Multicenter, Double-blind, Placebo-controlled, Randomized, Parallel-group Clinical Trial to Evaluate the Efficacy and Safety of Ergoferon as Non-specific COVID-19 Prevention During Vaccination Against SARS-CoV-2

Phase III

Sponsor	**OOO «NPF «MATERIA MEDICA HOLDING»**
Protocol number	**MMH-ER-010**
Version date:	**July 19, 2021**
ClinicalTrials.gov Id:	**NCT05069649**

Protocol Summary

This document represents the protocol summary for the study on human subjects. The study will be carried out in accordance with ICH GCP, Good Clinical Practice, approved by order of the Ministry of Health of the Russian Federation dated April 1, 2016 N 200n, Helsinki Declaration of World Medical Association, relevant requirements of the regulatory authorities as well as the study procedures.

Title of Study

A Multicenter, Double-blind, Placebo-controlled, Randomized, Parallel-group Clinical Trial to Evaluate the Efficacy and Safety of Ergoferon as Non-specific COVID-19 Prevention During Vaccination Against SARS-CoV-2.

Phase: III

Sponsor: OOO "NPF "Materia Medica Holding", Moscow, Russia

Protocol No. MMH-ER-010

Objective of the study

- To evaluate the efficacy and safety of Ergoferon as a non-specific COVID-19 prevention during vaccination against sars-cov-2.

Endpoints

Primary endpoint

- To evaluate and compare in two groups (Ergoferon and Placebo) the number of laboratory-confirmed cases of SARS-CoV-2 infections[1] (with or without symptoms) in vaccinated individuals during their participation in the study.

Exploratory endpoints

- To evaluate and compare in two groups (Ergoferon and Placebo) the proportions of hospitalized participants with COVID-19.

Safety assessment

- To evaluate and compare in two groups (Ergoferon and Placebo) the occurrence and nature of adverse events, their intensity (severity), causal relationship to the study drug, and outcomes.

Study design

Study design: double-blind randomized placebo-controlled parallel-group trial.

[1] A positive reverse transcription polymerase chain reaction (RT-PCR) test result for SARS-CoV-2.

The study will enroll adult participants of either gender aged ≥18 years who receive a COVID-19 vaccine. A participant signs a participant information sheet (Informed Consent Form) to participate in the clinical trial on the day of administration the first dose of the Gam-COVID-Vac (Sputnik-V) vaccine. The physician evaluates the participant's eligibility for inclusion in the study. A rapid test for SARS-CoV-2 (BIOCREDIT COVID-19 Ag)[2] is carried out.

If the participant meets all inclusion criteria and does not have any non-inclusion criteria, then he is included in the study, the doctor fills out the primary medical documentation.

After inclusion in the study (Day 1, Visit 1), the participant is randomized into one of two groups: participants in group 1 receive Ergoferon according to a preventive regimen for three weeks, participants in group 2 receive Placebo for three weeks.

On a day of administration of the second Gam-COVID-Vac dose[3] (Day 22, Visit 2 + 3 days), a rapid SARS-CoV-2 test (BIOCREDIT COVID-19 Ag) is performed.

After administration of the second dose of the vaccine, the participant is observed for 2 weeks. After 2 weeks, Visit 3 (telephone visit) is conducted to interview the participant about their health status (absence/presence of ARVI symptoms).

All participants are provided with classic axillary temperature thermometers. The study uses an electronic diary to record any possible deterioration in the participant's condition (if applicable) to assess efficacy, safety and reporting of adverse events. The investigator instructs the participant to complete the diary. Each participant will receive an SMS reminder once a week: “If you have any symptoms of the disease, record them in the diary. The investigator will contact you.”

If within five weeks of observation the participant develops symptoms of acute respiratory viral infection (increased body temperature to febrile/subfebrile values, weakness, headache, chills, cough, sore throat, other symptoms), then the study investigator performs an unscheduled visit, during which swabs are taken from the nasopharyngeal and oropharyngeal mucosa for PCR (RT-PCR) test (in the central laboratories).

If at Visits 1 or 2 a participant without ARVI symptoms has a positive rapid test result for SARS-CoV-2, his/her oropharyngeal and nasopharyngeal swabs are also collected for PCR testing (in the central laboratory).

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[2] If the participant tests positive for SARS-CoV-2, he/she is not enrolled in the study. The investigator’s approach should be in compliance with the current version of the guidelines “Prevention, diagnosis and treatment of a new coronavirus infection (COVID-19) by the Ministry of Health of the Russian Federation.

[3] Contraindications for the second dose of the vaccine: Severe post-vaccination adverse events (anaphylaxis, severe generalized allergic reactions, convulsive disorder, fever (≥40°C), etc.) following the injection of the first dose of the vaccine.

If a laboratory-confirmed case of SARS-CoV-2 infection (with or without symptoms) is detected, the participant prematurely completes the study as having reached the primary endpoint.

If the PCR test for SARS-CoV-2 is positive, in accordance with the requirements of Rospotrebnadzor, the information is transferred to the health care facility to which the participant is attached, where he will be provided with the necessary medical care (according to current standards). Health care facility employees report data on COVID-19 cases (in accordance with the recommendations of the Ministry of Health of the Russian Federation and the rules of health care facilities).

Possible post-vaccination symptoms;

- general (flu-like syndrome characterized by chills, fever, arthralgia, myalgia, asthenia, malaise, headache) and local (pain at the injection site, hyperemia, swelling) symptoms that develop on the first-second day and resolve within three days;
- nausea, dyspeptic disorder, loss of appetite;
- enlarged regional lymph nodes;
- allergic reactions;
- transient increase in serum levels of liver transaminases, creatinine, and creatine phosphokinase.

These post-vaccination symptoms are not recorded as adverse events (either associated with the study product administration or developing after discontinuation); they are registered by the participant in a diary and assessed by the physician as post-vaccination complications.

Transient flu-like syndrome should not be diagnosed as ARVI, in this case a PCR test for SARS-CoV-2 is not carried out.

If the participant develops COVID-19 or is hospitalized for COVID-19, then delayed telephone visit will be performed. The duration of the visit is determined by the study investigator on a case-by-case basis.

During the study participants are allowed to take medications for the treatment of underlying (chronic) diseases, with the exception of the drugs specified in the section "Prohibited concomitant treatment."

Inclusion and exclusion criteria

Inclusion criteria

1. Adults of either gender aged ≥18 years.
2. Participant has not had COVID-19 within the previous 6 months.
3. The participant has not been vaccinated against COVID-19 or other viral infections within the previous 6 months.
4. Negative result of the rapid test for SARS-CoV-2 (COVID-19 Ag).
5. Absence of clinical manifestations of any infectious disease, but not earlier than 14 days from its debut.
6. Consent to use reliable contraceptive methods during the study (for men and women of reproductive potential).
7. Availability of a signed information sheet and informed consent form for participation in the clinical trial.

Exclusion criteria

1. Presence of contraindications to vaccination:
    - hypersensitivity to any component of the vaccine or a vaccine containing similar components;
    - history of severe allergic reactions;
    - acute infectious and non-communicable diseases, exacerbation of chronic diseases.
2. Severe chronic hepatic and renal disorders, severe thyroid dysfunction, decompensated diabetes mellitus, severe disorders of the hematopoietic system, epilepsy and other CNS diseases, acute coronary syndrome, cerebrovascular accident, myocarditis, endocarditis, pericarditis, autoimmune diseases, or immunodeficiency.
3. Malabsorption syndrome, including congenital or acquired lactase or other disaccharidase deficiency, galactosemia..
4. Hypersensitivity to any components of study drug used in the treatment.
5. Pregnancy, breast-feeding; childbirth less than 3 months prior to the inclusion in the study.
6. Patients, who, from the investigator's point of view, will not comply with study observation requirements or study drug administration procedures.
7. Failure to observe the participant during the study period.
8. History of mental illness, alcoholism or drug abuse that the investigator's opinion will interfere with successful study procedures.
9. Participation in other clinical trials within 3 months prior to enrollment in the study.

10. Use of any medications listed in "Prohibited concomitant medications" within 4 weeks before enrollment.
11. Patient belongs to the study site personnel directly involved in the study or is the closest relative of the study investigator. "Immediate relative" means husband, wife, parent, son, daughter, brother, or sister (regardless of whether they are natural or adopted).
12. Patient who works for OOO “NPF “MATERIA MEDICA HOLDING” (i.e. i.e. they are employees of the Company, temporary employees on a contract basis or appointed officials responsible for conduction of the study or their immediate family members).

Criteria for Withdrawal or Termination

1. Screening failure.
2. Laboratory-confirmed case of SARS-CoV-2 infection (with or without symptoms).
3. Inability or refusal of the patients to comply with the protocol requirements.
4. Use of any medication listed in the section "Prohibited concomitant medications”.
5. An adverse event requiring discontinuation of the study.
6. Participant’s decision to complete the study early due to lack of the therapy efficacy or any other reasons.
7. Pregnancy.
8. Cases not specified by the protocol when, according to the investigator’s opinion, further participation in the study harms the patient.
9. Eligibility error.
10. Participation in any other clinical trial.
11. Unblinding.

Number of subjects

Study stage before adaptation:

1268 participants will sign the informed consent.

At least 1206 participants will be randomized.

Study stage after adaptation[4]:

Additional 0 to 2332 participants will sign the informed consent.

Therefore, additional 0 to at least 2214 participants will be randomized.

The total maximum sample size will be: 3600 participants will sign the ICF, n=**3420** of which will be randomized.

[4] Refer to the section Statistical Methods

Interim analysis

An "unblinded" interim analysis for 85% of the sample (0.85 information, 485 PP participants each) is planned in the protocol. It is assumed that the study can be stopped due to the rejection of the null hypothesis with the O'Brien-Fleming type I error spending function. Based on the results of this analysis (if the stopping parameters are not achieved), it is assumed that the study will be adapted to determine the required additional sample size.

Treatment

Group 1

Name of the medicinal product: Ergoferon

Active ingredient: affinity purified antibodies to human gamma interferon – 0.006 g*

affinity purified antibodies to histamine – 0.006 g*

affinity purified antibodies to CD4 – 0.006 g*

** applied onto lactose powder as a mixture of three active ethanol-water solutions of the drug substance diluted 100^{12}, 100^{30}, 100^{50} times, respectively*

Excipients: lactose monohydrate, microcrystalline cellulose – 0.03 g, magnesium stearate – 0.003 g.

Method of administration: For oral administration. One tablet twice daily. The drug is taken outside the meal (between meals or 15-30 minutes before meals). Keep the tablet in the mouth, without swallowing, until completely dissolved.

Dosage form: Tablets.

Description: White to almost white, flat- faced tablets with a score and a chamfer.

Storage conditions: At a temperature not higher than 25°C. Keep out of the reach of children.

Group 2

Name of the medicinal product: Placebo

Active ingredient: NA

Excipients: lactose monohydrate, microcrystalline cellulose, magnesium stearate.

Method of administration: For oral administration. One tablet twice daily. The drug is taken outside the meal (between meals or 15-30 minutes before meals). Keep the tablet in the mouth, without swallowing, until completely dissolved.

Dosage form: Tablets.

Description: White to almost white, flat- faced tablets with a score and a chamfer.

Storage conditions: At a temperature not higher than 25°C. Keep out of the reach of children.

Treatment duration

Ergoferon/Placebo treatment duration is 3 weeks.

Observation period

Generally, patients will be monitored for 5 weeks (screening, randomization, start of treatment - Day 1, treatment − 3 weeks, follow-up period − 2 weeks).

Concomitant medications

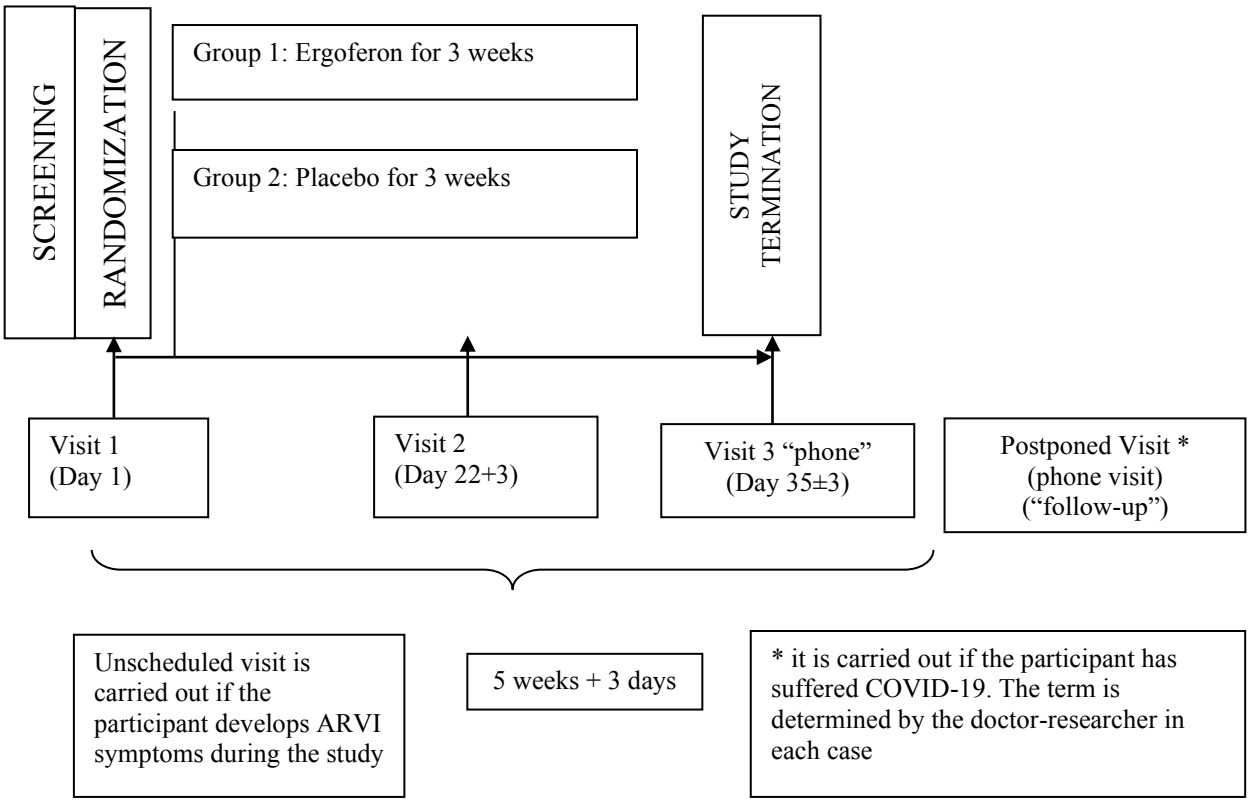
During the study, the patient may receive therapy for concomitant diseases and conditions that are not criteria for non-inclusion in this study, except for medicinal products specified in the section "Prohibited concomitant treatment."

Prohibited concomitant therapy

4 weeks prior to enrollment and during the study the following drugs are not allowed:

1. Antivirals (J05).
2. Immunostimulants, including:
    - interferon inducers (acridonoacetic acid, meglumine acridone acetate/cycloferon®, umifenovir/arbidol®, kagocel®, tiloron/amixin®, lavomax®, tilaxin®, polyadenyl acid + polyuridylic acid complex/poludan®, sodium deoxyribonucleate/derinat, etc.)
    - interferons;
    - bacterial immunomodulators (including ribomunyl®, IRS-19, imudon®, broncho-munal®, etc.);
    - pidotimod/immunorix;
    - interleukins;
    - synthetic immunostimulants (levamisole, alpha-glutamyl-tryptophan/thymogen, etc.);
    - drug products with thymus hormones;
    - herbal immunostimulants (immunal®, etc.).
3. Immunosuppressants (L04).
4. Antitumor drugs (L01) and antitumor hormonal drugs (L02).
5. Immune sera and immunoglobulins (J06).
6. Vaccines (J07).
7. Corticosteroids for systemic use (H02AB).
8. Any unapproved medicinal product.
9. Drugs that previously caused hypersensitivity/allergic reactions in patient.

Study design scheme



Schedule of study procedures

Procedure/ Visit	Visit 1 (Day 1)	Visit 2 (Day 22 + 3 days)	Unscheduled visit*	Visit 3 «phone» ▲ (Day 35 + 3 days)
Informed consent	+			
Registration in the IVRS and assignment of a personal code	+			
Rapid test for SARS-CoV-2 (COVID-19 Ag)	+	+		
Demographics	+			
Medical history	+			
Concomitant diseases and conditions	+	+	+	+
Concomitant therapy	+	+	+	+
Nasopharyngeal and oropharyngeal (throat) swabs for PCR diagnostics	+♥	+♥	+	
Pregnancy test	+			
Inclusion/exclusion criteria	+			
Randomization and prescription of study therapy	+			
E-diary supply	+	+	+	+
Study drug supply	+			

Study drug accountability, compliance assessment		+		
Evaluation of treatment safety	+	+	+	+
Visit completion	+	+	+	+
Study completion♦				
** Conducted in case of a participant's illness with COVID-19*				
▲ If the participant has had COVID-19 or has been hospitalized for COVID-19, the timing of the visit is determined by the study investigator on a case-by-case basis.				
♥ Conducted with a positive rapid test for SARS-CoV-2 (COVID-19 Ag).				
♦ If a patient falls ill with COVID-19, he or she will terminate participation in the study early.				

Statistical Analyses

Samples

Total set: All subjects who signed Informed Consent Form (ICF). This sample will consider all adverse events (AEs) throughout the study, including those occurred prior to the study therapy.

The sample including all enrolled and randomized patients who received at least one dose of the study drug to be used for ***analysis of the study treatment safety and tolerability*** (*Safety population*), as all AEs identified after the study drug administration will be recorded.

The AEs registered in patients of the *Total set* sample from the moment of signing the Informed Consent Form, but before the test drug administration will not be taken into account when analyzing the study therapy safety.

Full Analysis Set. This sample includes all the enrolled patients, except for those who have experienced at least one of the following events:

1) non-compliance with inclusion/exclusion criteria;
2) patient did not take any dose of study drug;
3) absence of any patient data after administration of study drug.

Patients who had at least one of the listed events may be excluded from the analysis.

This sample, the most consistent with the "Intention-to-treat" principle**,** will be used for the ***Intention-to-treat analysis (ITT analysis)*** *of the* ***the study therapy efficacy***.

Per protocol set. This sample includes all the patients who received full protocol therapy, completed all the scheduled visits. This sample will be used for ***Per Protocol analysis (PP-analysis) of the the study therapy efficacy***. *Per Protocol set* will not include the patients whose data are fully or partially invalid for analysis due to a protocol deviation.

Protocol deviations resulting in full or partial data invalidity:

1. Violation of visit schedule.
2. Inappropriate distribution/issue of the study drug.
3. Prescription of prohibited therapy.

4. Increase or decrease of 25% or more in the amount of study therapy received.
5. Inability to assess patient's objective compliance (adherence to therapy) according to the formula (e.g. loss of packaging).
6. Major discrepancies between source documents and CRF detected during monitoring or other authorized inspection.
7. Violations of the Informed consent procedure.
8. Non-compliance with the clinical study protocol procedures.
9. Inability to collect all patient's data used for evaluation of the study endpoints (e.g. lack of entries in source documents required for verification of inclusion/exclusion criteria, safety and efficacy criteria).
10. Any other protocol deviations that fall under definition of "significant deviation."

Data treatment and all statistical calculations under the protocol will be made using SAS-9.4 statistical software.[5]

Evaluation of sample size

The sample size has been assessed on the basis of the following rules and assumptions:

1. Statistical provisions.
   - 1.1 the power of the statistical tests "$P = (1 - \beta)$" is assumed to be 80% (the probability of correct rejection of the null hypothesis is 0.8);
   - 1.2 the probability of a type I error "α" is allowed to be less than 5% (the probability of the erroneous acceptance of an alternative hypothesis is less than 0.05);
   - 1.3 statistical criteria of intergroup comparisons will be two-sided unless otherwise specified;
   - 1.4 ratio between Ergoferon and Placebo sample sizes is 1:1 (1 Ergoferon patient per 1 Placebo patient);
   - 1.5 an "unblinded" interim analysis with possibility of early stopping due to the effectiveness on 85% of the sample is planned in the protocol. Error spending function - O'Brien-Fleming;
   - 1.6 sample size can be adjusted after the interim analysis based on the estimated conditional power (at the same time as the interim analysis is conducted);
   - 1.7 statistical null and alternative hypotheses regarding the superiority of Ergoferon over Placebo for the dosing regimen used:

     Primary endpoint:

     H_0: $OR_{1\,2} = 1$

[5] Holder of license: OOO "NPF "Materia Medica Holding", No. 70100045.

$\mathbf{H_a: OR_{1\,2} \neq 1}$

where $\mathbf{OR_{12}}$ – odds ratio of an event occurring between the Placebo and Ergoferon.

The following SAS code was used to determine the required sample size[6]:

proc seqdesign errspend;

design nstages = 2

info = cum (0.85 1)

method (alpha) = obf

alt = twosided

stop = reject

alpha = 0.05

beta = 0.2

samplesize model = twosamplefreq (nullprop=0.03 prop=0.005[7])

run

1.8 the final sample size is calculated with the following formula:

$$\mathbf{N = N_{PP} / (1 - К_в)},$$

where **N** – final sample size; $\mathbf{N_{PP}}$ – sample size value in c. 1.7, i.e. scheduled number of patients completing the study per protocol; $\mathbf{К_в}$ – withdrawal rate.

2. Assumptions about the expected effects of the clinical study:

It is assumed that the **odds ratio** for the occurrence of an event will be not less than 0.162 in favor[8] of Ergoferon (as part of the adaptation process, a possible deterioration in the magnitude of the prediction of the effect is assumed to be up to 0.55).

Population frequency: assumed to be 3%[9].

Therefore, the required size for each group is **570**[10] patients (PP sample). Considering the potential dropout of about 10% patients during the study for various reasons[11], at least **1268** patients (**634** in each group) will be required to sign informed consent, of which **1206** patients will be randomized (**603** in each group) (see cl. 1.8, the final total withdrawal rate will be ($\mathbf{К_в = 0.1}$).

[6] Minimum size for this study.
[7] Equivalent to effect size OR=0.162 (smaller is better).
[8] $OR = Odd_{tr}/Odd_{pl}$ – the higher, the greater the chance in Ergoferon group compared to the Placebo group.
[9] Rare event frequency assessment, is a population parameter and can be overestimated in a blinded interim analysis.
[10] Minimum size.
[11] Of them patients dropped out during the screening process (5%)

Sample Size Adaptation

It is intended to adapt the sample size during the study in accordance with the following algorithm[12]:

1) During the planned interim analysis (if the study was not completed due to rejection of the null hypothesis based on the interim analysis cutoff), the conditional power is calculated using the formula:

$$CPower = 1 - \Phi\left(\frac{z_\alpha * \sqrt{N_{min}} - z_1 * \sqrt{N_1}}{\sqrt{N_{min} - N_1}} - \frac{z_1 * \sqrt{N_{min} - N_1}}{\sqrt{N_1}}\right)$$

where $\mathbf{Z_1}$ is the value of the Z-statistic obtained at the interim analysis on $\mathbf{N_1}$ of the first patients from $\mathbf{N_{min}}$ (the minimum sample size of the study);

$\mathbf{Z\alpha}$ = 2.0255 (the value of statistics for the final analysis, taking into account the presence of an interim analysis);

$\mathbf{\Phi_{(x)}}$ – the probability value of event **X** for the standard normal distribution **(σ = 1, μ = 0)**.

2) The maximum allowable increase in sample size is assumed to be no more than **3240**[13].
3) Taking into account the above, one of the adaptation scenarios will be selected.
4) Optimistic scenario (conditional power **CPower > 0.8**, or equivalently $\mathbf{Z_1 > 2.168}$): sample size does not change ($\mathbf{N_{final} = N_{min}}$).
5) Medium scenario (**conditional power 0.3**[14] **< CPower < 0.8**, or equivalently value **1.6815 < Z1 < 2.168**): the sample size changes according to the formula:

$$N_{final} = N_1 + \left(\frac{N_1}{z_1^2}\right) * \left(\frac{z_\alpha * \sqrt{N_{min}} - z_1 * \sqrt{N_1}}{\sqrt{N_{min} - N_1}} + z_\beta\right)^2$$

6) Pessimistic scenario (**conditional power CPower < 0.3**, or, equivalently, value **Z1 < 1.6815**): sample size does not change ($\mathbf{N_{final} = N_{min}}$).
7) The final statistical analysis is carried out with the critical statistical values obtained by estimating the minimum sample size (**$\mathbf{Z\alpha}$ = 2.0255**).

Statistical criteria

All the statistical calculations will be performed using two groups of statistical criteria:

[12] Adaptive Increase in Sample Size when Interim Results are Promising: A Practical Guide with Examples Cyrus R. Mehta1,2, Stuart J. Pocock3 STATISTICS IN MEDICINE Statist. Med. 2000; 00:1–6
[13] Taking into account withdrawal - up to 3600
[14] This value is the minimum acceptable for the stated sample ratio for interim analysis, minimum and maximum samples (as well as statistical parameters of the study). Based on table 1 of the source. Adaptive Increase in Sample Size when Interim Results are Promising: A Practical Guide with Examples Cyrus R. Mehta1,2, Stuart J. Pocock3 STATISTICS IN MEDICINE Statist. Med. 2000; 00:1–6

- parametric – to obtain effective estimates for the parameters of random variables, if the corresponding conditions of applicability of methods/models are not violated (for example, sphericity, normality, proportionality of risks, etc.);
- non-parametric – in all other cases.

Parametric criteria

The application of parametric criteria will be accompanied by checking the models for applicability (for example, the Kolmogorov-Smirnov criterion, the Shapiro-Wilk criterion, etc.).

The following parametric methods and approaches are supposed to be used:

1. To assess the differences of continuous variables between two groups – Student t-test.
2. To assess the dynamics of the compared indicators – analysis of variance (ANOVA) or covariance (ANCOVA) in the modification with repeated measures.
3. In case of multiple comparisons between the groups will apply a variety of corrections for multiplicity (Dunnett), (Tukey), (Scheffe), Holm adaptive test, etc.
4. In case of abnormal data distribution, approaches with the Generalized Linear Models and/or Mixed Linear Models will be used.
5. Selection of the type of distribution, clarification of the factor and covariance structures of the model is carried out with fit statistics such as AIC (Akaike information criterion).

To perform the above-mentioned statistical tests and techniques, it is assumed that the following SAS procedures are used:

- UNIVARIATE – check for normality of the compared distributions;
- CORR, MEANS – calculation of descriptive statistics;
- TTEST – Student t-test with all the modifications;
- GLM – analysis of Generalized Linear Models for studying temporal dynamics (ANOVA, ANCOVA);
- GENMOD – analysis of Generalized Linear Models.
  MIXED – analysis of Mixed Linear Models.

Non-parametric criteria

Below, there are the main types of possible comparisons with the respective criteria:

1. To evaluate the dynamics of the compared indicators – Friedman test, nonparametric analogue of repeated measures analysis of variance.

2. For the frequency analysis of 2×2 cross tables – χ^2-test (if the compared frequencies are greater than 5) or Fisher exact test (if one of the compared frequencies is less than 5).

3. For the frequency analysis of cross tables with independent strata – Cochran–Mantel–Haenszel test (modification of the χ^2-test for multiple comparisons).
4. For the frequency analysis of data on the presence / absence of an event or outcome during repeated measures (cross tables with dependent strata) – survival analysis.

To perform the above-mentioned non-parametric statistical analysis options, it is assumed that the following SAS procedures are used:

- FREQ – Friedman test, χ^2-test and / or Fisher exact test; Cochran–Mantel–Haenszel test
- LIFETEST – survival analysis
- NPAR1WAY – Mann-Whitney U-test.

Safety parameters

Adverse events recorded during the study will be grouped into frequency tables by severity, seriousness and relationship with the study drug.

Data presentation

Descriptive statistics will be provided for each study continuous / interval variable. Numerical data will be presented by mean, standard deviation, min and max values, as well as 1st, 2nd and 3rd quartiles (other measures of central tendency and dispersion may be additionally provided if necessary). The categorical variables will be presented as frequency tables by visits. Comparisons suggesting statistical conclusion will have the relevant confidence intervals. Outliers will be analyzed individually. The data will be grouped by visits.

Incomplete/missing data

Missing data not requiring the patient exclusion from analysis will be processed as follows:

1. For sections of descriptive statistics the missing/incomplete data will be ignored specifying the number of complete and incomplete data points.
2. For efficacy criteria, if the type of gaps (MCAR, MAR, etc.) and the type of variable are acceptable, **multiple imputation** methods can be applied. Alternative methods: data will be populated according to the **LOCF** approach.
3. For additional criteria - similar to descriptive statistics.