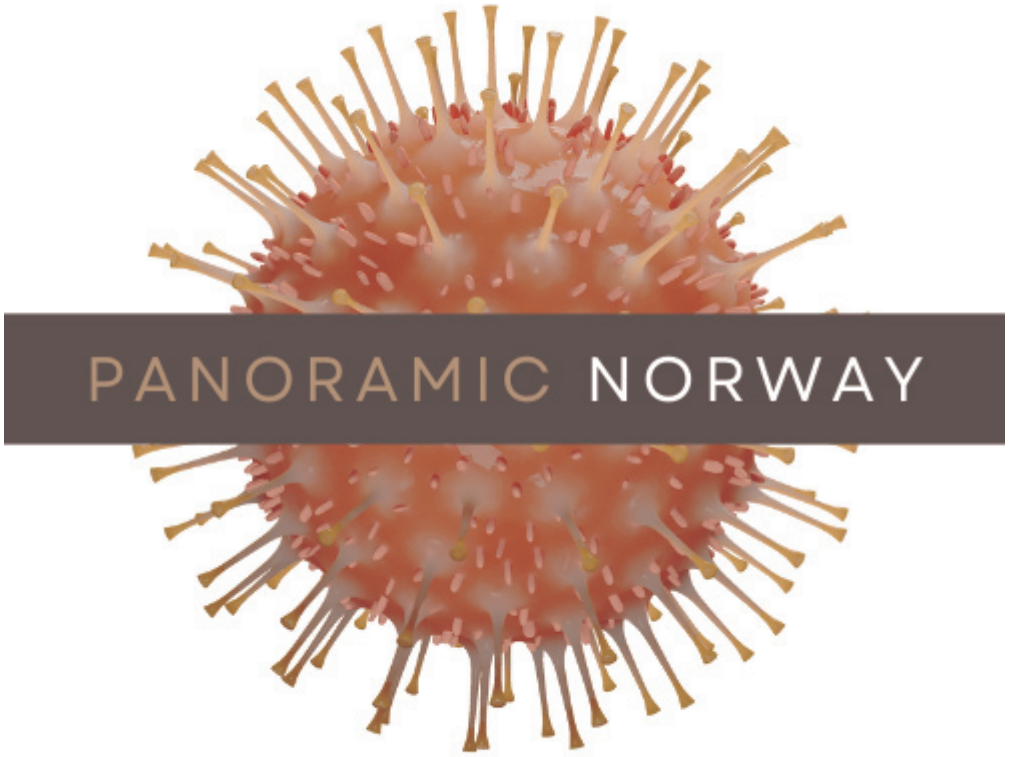

Statistical analysis plan (SAP)

PAxlovid loNg cOvid-19 pRevention triAl with recruitMent In the Community in Norway (PanoramicNOR)

Protocol ID: REC-SE-578741
Clinicaltrials.gov ID: NCT05852873
EudraCT ID: 2022-003244-2

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Administrative information

1. Title and trial registration number

Title:
PAxlovid loNg cOvid-19 pRevention triAl with recruitMent In the Community in Norway

Study acronym: **PanoramicNOR**

Trial registration numbers:
NCT05852873 (www.clinicaltrials.gov)
2022-003244-27 (EudraCT)
REC-SE-578741 (Regional Committees for Medical and Health Research Ethics)

2. SAP version

This is SAP version 1.0 (2023.05.10)

3. Protocol version

Based on protocol version 2.3 (2023.03.23)

4. SAP revisions

SAP revision history: First version
Justification for each revision: No revisions yet
Timing of SAP revisions in relation to interim analyses: No revisions yet

5. Roles and responsibilities

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6. Signatures

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Introduction

7. Background and rationale

Synopsis of trial background
The Covid pandemic has caused an estimated 6.8 million deaths. The number of Covid survivors exceeds this figure more than hundred-fold. Therefore, the finding of persistent symptoms after Covid at 3 months and beyond implies a huge public health burden. The syndrome of persistent symptoms, labelled post-Covid condition and often referred to as long-Covid, also occurs after mild Covid, and appears equally common with Omicron as with prior virus variants. The pathophysiology of long-Covid is still unclear, and no cure has been found. Early treatment with the novel antiviral combination nirmatrelvir / ritonavir (Paxlovid®) has proved to prevent hospitalization and death from Covid. In the current trial we assess whether Paxlovid treatment for acute Covid can prevent persistent symptoms or long-Covid at 3 months follow-up and beyond.

Research question:
Can treatment of acute Covid prevent occurrence of persisting symptoms at 3 months and beyond?

Justification for trial:
Over 600 million people have survived the Covid pandemic so far. Still there is rampant ongoing transmission of SARS-CoV-2, and emerging variants may alter both transmission and severity in the future. The high prevalence of persisting symptoms (long Covid) in survivors represents a large burden to healthcare systems and society in general. If a 5-day course of antiviral treatment can prevent persisting symptoms, it would be a feasible way to prevent long-Covid in the individuals' perspective, and an attractive public health intervention to reduce the societal burden of absence from work and over-use of health care services.

8. Objectives

Hypothesis:
Antiviral treatment of acute Covid can prevent occurrence of persisting symptoms at 3 months and beyond.

Specific objectives:
Primary objective: Assess whether a 5-day course of nirmatrelvir/ritonavir (Paxlovid ®) for acute Covid can reduce the prevalence of persistent symptoms at 3 months compared to placebo.

Study methods

9. Trial design

PANORAMIC Norway is a two-arm 1:1 randomized clinical trial assessing whether healthy adults (P) treated with Paxlovid (I) for acute Covid versus those treated with placebo (C) will have reduced probability of suffering persistent symptoms at 3 months and beyond (O).

10. Randomization

Participants will be randomized to antiviral treatment or placebo using fixed equal allocation ratios.

An external statistician will produce a randomization list that will be given to the pharmaceutical company packaging interventional drugs and placebo. The active drugs and placebos will be coated by the company so that they look identical, and packages will appear identical. Packages will be labeled with the ID number on the randomization list and patients will be allocated with this ID number.
At the time of inclusion in the study, study personnel will blindly allocate participants to receive active ingredient or placebo according to the randomization list.

11. Sample size

We expect to be able to recruit around 2000 patients for randomization in the Norway study. The presence of long covid is our primary endpoint. Prior knowledge suggest that long covid may be present among approximately 50% of the patients. With a total sample size of around 2000 we will be able to detect a 16% treatment effect with a power of 90% (5% significance level, Table 1x). If the prevalence of long covid drops to 40% or 30% in the placebo-group, we will still have 90% power to detect a 17.5% or 21.7% treatment effect, respectively, with a total sample size of approximately 2000.

Table 1x: Sample size scenarios

90% power and 5% significance level, two-sided test of superiority				
Placebo*	**Treatment***	**Treatment effect**	**NNT**	**Total sample size**
50%	42.5%	16%	14	1908
40%	33%	17.5%	15	2042
30%	23.5%	21.7%	16	2008

* Expected prevalence of primary outcome

12. Framework

The study will test the hypothesis of superiority of Paxlovid over placebo in preventing long-Covid. Comparison of the proportion of participants with persistent symptoms at 3 months will be presented.

13. Statistical interim analysis and stopping guidance

Interim analysis will be performed when 1000 patients have reached 28 days follow-up assessing any deaths and hospitalizations occurring in the study population.
The study will be stopped if the proportion of deaths at 28 days follow-up is higher in one of the groups by a significance of $p<0.02$ and effect size of odds ratio > 4.

Severe adverse events will be reported consecutively to the DSMB. The DSMB will evaluate this independently of the interim analysis.

14. Timing of final analysis

Final analysis of data will be performed without delay after all patients have completed 3 months follow-up. This analysis will be performed on anonymized data. Apart from this, blinding for investigators and patients will be maintained until the study is completed. Further analysis will be performed for data at 6, 12 and 24 months as they become available.

15. Timing of outcome assessments

Outcomes will be assessed at 3, 6, 12 and 24 months. Additionally, adverse events will be reported to the DSMB consecutively for independent evaluation.

Statistical principles

16. Levels of significance, P values

Analysis results for the primary outcome will be reported as odds ratio with 95% confidence interval with P-value. The standard cut-off of $p<0.05$ will be used for statistical significance levels. For secondary outcomes we will report appropriate effects measures with 95% confidence intervals without p-values.

17. Rationale for any adjustment for multiplicity, and, if so how the type 1 error is to be controlled

Type I error will be controlled at the traditional 0.05 two-sided level for the hypothesis test. We will perform a hypothesis test only for the primary outcome and we will not need to adjust for multiple tests.

18. Confidence intervals to be reported

Odds ratios and other relevant effect-measures will be estimated in appropriate regression models and will be reported with 95% confidence intervals.

19. Adherence and protocol deviations

Any deviations from the protocol will be documented in a protocol deviation form and filed in the study master file. A NorCRIN SOP is in place describing the procedure for identifying non-compliances, escalation to the central team and assessment of whether a non-compliance /deviation may be a potential Serious Breach.

20. Analysis populations

The primary analysis will be an “intention to treat” analysis performed on all patients who were randomized. In addition, per protocol analysis will be performed for patients who reported to have adhered to the ingestion of the study product (antiviral or placebo), and on other subgroups of the study population. If adherence is incomplete, we will attempt to estimate the biological effect of the medication by using instrumental variable analysis [1].

Trial population

21. Screening data

Patients attending municipal centers or pharmacies to obtain Covid rapid test will be presented with written information offering participation in the study. Patient testing positive for Covid at the municipal emergency medicine department will also be offered participation both by oral and written invitation. Patients testing positive will be encouraged to attend the study recruitment office for evaluation of eligibility for participation.

The trial team will use Norwegian health registries as source data for relevant medical information, including emergency hospitalization events (Norwegian Patient Registry (NPR)), details concerning COVID-related hospital admittance (Norwegian Pandemic Registry), mortality and cause of death (Norwegian Cause of Death Registry), contacts with primary care (Norwegian Registry for Primary Health Care (KPR)), COVID vaccine history (Norwegian Immunisation Registry (Sysvak)), drug prescription (Norwegian Prescription Database (NorPD) and sick leave (The Sickness Absence Registry).

Data collected will include participant identifiable information and will be accessed at the University of Bergen according to PC-CTU Information Governance policies and Norwegian GDPR. Data will only be held for the duration it is required; this will be reviewed annually. All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

22. Eligibility

Inclusion criteria:

Individuals aged 18 to 65 years with symptoms of 0 to 5 days duration consistent with Covid and a positive test for SARS-CoV-2 by rapid test and/or RT-PCR from throat or nasopharyngeal swab are eligible to be included.

Exclusion criteria:

Patients with symptom duration of more than 5 days will be excluded.
Pregnant women will not be included, women of child-bearing potential will be offered a pregnancy-test and only included after a negative result.
Persons with immunosuppressive conditions and comorbidities (see list) will not be included as they may have indication for Paxlovid treatment.

23. Recruitment

Patient testing positive for Covid attending the study recruitment office will be screened for eligibility by study staff, consisting of nurses and a medical doctor.

24. Withdrawal / follow-up

Participation is based on informed voluntary consent. Participants may withdraw at any time of the study without giving reasons or justification. Upon withdrawal, no further data will be collected. However, data recorded up until the time of withdrawal will be included in the analysis.

25. Baseline patient characteristics

Baseline data on demographic characteristics, relevant medical history and vaccination history will be recorded as detailed in the CRF.

Analysis

26. Outcome definitions

A total of 13 symptoms will be recorded. The following symptoms are recorded as binary variables: fever, tingling sensation, headache, dizziness, altered taste/smell, sleep disturbances, chest-pain, muscle/joint pains, nausea. The following will be recorded as graded symptoms (better than usual, as usual, worse than usual, much worse than usual): fatigue, dyspnea, memory problems, concentration problems, feeling depressed. Additionally, we will record, absence from work/school (number of days), hospitalization (number of days), any contact with doctor / emergency clinic.

Primary outcome

The primary outcome is a dichotomous variable for presence of any of the three most important long-COVID symptoms: (i) fatigue, (ii) dyspnea and (iii) cognitive symptoms (defined as memory and/or concentration problems). The outcome is coded 1 for the presence of any one or more of these 3 symptoms, and 0 for absence of all the 3 symptoms. The primary outcome will first be evaluated at 3-months follow-up, and then re-evaluated at 6-, 12- and 24-months follow-up.

Secondary outcomes

Secondary outcomes include assessment of the intervention's effect on:

- All individual symptoms separately, and grouped by systems (systemic symptoms, chest-symptoms, cognitive, other neuropsychiatric symptoms).

- Graded responses for separate symptoms and symptom constellations, including an ordinal variable graded 0-3 for the presence of the 3 symptoms in the primary outcome.
- Risk factors for long-COVID
- Severity of acute disease using an 8-step scale (ref: Beigel, NEJM) (score)
- Hospitalization (binary)
- Mortality at three months (binary)
- Severe adverse events (binary)
- Absence from work (binary)
- Societal cost / economic analysis, including estimated cost of absence from work/school, hospitalizations, deaths, QALYs lost according to EQ-5D-5L, and more.

27. Analysis methods

The primary outcome, i.e. the effect of intervention on a binary variable for the presence of any of 3 key long-COVID symptoms, will be analyzed with an appropriate logistic regression model. Depending on whether we obtain a good balance of prognostic factors between the randomized groups, we may consider adjustment for prognostic factors in the analyses. We will typically report an odds ratio with 95% confidence intervals and a p-value from this analysis.

In the analysis of follow-up data up to 24 months, we will use appropriate mixed models to account for correlation of symptoms over time. We will estimate the main effect of treatment and test whether the effect is uniform over time.

Secondary outcomes will be analyzed with appropriate regression models depending on the type of outcome variable. For binary outcomes, we will use logistic regression. For number of symptom counts, we will consider negative binomial regression and for score outcomes we will attempt ordinal logistic regression and quantile regression. Using quantile regression models, we will estimate the effect of the intervention also in the tails of the score-distribution.

Further analysis plans include cost-efficacy analyses and explorative analyses. We will estimate the resource inputs associated with providing the antiviral treatment in routine clinical practice. Societal costs will be estimated using data on primary care encounters, hospital inpatient/day case admissions, outpatient visits, and accident and emergency attendances. Loss of quality-adjusted life year (QALY) will be estimated. Unit costs will be valued using national reference tariffs. Compound total health care cost per trial participant over the trial time horizon will be estimated. Secondary expressions of cost-effectiveness will include incremental cost per hospitalization and/or death prevented over 28 and 60 days. Relevant data may be obtained from registries, including emergency hospitalization events (Norwegian Patient Registry (NPR)) and Norwegian Pandemic Registry (NIPaR), mortality and cause of death (Norwegian Cause of Death Registry), contacts with primary care (Norwegian Registry for Primary Health Care (KPR)), drug prescription (Norwegian Prescription Database (NorPD) and sick leave (The Sickness Absence Registry). Cost-effectiveness will be expressed in terms of incremental cost per QALY gained

Bivariate regression of costs and measures of health consequence, with multiple imputation of missing data, will be conducted to generate within-trial estimates of incremental cost-effectiveness. Sensitivity analyses will assess the impact of areas of uncertainty surrounding components of the economic evaluation. The probability of cost-effectiveness at alternative thresholds will be measured. Cost-effectiveness threshold values will be informed by guidance from government departments on the value placed by decision-makers on an additional QALY10 and on a statistical life.

28. Missing data

Missing data for both binary and continuous variables will in the main analyses be handled as non-responses. Depending on the degree of missingness, we will perform supplementary analyses with multiple imputation of missing values to assess the possibility that the missing data may introduce bias.

29. Additional analyses

30. Harms

Harmful events that will be recorded and analyzed include:

- Maximum severity of disease course measured on an 8-step scale (asymptomatic, symptomatic, hospitalized, hospitalized with medical needs, need for O2, need for non-mechanical ventilation, need of respirator / ECMO, death) (ref Beigel, NEJM)
- Hospitalizations
- Any deaths occurring during the study period
- Any severe and non-severe adverse events occurring during the study period.

31. Statistical software

Statistical analysis will be performed in Stata version 17 (StataCorp LLC, College Station, Texas) and R version 4.2.2 or higher (The R Foundation for Statistical Computing, Vienna, Austria). All the relevant regression models are fully implemented in Stata. If imputation is considered necessary or useful, regression analysis with multiple imputation will be performed in Stata using the mi-command. Mixed effects models analysis in R will be performed using the "lme4" or "lmerTest" packages, and imputation will be performed using the mice.impute.bygroup function in the "mice" and "miceadd" libraries in R. We will develop scripts in both systems and check the results for consistency.

Publication plan

Primary outcome – impact on long-Covid symptoms

The first main paper will present the effect of Paxlovid versus placebo on persisting symptoms at 3 months follow-up. It is planned to be published without delay, and before the completion of later milestones in the study.
Safety of the interventional drug will be described in the same paper, with focus on adverse events, severity of disease, hospitalizations and any deaths occurring during the study period.

The effect on the primary outcome at 6, 12 and 24 months will be published subsequently, either as one paper per milestone, or aggregating one or more time-points.

Secondary outcomes

Further analysis of the effect of the interventional drug on specific symptoms may be published separately.

The effect of the intervention on the acute Covid infection will be analyzed, including variables on severity of acute illness, duration of hospital stay, and length of sick leave.

Risk factors for long-Covid

Risk factors for persisting symptoms, including demographic characteristics, comorbidities, vaccination history and medications, will be analyzed.

Cost-efficacy and ethical issues

Cost-benefit considerations of Paxlovid-treatment will be published focusing on the perspectives of the individual patient and society at large, including data on hospitalization, healthcare use, absence from work, sick-leave, loss of employment etc.

32. References

1. Sussman JB, Hayward RA: **An IV for the RCT: using instrumental variables to adjust for treatment contamination in randomised controlled trials.** *BMJ* 2010, **340:**c2073.