Statistical Analysis Plan (SAP)

Benefits of in-prison OROS-methylphenidate vs. placebo treatment in detained people with attention-deficit/hyperactivity disorder: A randomised controlled trial

BATIR

Administrative Information

Trial registration number:	ClinicalTrials.gov NCT05842330; Kofam.ch SNCTP000005388
SAP version:	SAP version number with dates. 1 of 03.03.2026
Protocol version:	V1 of 03.03.2026

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Revision	Justification	Timing

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Abbreviations

ADHD	Attention deficit hyperactivity disorder
AE	Adverse event
ASR	Annual Safety Report
AIC	Akaike Information Criterion
BIC	Bayesian Information Criterion
FAIR	Findable, Accessible, Interoperable and Re-usable
FAS	Full Analysis Set
ICE	Intercurrent Event
ITT	Intention To Treat
MAR	Missing At Random
MICE	Multiple Imputation with Chained Equations
PP	Per Protocol
SAE	Severe Adverse Event
SAF	Safety Population
SAP	Statistical Analysis Plan
CA	Competent Authority (e.g. Swissmedic)
CEC	Competent Ethics Committee
CCER	Commission cantonale d'éthique de la recherche de Genève
CRF	Case Report Form
ClinO	Ordinance on Clinical Trials in Human Research *(in German: KlinV, in French: OClin, in Italian: OSRUm)*
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IB	Investigator's Brochure
H_0	Null hypothesis
HRA	Federal Act on Research involving Human Beings *(in German: HFG, in French: LRH, in Italian: LRUm)*
IMP	Investigational Medicinal Product
OROS-MPH	Osmotic-release oral system methylphenidate
PI	Principal Investigator
RCT	Randomised controlled trial
SNCTP	Swiss National Clinical Trials Portal
SUSAR	Suspected Unexpected Serious Adverse Reaction
SNSF	Swiss National Science Foundation

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1. Introduction

1.1 Background and rationale

1.1.1 ADHD in prison

Attention deficit hyperactivity disorder (ADHD) is a disorder characterized by difficulties paying attention, poor impulse control, and hyperactive behaviours (1). ADHD usually starts in childhood and persists in adulthood in 40 to 60% of cases (2). There is growing evidence that adult ADHD is associated to a wide range of adverse outcomes and thus constitutes a significant public health concern (3, 4). It affects several areas of life, such as psychosocial functioning, school, work, as well as health care access and use (5-7). It is also associated with an increased risk of having judicial contact at a younger age, including rule-breaking behaviours, delinquency, criminality, and recidivism (8-10). Consequently, ADHD is significantly more prevalent in incarcerated populations in comparison with the general population and there is a growing recognition that ADHD in prison is a major concern (9, 11).

Several studies have already been conducted to estimate the prevalence rate of ADHD in prison. In a recent meta-analysis conducted on around 70'000 detained persons worldwide, we found an ADHD prevalence rate of 26.2% (11). This corresponds to a five-fold increase in comparison with the general population (5%, 12, 13). It means that ADHD should be considered as a major challenge for prison health care.

Compared with other detained persons, incarcerated individuals with ADHD experience functional impairment likely to interfere with prison life. For example, they are likely to be verbally and physically aggressive and to have disciplinary infractions (14, 15). They also have more unsuccessful experiences with the criminal justice system (16). These actions may be (mis)interpreted as intentional misconducts instead of features of undiagnosed ADHD (16). In the general population, individuals usually develop coping mechanisms to deal with ADHD (e.g., favouring flexible environments with various short-termed tasks and flexible deadlines). Use of such strategies is not easy in the strict prison environment, which further emphasizes the importance of access to treatment in prison (17).

A corpus of evidence also suggests that, after release, detained persons with untreated ADHD have high rates of recidivism (8, 18-21). In Switzerland, 8'691 persons are released each year (22). Therefore, identifying and treating ADHD in detained persons may help preventing recidivism (23).

1.1.2 ADHD treatment in prison

ADHD is a treatable condition. Pharmacotherapy is a first-line treatment for ADHD (24, 25). Psychostimulants, such as osmotic-release oral system methylphenidate (OROS-MPH) have demonstrated excellent short-term effectiveness among different populations (4, 26). Furthermore, there are potential long-lasting effects of OROS-MPH on ADHD symptoms even after treatment discontinuation. Previous studies have reported promising enduring effects after discontinuation (27, 28). This can be due to neuroplasticity and development of coping strategies to deal with ADHD-related impairments (28).

In previous studies, combination of pharmacological and non-pharmacological treatments was most consistently associated with long-term improvement of ADHD symptoms and global functioning (29, 30). This is especially true for cognitive behavioural therapy, which aims to develop behavioural strategies to compensate the core deficits of ADHD (25, 31). There are also potential long lasting effects of psychotherapy, with twelve-months enduring effects (31). A multimodal treatment is therefore recommended to treat ADHD (26).

Stimulant drugs such as OROS-MPH are often under-prescribed in prison because of concerns about abuse (17, 32), even if such claims are not empirically supported. ADHD is likely to be under-diagnosed and under-treated in prison (33). One primary principle of prison healthcare is equality of treatment (34, 35): Prison populations should be able to access and benefit from the same treatments as the general population. A restricted access to stimulant drugs violates this important principle. The lack of empirical

evidence on abuse of stimulants such as OROS-MPH should be considered as an important ethical issue.

In addition, continuity of care is a major challenge for prison populations. Health care linkage programs between prison and community services are lacking and there are several lost opportunities to treat this vulnerable population with high health needs (36-40). A recent meta-analysis concluded that continuity of care between prison and the community should be prioritized (41). Thus, studies designed to explore and improve medical adherence after release are needed among prison populations. Empirical-based evidence for the efficacy of in-prison ADHD treatment for this population's rehabilitation is therefore needed (42), as well as robust evidence studies testing treatments likely to address modifiable risk factors for recidivism (41).

1.1.3 Investigational Product (treatment) and Indication

Name of the product: Concerta®

Class: CNS stimulant indicated for the treatment of ADHD in patients aged 6-65.

ATC code: N06BA04.

Active ingredient: Methylphenidate hydrochloride (18mg, 36mg, or 54mg)

List of other excipients: butylated hydroxytoluene, carnauba wax, cellulose acetate, hypromellose, lactose, phosphoric acid, poloxamer, polyethylene glycol, polyethylene oxides, povidone, propylene glycol, sodium chloride, stearic acid, succinic acid, synthetic iron oxides, titanium dioxide, and triacetin.

Form: Extended-release tablets for once-a-day oral administration (12-hour effect duration).

Mechanism of action: The mode of therapeutic action in ADHD is not known. MPH is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and to increase the release of these monoamines into the extraneuronal space.

Pharmacodynamics: MPH is a racemic mixture comprised of the d- and l-isomers.

For preclinical and clinical evidence, refer to the study protocol.

1.1.4 Rationale for the dosage, route, regimen

Dosages of Concerta® will be defined according to the Swiss Compendium (from 18 to 72 mg/d). Higher dosages can be used, especially in case of comorbid substance use disorders (43) and will be considered when needed. In a previous study conducted among patients with comorbid ADHD and substance use disorders, a higher dosage of Concerta up to 180mg/d reduced ADHD symptoms and the risk for relapse to substance use (44).
The psychiatrist will start with the smallest dosage (18 mg) and will adapt it on a weekly basis or on need, depending on tolerance (side effects measured at each visit), clinical response (subjective improvement felt by the patient in terms of attention, impulsivity, and hyperactivity), and according to the observations made by the professionals or patient's entourage in term of attention, impulsivity, hyperactivity, and for this project, behavioural problems. In general, the dose can be increased in 18 mg at weekly intervals.
The treatment will be monitored weekly the first month, and then monthly, except for side effects which will be monitored daily in prison and every two weeks after release.
As the effect has been shown to last for 12 h from the time of intake, Concerta® will be taken orally once a day in the morning. Concerta® tablets should not be chewed, crushed, or cut into piece, because the active ingredient is inside a non-absorbable shell. Concerta® can be taken with or without food.

1.1.5 Explanation for choice of comparator (or placebo)

The use of a placebo group was considered as important to distinguish the effect of OROS-MPH and is justified, as all study participants receive a psychotherapeutic intervention. Data on the efficacy of OROS-MPH in prison are scarce, especially including acute events in prison and post-release outcomes. To answer this question, the active treatment will be compared to a placebo condition.

As there is no well-defined standard of care for ADHD treatment in prison and because detained persons are usually not diagnosed nor treated for ADHD (33), a placebo condition is ethically acceptable.

1.2 Objectives

1.2.1 Overall Objective

This project aims to compare the efficacy of a 3-month in-prison OROS-MPH vs. placebo treatment on clinical, behavioural, recidivism-related, economical, and side effect outcomes. The exact and maximum duration of the treatment is 12 weeks, with a time window of one week (11-13 weeks). Below, "three months" refers to this period.

1.2.2 Primary Objective

O1. The study will compare the 3-month in-prison efficacy of OROS-MPH vs. placebo on the severity of ADHD core symptoms.

1.2.3 Secondary Objectives

Three-month secondary research objectives
O2. The study will compare the 3-month in-prison efficacy of OROS-MPH vs. placebo on acute events during detention.
O3. The study will compare the 3-month in-prison efficacy of OROS-MPH vs. placebo on the risk of recidivism.

Overall (15 months) secondary research objectives
O4. The study will compare the efficacy of having received OROS-MPH vs. placebo three months during imprisonment on adherence to medication for the whole study period (during detention, on their decision to have the treatment after three months, and 12 months as outpatient follow-up).
O5. The study will compare the efficacy of having received OROS-MPH vs. placebo three months during imprisonment on study retention for the whole study period (15 months: 3 months of treatment + 12 months of outpatient follow-up).
O6. The study will conduct a cost/benefit analysis of ADHD treatment (OROS-MHP *vs.* placebo) in a prison setting for two-time horizons and according to two perspectives:

- The *healthcare system perspective* (third party payer): Costs and induced benefits of the ADHD treatment will be evaluated in terms of costs associated with healthcare services use (outpatient care, inpatient care, emergency intervention, and medications), during the first 3 months.
- The *prison system perspective*: Costs and induced benefits of the ADHD treatment will be evaluated in terms of costs avoidable related to acute events in term of security (e.g., sanctions) and recidivism (increased costs when released persons are reincarcerated), during the first 3 months and 12-month of outpatient follow-up.

Fifteen-month secondary research objective
O7. The study will compare the efficacy of having received OROS-MPH vs. placebo three months during imprisonment on rule-breaking behaviours (disciplinary infractions in prison or recidivism after release into the community) over the 12-month outpatient follow-up.

1.2.4 Safety Objectives

O8. The study aims to assess the 3-month side effects of OROS-MPH vs. placebo and its tolerability in terms of incidence of main side effects before release.
Side effects of OROS-MPH are already well known, this objective will serve as a complement for a vulnerable population likely to have psychiatric comorbidities and living in a specific (stressful) environment.

1.3 Timing of SAP writing

This SAP version was written and finalized before enrolment of participants was finished.

2. Study Methods

2.1 Trial design

This is a phase III double-blinded superiority randomised controlled trial of OROS-MPH *vs.* a placebo on a clinical outcome, with a parallel design. After randomisation, participants will undertake approximately three months of treatment (between 11 and 13 weeks, allowing for minor scheduling constraints) with either OROS-MPH or placebo (1:1 ratio) while they are incarcerated. After approximately three months, all participants will be offered OROS-MPH treatment, without being unblinded on the treatment OROS-MPH vs. placebo they received. They will be followed-up as outpatient for twelve months, to estimate long-term effects of in-prison treatment (total study duration: 15 months).

2.2 Randomisation

The HUG pharmacy will randomise the sequence of treatments through a generated list (Excel macro using Visual B) and will conceal the list. The repartition ratio between the two arms is 1:1 with a block size of 4. A unique randomisation number will be assigned to eligible participants after the eligibility visit.

The study team will receive a list with sequential numbering. Each eligible participant will be assigned a unique randomisation number that corresponds to the lowest number available on the list. Allocation is made by the researcher/interviewer. The participants and the study team (interviewer, psychologists, nurses, physicians, statistician, investigator, sponsor) are blinded to group allocation.

2.3 Sample size

We calculated the sample size using G*Power 3.1, with means difference between two independent groups (t-test), assuming equality of variances between groups. Participants are incarcerated in four prisons in Geneva, but on average, we expect no difference between participants in these four prisons. With α=.05, 1-ß=.80, allocation 1:1 and standardized mean difference=0.5 (average standardized effect size of 12-week treatment with OROS-MPH on change in severity of ADHD core symptoms, 26), we need n=126. Attrition for the primary outcome is unlikely, as participants will be imprisoned. In addition, the primary analysis will use multiple imputation by chained equations (MICE) to handle missing values. However, to take into account a potential attrition (e.g., participants moved to a prison in another canton), we increased the sample to n=150 (n=75 in each group), which corresponds to an attrition rate of 16%.

2.4 Framework

This is a double-blinded superiority randomised controlled trial, comparing participants who receive OROS-MPH to those who receive a placebo.

2.5 Statistical interim analyses and stopping guidance

No interim analysis is planned.

2.6 Timing of final analysis

All outcomes will be analysed after study completion, once the database is cleaned, validated, and locked.

2.7 Timing of outcome assessments

	Eligibility visit	First visit	In-prison follow-up	Outpatient follow-up[1]
Visit	**0**	**1**	**2**	**3**
Time (months)	**-1**	**0**	**3**	**15**
In/exclusion criteria	✕			
Patient information and informed consent	✕			
Randomisation		✕		
Medical history		✕		
Demographic data		✕		
Severity of ADHD core symptoms (primary outcome)		✕	✕	
Acute events (secondary outcome)		✕	✕	
Risk assessment tools (secondary outcome)		✕		
Medication adherence (secondary outcome)			✕(daily)	✕(daily)
Side effect outcomes (safety outcome)			✕(daily)	
Economical outcomes (secondary outcome)			✕	✕
Rule-breaking behaviours (secondary outcome)				✕

[1] The 15-month follow-up will be performed in participants who stay in Switzerland (either in prison or in the community.

2.8 Blinding

Trial participants, care providers, outcome assessors, investigators, and study team will be blinded to group allocation. The clinical trial unit of the HUG pharmacy will oversee the blinding. Concerta® will be supplied in coloured over-encapsulated tablets. The placebo will be strictly identical. Details are available in the study protocol.

3. Data Management

3.1 Data export

The database is hosted in the REDCap database system of University of Bern. It will be exported as a CSV file and imported in Stata 18 for analyses. Data will be stored on the server of the University of Lausanne for analyses.

3.2 Data validation

Central data monitoring is performed by the biostatistian Katia Iglesias. Data will be cleaned and validated by the biostatistician Stéphanie Baggio with the support of the study team and under the supervision of Katia Iglesias. We will check for outliers, implausible values, and missing data, as well as inconsistencies. We will particularly check outcomes.

3.3 Data preparation

Outcomes will be created as explained in section 6.

3.4 Data sharing (if applicable)

Once the statistical analysis completed, data will be prepared for sharing and storage. Documents will include database and metadata (e.g., SAP, codebook, and statistical code). They will be shared on FAIR data repository, with data available upon request to the sponsor, as it includes sensitive data from vulnerable participants.

4. Statistical Principles

4.1 Confidence intervals and *P* values

For all statistical analyses, we will use a two-sided α=.05. We will use a Bonferroni-Holms adjustment in case of multiple testing. Statistical software will include Stata and R.

4.2 Analysis populations

4.2.1 Randomised Population

The randomised population consists of all participants who are randomised, irrespective of whether they receive the assigned study treatment. This population defines the target population for all estimands unless otherwise specified.

4.2.2 Full analysis set (FAS)

The Full Analysis Set (FAS) includes all randomised participants. Participants will be analysed according to the treatment group to which they were randomised, regardless of treatment discontinuation, protocol deviations, or non-adherence. Analyses will follow the intention-to-treat (ITT) principle, with participants analysed according to their assigned group.

The primary estimand targets the effect of assignment to the investigational intervention compared with control in the randomised population, regardless of intercurrent events such as treatment discontinuation or protocol deviations (treatment policy estimand). The FAS is used for the estimation of the primary estimand and all secondary estimands unless explicitly stated otherwise. Accordingly, the use of the FAS and analysis according to randomised treatment assignment is aligned with the primary estimand.

4.2.3 Per-protocol Set (PP)

No PP analysis set is defined for primary analyses. Analyses based on subsets of participants defined by post-randomisation characteristics (e.g., adherence to treatment or absence of protocol deviations) may lead to loss of comparability between treatment groups and are therefore not considered appropriate for primary estimation of treatment effects.

Analyses restricted to specific post-randomisation subgroups are presented as supplementary analyses with an explicitly defined estimand and interpreted descriptively. PP analyses will be conducted in participants without any intercurrent events (ICEs). ICEs include:

ICE1: Non-respect of the treatment strategy, including:

- non-adherence to treatment (adherence is defined as missing the treatment ≤ 25% over the study period when participants receive OROS-MPH vs. placebo)
- discontinuation of treatment (e.g., due to AEs, lack of efficacy, moving to another prison, early release, or any other reason)
- cross-over (using OROS-MPH in the control group or placebo in the intervention group)
- starting another ADHD treatment during the 3-month OROS-MPH vs. placebo period.

ICE2: Protocol deviations.

ICE3: Terminal events, such as death.

4.2.4 Safety population (SAF)

The Safety Analysis Set will include all participants who received at least one dose of study treatment (MPH or placebo).

In safety analyses, participants will be analysed according to the treatment received.

4.3 Estimands

4.3.1 Primary estimand

The primary estimand targets the effect of assignment to OROS-MPH or placebo during the incarceration period on the severity of ADHD symptoms at 3 months (O1). It reflects the effect of initiating an OROS-MPH treatment strategy during incarceration compared with placebo.

The attributes of the primary estimand are defined as follows:

- Treatment conditions: assignment to OROS-MPH versus assignment to placebo during the 3-month incarceration period.
- Target population: All randomised participants meeting the study inclusion and exclusion criteria (ITT).
- Variable (endpoint): ADHD symptom severity measured by the Conners' Adult ADHD Rating Scale (CAARS) at approximately 3 months post-randomisation (week 12–14).
- ICEs and handling strategy: ICEs occurring between randomisation and the 3-month assessment will be handled using a treatment policy strategy. The outcome is defined irrespective of the occurrence of these ICEs.
- Population-level summary: Adjusted* mean difference of CAARS score at 3 months between the OROS-MPH and placebo groups.

* Adjusted for baseline characteristics selected based on a literature review: age, level of education, type of incarceration, presence of psychiatric disorders (other than ADHD), ADHD subtype, baseline CAARS, and impulsivity assessed with the UPPS-P (45-51).

Gender will not be included as a covariate because the number of women is expected to be very low. If there are 15 women or more, gender will be added in the adjusted model.

If a covariate has a very low variance (e.g., < 15 cases for binary variables), the variable will be removed from the model. For categorical variables (e.g., level of education, ADHD subtypes), broader categories may be created. We do not expect lack of variance for continuous variables (age, baseline CAARS, UPPS-P). In case of multicollinearity, one colinear variable will be removed based on theoretical reasons.

If the assumptions of the regression model are not met, we will use a log transformation.

4.3.2 Secondary estimands (during incarceration)

Secondary estimands corresponding to secondary outcomes measured during the incarceration period. For each secondary outcome assessed at or before 3 months, the estimand targets the effect of assignment to OROS-MPH versus placebo in the randomised population, using a treatment policy strategy for ICEs.

Common attributes include:

- Treatment conditions: assignment to OROS-MPH versus assignment to placebo during the 3-month incarceration period.
- Target population: All randomised participants meeting the study inclusion and exclusion criteria (ITT).
- ICEs and handling strategy: ICEs occurring between randomisation and the 3-month assessment will be handled using a treatment policy strategy. The outcome is defined irrespective of the occurrence of these ICEs.

For the secondary estimand targeting the effect assignment to OROS-MPH or placebo during the incarceration period on acute events at 3 months (O2):