Title of the study: Physical Activity and the Course of COVID-19.
NCT number: NCT05200767
Date of the document: Nov-01-2021
Main Researcher: Edyta Sutkowska

APPLICATION
to the Bioethics Committee of the Wroclaw Medical University
for giving an opinion on the research project
carried out as part of the statutory activities of the University

Study Plan/SAP

1. Title, academic degree, name and surname, and place of employment of the applicant:
   Dr hab. n. med. Edyta Sutkowska
   Uniwersyteckie Centrum Rehabilitacji (UCR)
   ul. Borowska 213, Wrocław 50-556

2. Phone number: *+503077016*
3. Name of the organizational unit of the Wroclaw Medical University implementing the project:

Uniwersyteckie Centrum Rehabilitacji – <u>place of data collection and analysis</u>
USK - Szpital Tymczasowy na ul. Rakietowej 33, Wrocław - <u>place of surveys; p</u>ossibly additional centers after their authorities' decision that will not impact study design (only for Team members).

4. Project title: **<u>Physical Activity and the Course of COVID-19.</u>**
   - *in hospitalized patients*

5. Registration number of the Center for the Support of Science of the Wroclaw Medical University - *none*
6. Detailed description of the project together with justification of its purposefulness and feasibility assessment:

Physical activity is one of the factors modulating human immunity and affecting general efficiency, including respiratory one. For this reason, its level may be associated with the severity of the course of COVID-19.

***The study aims** to assess the relationship between physical activity levels before the onset of COVID-19 and the course of the disease. The course of the disease is often surprising and independent of selected poor prognostic factors; therefore, it is advisable to look for relationships between those variables that have not yet been analyzed.*

Methodology:

The study consists of a survey on physical activity prior to contracting COVID-19 among patients hospitalized due to this disease at the USK (Temporary Hospital for COVID patients).

Time Frame: 01 Nov 2021- throughout the entire period of hospital activity

<u>Inclusion criteria:</u>

- *adult*
- *sex – any*
- *race – any*
- *confirmed COVID-19 infection and hospitalization in the COVID-19 treatment unit*

<u>Exclusion criteria</u>:

-pregnancy;

-inability to complete the questionnaire during hospitalization or up to a week after discharge;

-history of a significant cardiovascular event in the last 6 months (acute coronary syndrome, stroke, amputation, revascularization of peripheral vessels, pulmonary or peripheral embolism of any etiology) if the patient did not complete the rehabilitation process;

-symptomatic chronic respiratory disease not responding to therapy before hospitalization for COVID-19 (or no therapy);

-any dyspnea at rest in the last month before COVID-19;

-injury to the locomotor system in the last month before contracting COVID-19;

-hospitalization in the last month before contracting COVID-19.

In order to describe the group and analyze the survey results, information from the patient's interview, physical examination, and the results of basic and additional tests contained in the patient's hospital documentation during the stay due to COVID-19 will be used.

The International Physical Activity Questionnaire (IPAQ) short form will be used to determine the level of physical activity.

After consenting to participate in the study, the patient will be asked to answer 7 survey questions. If the patient's condition prevents participation in the survey, the patient will be allowed to participate on a different day, including within 7 days from discharge, or indicate a relative who can fill out the survey for the patient.

Each patient will be given an identification number, and the list of participants will be prepared.

Data from medical records will be prospectively collected for Primary Outcome Measures: death due to COVID-19, recovery – patients discharged home, transfer to intensive care unit (ICU), and Secondary Outcome Measures: hospitalization length before transfer to intensive care unit, laboratory tests. Additional data – lab results, comorbidities, pharmacotherapy history, and complications related to hospitalization – will be collected if available.

Then, they will be combined with the IPAQ results (the surveys will be analyzed anonymously, and paper version of IPAQs will be archived in Uniwersyteckie Centrum Rehabilitacji, Borowska 213) in one document (Excel, based on the patient number).

Data ready for statistical analysis will be sent to a statistician and analyzed according to the Statistical Analysis Plan (SAP).

Feasibility assessment: *The project will involve physical activity specialists and personnel of the temporary COVID hospital. Given the current pace of the pandemic, I assess feasibility as high.*

7. Name and surname of the person who is to direct the experiment at the University, address, contact telephone number:
   dr hab. n.med. Edyta Sutkowska, UCR, ul. Borowska 213, 50-556 Wrocław, +503077016

8. Composition of the research project team, including professional and scientific qualifications
   - *dr hab. n.med. Edyta Sutkowska- MD, Ph.D., Assistant Prof; physician (internal medicine, vascular medicine, diabetology) and physiotherapist, Uniwersyteckie Centrum Rehabilitacji UMW, Wrocław*
   - *dr n.med. Janusz Sokołowski- MD, Ph.D., physician (emergency medicine specialist), Katedra i Klinika Medycyny Ratunkowej UMW, Dyrektor Szpitala Tymczasowego, Wrocław, ul. Rakietowa 33, Lekarz Kierujący SOR USK*
   - *dr hab. n.med. Katarzyna Madziarska, MD, Ph.D., Assistant Prof, physician (internal medicine, diabetology, nephrology) Katedra i Klinika Nefrologii i Medycyny Transplantacyjnej UMW, we Wrocławiu, Lekarz Kierujący Oddziałem Chorób Wewnętrznych i Zakaźnych w Szpitalu Tymczasowym, Wrocław, ul. Rakietowa 33*
   - *prof. dr hab. Ewa Jankowska – MD, Prof, physician, (internal medicine, cardiology, geriatry), Instytut Kardiologii i Zakład Kardiologii Translacyjnej i Rejestrów Klinicznych UMW, Wrocław*
   - *prof. dr hab. Adrian Doroszko, -MD, Prof., physician (internal medicine, cardiology), Klinika Chorób Wewnętrznych, Zawodowych i Nadciśnienia Tętniczego UMW, Wrocław*
   - *dr n.med. Marcin Madziarski, MD, Ph.D., physician, Klinika Reumatologii i Chorób Wewnętrznych USK, Wrocław*
   - *dr Karolina Biernat- PhD, physiotherapist Uniwersyteckie Centrum Rehabilitacji, Wrocław*
   - *dr Justyna Mazurek- MD, Ph.D., physician and physiotherapist (medical rehabilitation) , Uniwersyteckie Centrum Rehabilitacji, Wrocław*

- *dr Dominik Marciniak- Ph.D., statistician Katedra i Zakład Technologii Postaci Leku (Wydział Farmaceutyczny), Wrocłąw*
- *lek. Karolina Sutkowska- MD, physician, USK Wrocław*

9. Place(s) of survey
Szpital Tymczasowy USK, Oddział Chorób Wewnętrznych i Zakaźnych, Wrocław, ul. Rakietowa 33.

10. Data on the expected therapeutic and cognitive benefits and possibly other benefits for persons participating in a medical experiment:

There is no information in the literature on the impact of daily physical activity (obtained directly from patient questionnaires) on the course of COVID-19. Learning what relationships (if any) exist between them can help plan the prevention of this infectious disease and assess the strength of behavioral actions with their impact on the prognosis.

Additional documents (underline as appropriate)

a) a copy of the Rector's decision to grant funding as part of the statutory activities of the University
b) information for persons participating in a medical experiment containing detailed data on the purposes and principles of conducting the research, expected therapeutic and other benefits for these persons, and the risk associated with participation;
c) a written commitment signed by the researcher to obtain informed consent from all test subjects or their legal representatives;
d) a template of the patient's or their legal representative's consent form, which contains statements regarding:
    - voluntary consent to participate in the medical experiment after reading the information,
    - confirmation of the right to ask the researcher questions and receive answers to these questions,
    - information about the possibility of withdrawing from participation in the study at any stage;
e) information on the method of collecting and processing personal data for the person participating in a medical experiment;
f) research insurance information;
g) consent of the person participating in a medical experiment or their legal representative to the processing of data relevant to participation.
h) consent of the Head of the USK Temporary COVID Hospital/s (available at the Bioethics Committee office)
i) IPAQ – polish version- https://www.academia.edu/19229070/Mi%C4%99dzynarodowy_Kwestionariusz_Aktywno%C5%9Bci_Fizycznej_IPAQ_wersja_polska

Head of the organizational unit implementing the project	Applicant
.....	.....
Signature, stamp	*Signature, stamp*

Wrocław, ...

References:

Brodin P. Immune determinants of COVID-19 disease presentation and severity. Nat Med. 2021 Jan;27(1):28-33. doi: 10.1038/s41591-020-01202-8. Epub 2021 Jan 13. PubMed ID: 33442016

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Biernat E, Stupnicki R, Gajewski AK. International Physical Activity Questionnaire (IPAQ) - Polish version. Wych Fiz Sport. 2007;51(1):47-54. (In Polish).

Ad b)
INFORMATION ABOUT THE STUDY

Study title: Physical Activity and the Course of COVID-19

Researcher Name: Edyta Sutkowska

Dear Sir or Madam,
You have been asked to participate in a research project. Before giving your consent, please read this "Notice" and make sure you understand it. This document describes the study's aim, procedures, benefits, and risks.
The researcher will clarify your doubts if necessary.
If you decide to participate in this research project, you will be asked to sign an "Informed Consent to Study Participation."
You may resign from participation at any time without giving any reason and without any consequences.

I. Aim of the study:

An assessment of whether the level of physical activity before contracting the disease (COVID-19) impacted its course.

II. How the research will proceed

If you have been invited to this study, you have been confirmed with COVID-19 and required hospital admission for this reason.
The study analyzes the level of your daily physical activity before COVID-19 diagnosis and relates it to your lab results and the course of the disease (its duration, medications used, respiratory support, etc.). The only action you will be asked to do is to answer 7 survey questions that relate to your physical activity. The person asking the questions will explain them to you if needed during the survey. Depending on your health condition, the survey may take up different amounts of time. It usually takes about 10 minutes (sometimes even less), but you can ask to stop it and return to the survey on another day if you are not feeling up to it. However, this postponement cannot take longer than 7 days after leaving the hospital. You can also indicate a person who can answer questions on your behalf, but it must be a close relative who knows your habits well so that the answers are truthful and reliable.
For the purpose of the study, it will also be necessary to analyze the course of your disease and test results during illness. This information will be obtained from your hospital medical records and the doctor who treated you. We do not plan to perform additional tests or test any drugs or medical procedures. In this respect, our study is not a medical experiment and is merely an observational study without intervention. Therefore, by granting consent to participate in this study, you agree to:
- answer survey questions (in person or by a person indicated by you)
- the use of the information in your medical records from a hospital stay due to COVID-19.

The data will be analyzed anonymously. Your personal data will be only needed at the beginning of the study to compare the survey results with the information in the medical documentation.
If you remain under the care of the hospital staff, you will receive the same care as patients not taking part in this study.

III. Risk related to study participation

Participation in the study is not associated with the risk of significant adverse effects or events. When answering questions, the only adverse effect may experience is fatigue/shortness of breath. However, please note that you can:
- postpone the survey to another date
- withdraw your consent at any stage of the study without any consequences.

IV. Benefits related to study participation

There is no direct benefit to you from this study.
However, please remember that the medical world is learning how to treat and prevent COVID-19, and any information related to this disease may help you, your loved ones, and the entire population. Therefore, we will be grateful for your participation, which may contribute to improving activities aimed at COVID prevention and treatment.

Ad c)

RESEARCHER'S STATEMENT

MD, Ph.D., Assistant Prof.
Edyta Sutkowska

Study title: Physical Activity and the Course of COVID-19

Obligation to obtain informed consent from an adult
I hereby declare that all persons participating in the above research project (or their statutory representatives) will be informed about the research purpose and methods, the possible benefits and risks of participation, the voluntary nature of participation, the possibility of withdrawing from it at any time, as well as the method of collecting and processing personal data.
Only persons who give their prior written consent will be included in the study.

.....
Researcher signature

Wrocław, date .....

Ad d)

INFORMED CONSENT TO STUDY PARTICIPATION

NCT :…… ; ID: 1081/2021

Study title: Physical Activity and the Course of COVID-19

Principal Investigator Name: Edyta Sutkowska

1. I confirm that I have read:
• Information about the study,
• Information on how personal data will be collected and processed,
• Research Insurance Information,
and I consent to participate in the study.

2. I had the opportunity to ask questions and was given answers and necessary explanations.
3. I am aware of the risks and benefits of participating in the study.
4. I understand that my participation is voluntary and that I can withdraw from the study at any time without giving a reason.
5. I consent to the inspection of the correctness of the research project by the representatives of domestic, foreign, or international institutions supervising the research and grant access to my personal data and medical documentation (data regarding my health condition), provided that they are relevant to the study.
6. I consent to the processing of data in this study in accordance with laws applicable in Poland (Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC.
7. I consent to the transfer of my anonymous data to other countries, both within and outside Europe.

I am aware that the results of this research project will be used to prepare scientific publications in the future, and the data available in them will be used only in an anonymous form.

……. ……..
Researcher name Participant name

……
……
Date, Researcher signature Date, Participant signature

Ad e)

INFORMATION ON THE COLLECTION AND PROCESSING OF PERSONAL DATA

Study title: Physical Activity and the Course of COVID-19.
Researcher Name: Edyta Sutkowska

INFORMATION CLAUSE
According to Art. 13 of Regulation (EU) 2016/679 of the European Parliament and of the Council (General Data Protection Regulation, GDPR), I inform you that:
1. The controller of your personal data is Wroclaw Medical University, Wybrzeża Pasteura 1, 50-367 Wrocław, represented by the Rector.

2. The controller has appointed a data protection officer who can be contacted in matters concerning personal data processing at the following e-mail address: iod@umed.wroc.pl

3. Your personal data will be processed to conduct the research project described in detail in "Information about the study."
4. The legal basis for the processing of your data is point (a) of Art. 6(1) of GDPR.
5. The controller does not share your personal data with any recipients, except when such an obligation results from the provisions of generally applicable law or an agreement* concluded by the controller.

6. The controller may entrust another entity with the processing of your personal data on behalf of the controller based on a written agreement.*

7. Personal data will be stored for the duration of the study and the full development and use of its results.

8. You have the right to:
- access the content of your personal data
- have your personal data rectified
- have your personal data erased
- restriction of your personal processing
- object to the processing of your personal data.
9. You have the right to lodge a complaint with the President of the Personal Data Protection Office if you suspect that your personal data is being processed in violation of the law.
10. Withdrawal of consent to the processing of your personal data will not affect the lawfulness of the processing before the consent withdrawal.
11. Providing personal information is voluntary.
12. Decisions will not be made in an automated manner, and you will not be subject to profiling.

* Provide names of entities with which such contracts/agreements have been concluded

.....
Participant signature

Ad f)

RESEARCH INSURANCE INFORMATION

Participant Name.....
Age.....

Adress:.....

Study title: Physical Activity and the Course of COVID-19.

I hereby declare that I have been informed about the insurance of my participation in the above-mentioned study, included in the insurance of the scientific activity of Wroclaw Medical University.
I acknowledge this information.

.....	.....
Researcher signature	Participant signature

Wrocław, date: .....

Ad g)

Consent to Personal Data Processing

I consent to the processing of my personal data to carry out the following study by Wroclaw Medical University:
Physical Activity and the Course of COVID-19.
I acknowledge that my consent may be revoked at any time by submitting a relevant declaration of will to Wroclaw Medical University.

……..
Date and legible participant signature

Statistical Analysis Plan

Sample size calculation for confidence interval: 95%; fraction size: 0.5; max error: 5%: 384 participants.

The variables subjected to statistical analysis will be on nominal scales – including dichotomous ones – and ratio scales:

- variables expected in the ratio scales: raw MET, hospitalization length, age, BMI, and concentration levels of all biochemical factors studied;
- variables expected in dichotomous scales: sex, oxygen therapy need (Yes/No), information about patient death or transfer, information about complications, variables describing the study group in terms of history and comorbidities, and medication groups.

The variables in the interval scales are nicotine addiction and IPAQ level (the latter will be treated as a directional, three-item interval variable).

Statistical analysis will begin by verifying the accuracy of the data contained in the compiled database. For this purpose, descriptive statistics with histograms will be determined for ratio variables and tables of sample sizes for nominal variables. Then all extreme outliers and dubious results will be verified again with the source materials. Gaps found in the database will not be replaced with any other values.

In the case of variables on ratio scales, their normality of distribution will be assessed. The Shapiro-Wilk W test will determine the normality of distribution. Characterization of this group of variables will be based on the statistical significance of the W-test. The following descriptive statistics will be defined for variables with a normal distribution: size, mean value, standard deviation, and 95% confidence interval for the mean value. While size, median, and range will be determined for variables that are not normally distributed.

The Shapiro-Wilk W test with a significance level of $\alpha=0.05$ will be used to evaluate the normality of distributions.

Principal component analysis (PCA) will assess global relationships between the key variables, regardless of scale. PCA additionally allows the identification of non-obvious and difficult-to-predict correlations between analyzed variables on different measurement scales. The developed PCA model will be estimated using the NIPALS algorithm. The convergence criterion will be set at 0.00001, and the maximum number of iterations will be 100. The number of components will be determined by establishing the maximum predictive ability of Q^2 using V-fold cross-validation, adopting V_max=7. The optimal PCA model will be reduced to principal components, and the results will be presented in a graph, including the contribution of each component to the overall percentage of explained variance and information on their statistical significance.

Pearson correlation coefficient matrices and Spearman's rank correlation coefficients will be calculated to determine correlations between variables of ratio scales.

Their statistical significance will be determined with a t-test adopting a significance level of $\alpha=0.05$.

The basis for assessing the correlation of nominal variables will be the significance of Pearson's chi-squared test. In the case of dichotomous variables, for which it will be possible to construct bivariate (2x2) tables, an additional odds ratio (OR) will be determined, along with a 95% confidence interval (OR±95%CI).

A nonparametric Cox proportional hazards model will be used to evaluate the effect of the IAPQ value on survival probability.

The data analysis will also involve testing the statistical significance of differences between mean values: the parametric Student's t-test for independent samples and parametric analysis

of variance (ANOVA) with the post-hoc least significant difference (LSD) test for variables that meet the normality of distribution and homogeneity of variance assumptions, or the nonparametric Mann-Whitney U-test and nonparametric Kruskal-Wallis ANOVA for variables not meeting these assumptions. In addition, Levene's test and the Brown-Forsythe test will assess the homogeneity of variance.
A significance level of $\alpha=0.05$ will be assumed for all statistical analyses.
Statistical analysis will be performed using StatSoft's Statistica 13.3 PL.