiplicity is planned.

Adherence and protocol deviations

Adherence and protocol deviations are described in full within the Study protocol, chapter 6.4.4, Procedures/Compliance.

Analysis populations

The analysis populations will be defined according to the following strategy:

1. The primary analysis population (Full Analysis Set, FAS) is defined by all randomized individuals who has post-baseline outcome data.
2. The per protocol population will include all participants who have missed a maximum of two out of the seven group sessions (as defined at protocol level).
3. Regarding the brain tumor group, progress of disease during the time of the study is possible. We therefore plan for the following post-hoc analysis: A third analyses population will be defined to assess treatment effects in participants that did NOT show objective signs of disease progress or intracranial complication (eg related to shunt) at the time of T3 testing, the condition need to be verified by treating pediatric oncologist/neurosurgeon, who is blinded to treatment allocation.

Section 5: Trial Population

Participants were recruited at two sites in Norway; St. Olav`s Hospital (SOH) in Trondheim and Oslo University Hospital, Rikshospitalet (OUH-RH). In addition, patients from the University Hospital of North Norway (UNN) were invited to participate. SOH, OUH-RH and UNN are the trauma referral centres for the Central, South-Eastern and Northern regions of Norway respectively, and have a population base of more than two thirds of the Norwegian paediatric population. The recruitment period lasted from November 2017 until June 2019.

Screening data

The following summaries are presented for all screened patients in a flow diagram (Appendix A) according to the CONSORT guidelines:
Enrolment: the number of patients screened, the number of patients recruited, the number of screened patients not recruited and reasons for non-recruitment. The summary statistics will be provided for the overall group.

Participants with pABI will be invited to participate in the study based on hospital discharge diagnosis, hospital records and by inclusion in the standardized patient care. After identification, each individual patient record will be inspected using a pre-set data extraction sheet with defined factors to systematize and ensure proper injury information and diagnosis. After written consent, eligibility will further be assessed by a semi-structured telephone-interview prior to randomization and allocation.

Eligibility

The study population will consist of children and adolescents diagnosed with ABI resulting from traumatic (TBI) and non-traumatic injuries (brain tumour, stroke, hypoxia/anoxia and brain infections/inflammations) from the age of 10 up to 17 years at the time of the intervention. Participation requires a period of at least 12 months since injury/illness or more than 12 months since ended cancer therapy, in addition to experiencing executive dysfunction in daily life as determined by a semi-structured telephone interview. Exclusion criteria are as follows: (i) injury acquired before 2 years of age; (ii) cognitive, sensory, physical, or language impairment affecting the capacity to attend regular school (i.e., primarily follow educational goals of peers and regular classroom teaching) and/or complete the training program; (iii) pre-injury neurological disease, severe psychiatric disorder and/or stimulant medication; (iv) recently detected brain tumour relapse; (v) unfit for evaluation of outcome (independent evaluation by 2 investigators); (vi) not fluent in Norwegian.

The number of ineligible patients randomized is reported in the flow diagram with reasons of ineligibility.

Recruitment

A CONSORT flow diagram (Appendix A) will comprise the number of:

- Patients identified on the basis of discharge diagnoses and hospital records screened
- Invited patients assessed for screening
    - Eligible at screening
    - Ineligible at screening *
- Eligible and randomized
- Eligible but not randomized *
- Received the randomized allocation
- Did not receive the randomized allocation *
- Discontinued the intervention*
- Lost to follow-up *
- Randomized and included in the primary analysis
- Randomized and excluded in the primary analysis *

* reasons will be provided.

Withdrawal/follow-up

The level of consent withdrawal will be tabulated and presented in flow diagram A.

Timing of withdrawal/lost to follow-up

This will be presented in the flow diagram, with numbers and reasons for withdraw and/or exclusion from analysis given at each stage (delivery of intervention, immediately after intervention and at 6 months follow-up).

Reasons and details of how withdrawal/lost to follow-up data will be presented

The numbers (with reasons) of losses to follow-up (drop-outs and exclusions) over the course of the trial will be summarized by treatment arm.

Baseline patient characteristics

Distributions of participant characteristics at baseline will be displayed according to age at inclusion, sex, IQ, maternal education and intact family unit. Further, we will display distributions related to injury: aetiology, age at injury/diagnosis, years since injury/diagnosis, lesion characteristics/MRI, injury severity and treatment descriptions. Other relevant baseline information will be described: neurological status at baseline (normal vs not normal), reported sleep disturbances (yes/no), reported headache (yes/no), epilepsy (yes/no), daily medicine use (yes/no), fatigue (cut off), school attendance (cut off, %), and/or individualized education and academic preformance. Data will be presented both overall and separately for the two intervention groups.

Details of how baseline characteristics will be descriptively summarized.
Categorical data will be presented by numbers and percentages. Continuous data will be summarised median, IQR and range. Minimum and maximum values will also be presented for continuous data.

Section 6: Analysis

Outcome

The efficacy of treatment will be assessed by a battery of standardized questionnaires and neuropsychological tests designed to measure executive functioning and attention as displayed in table 1.

Primary and secondary outcomes
The two co-primary endpoints are the subscores *The Behavioral Regulation Index (BRI)* and *Metacognition Index (MI)* from the standardized questionnaire *the Behavioral Rating Inventory of Executive Function (BRIEF)*, parent report.

Table 1: Details of primary and secondary outcome measures with specifications of units

	Function		**Outcome measure**	**Measurement /units**	**Ref.**
Primary outcome	EF	Q	Behavioral Rating Inventory of Executive Function, parent report (BRIEF)	1-3	[13]
			- BRI		
			- MI		
Secondary outcomes	EF	Q	BRIEF, self- and teacher report	1-3	[13]
		Q	BRIEF, parent report, subscales and GEC		
		Q	Dysexecutive Questionnaire for Children (DEX-C), parent- and teacher report	0-4	[22]
		Q	ADHD Rating Scale IV, parent and teacher report	0-3	[23]
		NP	Conners Continuous Performance Test 3rd edition (CPT-III)		[24]

		NP	Color-Word Interference Test (CWIT 3 - 4), Delis-Kaplan Executive Function System (D-KEFS)		[25]
		NP	Trail Making Test 3-4 (TMT 3-4), D-KEFS		[25]
		NP	Behavioral Assessment of the Dysexecutive Syndrome in Children (BADS-C)		[22]
		NP	Tower of London (TOL)		[26]
		OA	Children's Cooking Task (CCT)		[27]

* EF: *Executive function*, Q: *Questionnaire*, NP: *Neuropsychological tests*, OA: *Observational assessment tool,* BRI= *The Behavioral Regulation Index,* MI= *Metacognition Index,* GEC= *Global Executive Composite.*

BRIEF parent report[13] contains of 86 items that captures parents perceptions of a child's EF in his or her everyday environment. Each item's frequency of occurrence is rated on a 3-point Likert scale from 1 (never) to 3 (often). It encompasses eight clinical scales (Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Organization of Materials, Monitor). The clinical scales form two broader Indexes; *The Behavioral Regulation Index (BRI)* consisting of Inhibit, Shift, Emotional Control, and the *Metacognition Index (MI)* consisting of Initiate, Working Memory, Plan/Organize, Organization of Materials and Monitor.

In addition to BRI and MI the BRIEF parental report, includes the *Global Executive Composite (GEC)*. Brief has demonstrated good reliability, with high test-retest reliability (rs = .88 for teachers, .82 for parents), internal consistency (Cronbach's alphas = .80 – .98), and moderate correlations have been detected between teacher and parent ratings (*r*s = .32-.34). The questionnaire has been applied to several clinical groups in Norway[28]. There are no Norwegian norms for BRIEF, but there is support for the use of American norms, as these norms were within the 95 % confidence interval of the scores from a Norwegian sample. The instrument has shown good validity by significantly differentiate between children in clinical groups, more specifically between children with attentional problems (ADHD) and their peers. Moderate to high correlations with comparable questionnaire measures indicate good construct validity (self and teacher report). As secondary outcomes we will employ BRIEF subscales, Dysexecutive Questionnaire for Children (DEX-C, parent and teacher report), ADHD Rating Scale IV (parent and teacher report), Conners`Continuous Performance Test 3rd edition (CPT-III), Delis-Kaplan Executive Function System (D-KEFS), subtests Color-Word Interference Test (CWIT 3 - 4) and Trail Making Test 3-4 (TMT 3-4), Behavioral Assessment of the Dysexecutive Syndrome in Children (BADS-C), Tower of London (TOL) and Children's Cooking Task (CCT).

Note; despite a widespread application of the BRIEF and well-documented psychometric properties, it must be declared that it may be vulnerable to changes in insight. This is a mechanism often observed in clinical work. Enhanced knowledge and insight concerning the child's dysfunction attained in the intervention period, may lead to increased reported dysfunction immediately after the intervention. Thus, we anticipate a possible increase in reported executive dysfunction at T2 in some parents (participants or teachers) compared to baseline, reflecting increased insight rather than increased difficulties. Should this occur, it is expected to equally affect both treatment groups. By using a mixed model analysis, which

considers all of the time points, and focusing on the difference between treatment groups rather than over time within groups, we hope to overcome this challenge.

Specification of outcomes and timings. Primary and secondary outcomes specific to EF are listed in table 1, with specific measurement and units.

Analysis methods

The primary analyses of the two co-primary endpoints ($BRIEF_{Parent\ report}$; BRI and $MI_{Raw\ scores}$) will be performed in the FAS. Repeated measures analyses using BRI and $MI_{Raw\ scores}$ at T2 and T3 as the outcome. The model will include baseline Raw score as a covariate and treatment group, the interaction between time and treatment, and the stratification factors (research site and age group) as fixed effects. Baseline is included as a baseline rather than an additional time point because e.g. it increases statistical efficiency. Time is included as categorical with unstructured covariance as the starting point. The primary analyses will be adjusted for the study stratification factors site and age at intervention.

Distributional assumptions will be checked by visual inspection of residual plots. If the normality assumption is obviously violated, as log-transformations or other appropriate transformations will be done to assess robustness of the estimates.

Subgroup analyses will be performed according to stratification factors used in the randomization process 1) research site (Trondheim or Oslo) and, 2) age at the time of intervention (10 - 13 years or 14 - 17 years), if an interaction between research site and treatment, or age and treatment is seen, and results will then be presented separately.

Sensitivity analyses will be performed by exploring the effect of additional covariates thought to be of prognostic importance: Type of injury (Brain tumor versus other age at injury, time since injury, injury severity, fatigue, treatment/ rehabilitation, deficient school attendance.

The above strategy will be applied for analyses of the per protocol population as well as for the intention to treat population.

Missing data

A linear mixed model uses all available information, and no imputation of missing scores on each time point is planned.

Additional analyses

Details of any additional statistical analyses required, eg, complier-average causal effect10 analysis

Harms

Summarized safety data will be displayed: adverse events definition and coding will be tabulated.

Statistical software

Data analysis will be performed using IBM-SPSS version 25, Stata15 and SAS v9.4.

References to protocol and Trial Master File

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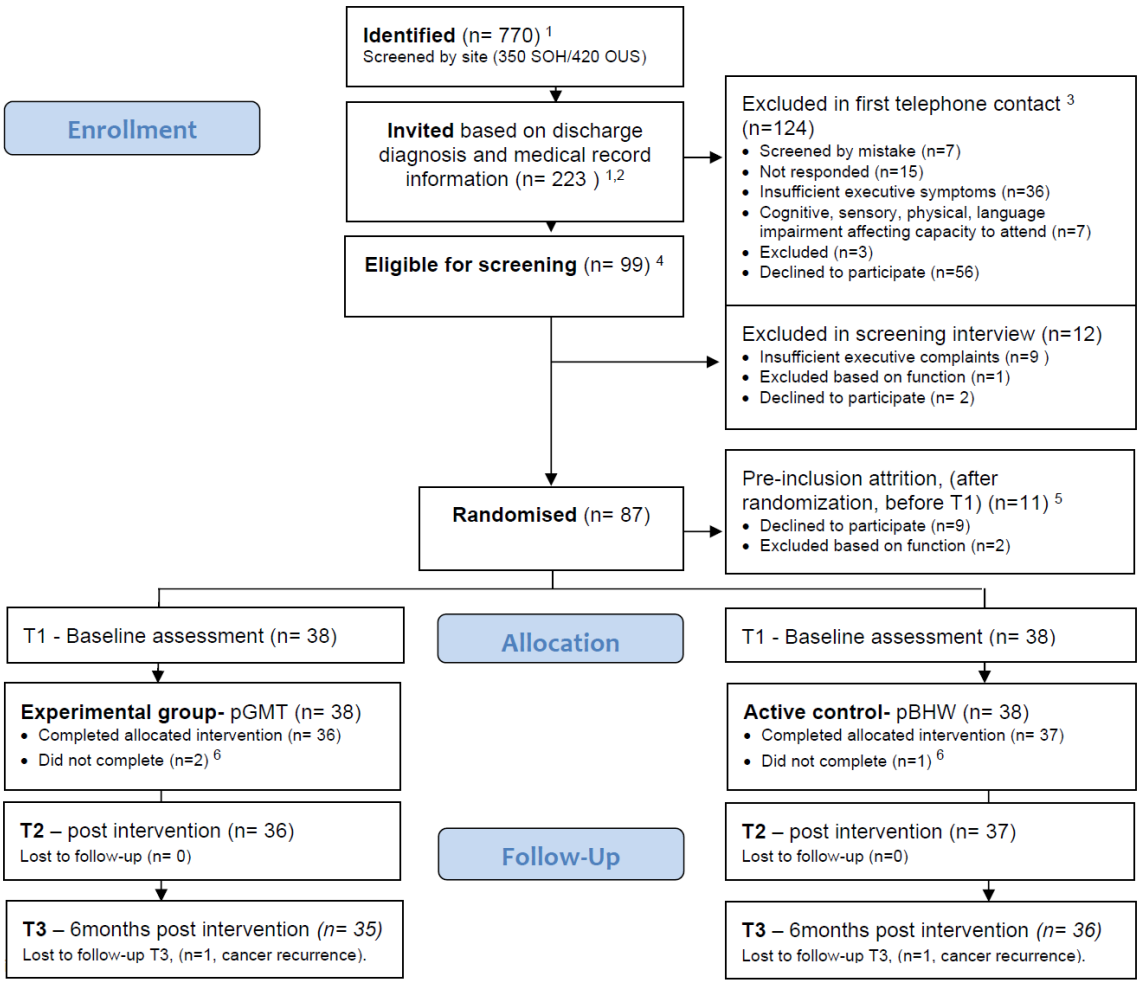
Appendix A



[1] Primary eligibility criteria were identified by discharge diagnosis and hospital record information. The following ICD-10 codes (WHO) were utilized in the search: B00.3, B00.4, B02.0, B02.1, A85, A86, G04, G05, F07.1 (Inflammation); C71, C72 (Brain tumor); G93.1/R09.0, T75.1, T90.1 (Anoxia/hypoxia); G93.6, I60- I69 (Stroke); S02, S06-S09, T90 (TBI); F07.2, T90 (Post-commotio-syndrom). In addition to diagnosis, participants were identified on the basis of inclusion in the standardized patient care for children with brain tumors and for children with aquired brain injury implementet at St Olavs Hospital ,Trondheim university hospital and Oslo University hospital (Rikshospitalet). After identification, each individual journal was inspected using a pre-set data extraction sheet with defined factors to systematize and ensure proper injury information and diagnosis.

[2] *Eligibility criteria:* (i) diagnosed with TBI, brain tumor, stroke, anoxia/hypoxia or damage by inflammation in the brain; (ii) between the age of 10 up to 18 years at the time of the intervention; (iii) > 12 months since injury/illness OR > 12 months since ended cancer therapy; (iv)evidence of executive dysfunction in everyday life. *Exclusion criteria:* (i) cognitive, sensory, physical, or language impairment affecting the capacity to attend mainstream school and/or complete the training program; (ii) pre-injury neurological disease or psychiatric disorder; (iii) recently detected brain tumor relapse; (iv) unfit for evaluation of outcome (independent evaluation by 2 investigators); (v) not fluent in Norwegian.

[3] 7 children who did not meet the inclusion criteria were incorrectly invited based on missing or incorrect information provided in their hospital records.

[4] Inclusion and exclusion criteria was further assessed by semi-structured interviews after written consent.

[5] Potential participant was blinded to allocation at the time of pre-inclusion attrition. Nevertheless, of the 9 who declined participation (SOH:3had been allocatet to pGMT and 1 to pBHW). Of the two excluded based on function, one was allocateded to pGMT and the other to pBHW.

[6] A total of 3 participants did not complete the interventions, in the experimental gruoup there was one drop-out after session# 2 and one excluded based on function. In the active control one participant was excluded based on function.