Plan Overview

A Data Management Plan created using DMPonline

Title: Hyperbaric Oxygen for Treatment of Long COVID syndrome; A Randomized, Placebo-Controlled, Double-Blind, Phase II Clinical Trial

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Project abstract:

Long Covid Syndrome (LCOV) or (Long COVID) is defined as ’signs and symptoms that develop during or following an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis’. Common symptoms are fatigue, post-exertional malaise, brain fog, neurologic sensation, headaches, memory issues, insomnia, muscle aches, palpitations, shortness of breath, dizziness and speech issues. Many patients report very low Health Related Quality of Life (HRQoL) One in ten infected individuals may suffer persistent symptoms, and we are facing an emerging problem that will severely affect individuals, health care systems and society for years to come. Subjects will be recruited once they have been diagnosed with Long COVID through assessment by a multidisciplinary team with a thorough diagnostic work up including medical history, routine blood tests, questionnaires, physical tests and radiology. We explore hyperbaric oxygen administered in a randomized placebo-controlled clinical trial as a potential treatment for patients suffering from Long COVID. The overall hypothesis to be evaluated is that hyperbaric oxygen (HBO2) treatment (HBOT) reduces oxidative stress and chronic inflammation, improves endothelial dysfunction and thereby alleviates symptomsdisp associated with Long COVID.

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Hyperbaric Oxygen for Treatment of Long COVID syndrome; A Randomized, Placebo-Controlled, Double-Blind, Phase II Clinical Trial

Description of data

How will data be collected, created or reused?

Data will be prospectively collected in an electronic Case Report Form (eCRF).
Before start of the trial all source data will be defined in the "source data log". In most cases source data will be the subjects medical records.
For the physical tests, the paper protocol and/or printout from the monitor will be source data.
Data from activity meter will be collected automatically into a database which will be source data.
Blood samples (Plasma, Erythrocytes and Peripheral Blood Mononuclear Cells) will be collected and stored in a biobank for later analysis such as RNA sequencing.
All data collected is pseudonymised

What types of data will be created and/or collected, in terms of data format? Include version numbers if applicable.

Observational data including results from surveys is recorded from medical records.
Experimental data from physical tests will be saved into the data base from the test-protocols.
Experimental data from lab equipment will be saved as .jpeg, .fcs, .raw, and .csv formats.
All data from the eCRF will be saved in .cvs format for the final data analysis.

What volumes of data will be created and/or collected?

- < 100 GB

Experimental data from a randomised controlled trial
NGS data: gene-expression (RNA seq) and Proteomics

Documentation and data quality

How will the material be documented and described, with associated metadata relating to structure, standards and format for descriptions of the content, collection method, file naming-format-versioning, etc

- Documentation will include a standardized folder structure, codebooks (metadata about the data), logbooks (metadata about data processing), analysis plans, input and output files from databases and statistical softwares.

How will data quality be safeguarded and documented (for example repeated measurements, validation of data input, etc.)?

- Data input is validated at the point of entry (OpenClinica). Data will be checked to verify that all responses are within the possible range of data values.
- Data will be checked for double entries, completeness, missing data, unreasonable values and linkage between the data sources.
- Data will be quality-checked at collection and checked agains source data by an independent monitor organisation (Karolinska Trial Alliance). The monitor is certicied in ICH-GCP and experienced in clinical trials.
- RNA seq data will be quality controlled in terms of sequence quality, sequencing depth, reads duplication rates (clonal reads),

alignment quality, nucleotide composition bias, PCR bias, GC bias, rRNA and mitochondria contamination, coverage uniformity. Only high-quality data will be included in the subsequent analysis.

Storage and backup

How is storage and backup of data and metadata safeguarded during the research process?

- Other, please specify

We will use a eCRF (Open Clinica) and a server in Germany, set up by our data manager for data storage. All systems fulfil the FDA requirements of FDA 21 CFR Part 11 and CDISC/CDASH ODM version 1.3, and the ICH guideline.
SLL encryption, encryption at rest, data center cecurity certifications: SSAE16 SOC1, SOC2 Type II, ISO 27001

How is data security and controlled access to data safeguarded, in relation to the handling of sensitive data and personal data, for example?

- Access to the data saved on the server is restricted to staff delegated in the trial.
- Only pseudonymized data is entered in the eCRF, with the key stored in a safety cabinet located at Hyperbaric medicine/Karolinska University Hospital to which only delegated staff have access.

Legal and ethical aspects

How is data handling according to legal requirements safeguarded, e.g. in terms of handling of personal data, confidentiality and intellectual property rights?

- The study will be performed in compliance with the study protocol, the Declaration of Helsinki, ICH-GCP (Good Clinical Practice) guidelines and current hospital, national and international regulations governing this clinical trial. This is to ensure the safety and integrity of the study subjects as well as the quality of the data collected.
- The final study protocol for clinical trials has been approved, as a part of the application for a permit for clinical trials, by both the Swedish Ethical Review Authority (Etikprövningsmyndigheten, EPM) and the Swedish Medical Products Agency (MPA) before the trial can be conducted. The final version of the informed consent form and other information provided to subjects, must be approved or given a written positive opinion by EPM. EPM and MPA must be informed of any changes in the study protocol in accordance with current requirements.
- Data processing agreement (DPA) and Data transfer agreement (DSA) are preformed. If necessary, further DPA or DSA will be performed between our trial group and collaborators for data transfer.

How is correct data handling according to ethical aspects safeguarded?

- Patient data is pseudonymized at Karolinska University Hospital (KUH), and the code is only accessible to delegated staff in the trial group. The material will arrive to KI coded, and the original code will be saved by KUH.
- Consent has been acquired form human participants to process/share data.
- Data Transfer/Processing agreements will be signed prior to any data sharing.
- Ethical approvals/amendments and informed consent forms for the project are registered in the diary.

Accessibility and long-term storage

How, when and where will research data or information about data (metadata) be made accessible? Are there any conditions, embargoes, licenses and limitations on the access to and reuse of data?

- Only metadata is published openly, underlying data is made available upon request after ensuring compliance with relevant legislation and KI guidelines.
- Data will be made available upon publication as a supplement to the publication.
- Data will be deposited at a repository/database (please provide name) immediately and without embargo, using a license (CC-BY).

In what way is long-term storage safeguarded, and by whom? How will the selection of data for long-term storage be made?

- Long-term storage will take place at Karolinska University Hospital. Data will be stored at least 10 years after publication. Source data will be stored digitally in medical records and if not digital, paper format and the e-CRF as an excel-file. The data will include raw data and the final data analysis file. Intermediate working files will be deleted.

Will specific systems, software, code or other types of services be necessary in order to open and use/analyse data in the long term?

- The data from the eCRF can be read by any software compatible with .csv files

How will unique and persistent identifiers for the research data, such as a Digital Object Identifier (DOI), be obtained?

A DOI will be assigned to the dataset by the data repository

Responsibility and resources

Who is responsible for data management while the research project is in progress?

- Data management is performed by an external partner, for whom non disclosure agreement (NDA), DPA and DSA has been signed.

Who is responsible for data management, long-term storage after the research project has ended?

- The PI is responsible for data management and the archive function will be responsible for long-term storage

What resources (costs, labour or other) will be required for data management (including storage, back-up, provision of access and processing for long-term storage)?

- Salary for the data manager at EDC Scandinavia which also includes storage, back-up etc is budgeted 200kSEK under Driftskostnader "Data management, Statistician" and is partially funded by this project.

What resources will be needed to ensure that data fulfil the FAIR principles?

- We will require assistance from the KI Research Data Office to structure metadata in a repository

Planned Research Outputs

Publication - "Hyperbaric Oxygen Therapy for Long COVID (HOT-LoCO), an interim safety report from a randomised controlled trial"

Abstract BackgroundWith ˜50 million individuals suffering from post-COVID condition (PCC), low health related quality of life (HRQoL) is a vast problem. Common symptoms of PCC, that persists 3 months from the onset of COVID-19 are fatigue, shortness of breath and cognitive dysfunction. No effective treatment options exist. Hyperbaric oxygen (HBO2) is a candidate drug. ObjectivesThis interim analysis describes our cohort and evaluates the safety of HBO2.MethodsIn an ongoing randomised, placebo-controlled, double blind, clinical trial, 20 previously healthy subjects with PCC were assigned to HBO2 or placebo. Primary endpoints are physical domains in RAND-36; Physical functioning (PF) and Role Physical (RP) at 13 weeks. Secondary endpoints include objective physical tests. Safety endpoints are occurrence, frequency, and seriousness of Adverse Events (AEs). An independent data safety monitoring board (DSMB) reviewed unblinded data. The trial complies with Good Clinical Practice. Safety endpoints are evaluated descriptively. Comparisons against norm data was done using t-test.Results20 subjects were randomised, they had very low HRQoL compared to norm data. Mean(SD) PF 31.75(19.55) (95% Confidence interval; 22.60-40.90) vs 83.5(23.9) p<0.001 in Rand-36 PF and mean 0.00 (0.00) in RP. Very low physical performance compared to norm data. 6MWT 442(180) (95% CI; 358-525) vs 662(18) meters p<0.001.31 AEs occurred in 60% of subjects. In 20 AEs, there were at least a possible relationship with the study drug, most commonly cough and chest pain/discomfort.ConclusionsAn (unexpectedly) high frequency of AEs was observed but the DSMB assessed HBO2 to have a favourable safety profile. Our data may help other researchers in designing trials. Trial Registration ClinicalTrials.gov: NCT04842448. Registered 13 April 2021, https://clinicaltrials.gov/ct2/show/NCT04842448

Publication - "Hyperbaric oxygen for treatment of long COVID-19 syndrome (HOT-LoCO): protocol for a randomised, placebo-controlled, double-blind, phase II clinical trial"

IntroductionLong COVID-19, where symptoms persist 12 weeks after the initial SARS-CoV-2-infection, is a substantial problem for individuals and society in the surge of the pandemic. Common symptoms are fatigue, postexertional malaise and cognitive dysfunction. There is currently no effective treatment and the underlying mechanisms are unknown, although several hypotheses exist, with chronic inflammation as a common denominator. In prospective studies, hyperbaric oxygen therapy (HBOT) has been suggested to be effective for the treatment of similar syndromes such as chronic fatigue syndrome and fibromyalgia. A case series has suggested positive effects of HBOT in long COVID-19. This randomised, placebo-controlled clinical trial will explore HBOT as a potential treatment for long COVID-19. The primary objective is to evaluate if HBOT improves health-related quality of life (HRQoL) for patients with long COVID-19 compared with placebo/sham. The main secondary objective is to evaluate whether HBOT improves endothelial function, objective physical performance and short-term HRQoL.Methods and analysisA randomised, placebo-controlled, double-blind, phase II clinical trial in 80 previously healthy subjects debilitated due to long COVID-19, with low HRQoL. Clinical data, HRQoL questionnaires, blood samples, objective tests and activity metre data will be collected at baseline. Subjects will be randomised to a maximum of 10 treatments with hyperbaric oxygen or sham treatment over 6 weeks. Assessments for safety and efficacy will be performed at 6, 13, 26 and 52 weeks, with the primary endpoint (physical domains in RAND 36-Item Health Survey) and main secondary endpoints defined at 13 weeks after baseline. Data will be reviewed by an independent data safety monitoring board.Ethics and disseminationThe trial is approved by the Swedish National Institutional Review Board (2021–02634) and the Swedish Medical Products Agency (5.1-2020-36673). Positive, negative and inconclusive results will be published in peer-reviewed scientific journals with open access.Trial registration numberNCT04842448.

Planned research output details

Title	DOI	Type	Release date	Access level	Repository(ies)	File size	License	Metadata standard(s)	May contain sensitive data?	May contain PII?
Hyperbaric Oxygen Therapy for Long COVID (HOT-LoCO ...	10.1186/s12879-023-08002-8 ...	Publication	2022-08-22	Open	None specified		Creative Commons Attribution 4.0 International	None specified	No	No
Hyperbaric oxygen for treatment of long COVID-19 s ...	10.1136/bmjopen-2022-061870 ...	Publication	2022-11-01	Open	None specified		Creative Commons Attribution 4.0 International	None specified	No	No