Artificial intelligence research in the COVend COVID-19 clinical trial project

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Abstract

The COVend project aims at delivering a new effective therapy, FX06, against the SARS-CoV-2 virus infection for the management of the COVID-19 disease in hospitals. Nine of the 17 partners of the project consortium are hospitals responsible for collecting study subjects and administering the FX06 therapy to the patients. Although the clinical trial (IXION) has the main role in the project, the project has also a work package which develops and applies artificial intelligence (AI) methods to the data collected during the 28-day study period from the patients receiving the therapy. The AI work package applies exploratory data analysis methods to find patterns and profiles of the patients. Combined with the data about treatment methods and patient outcomes, the aim is to provide decision support for the therapy intervention in the later stage of the project.

Keywords: COVID-19, artificial intelligence, FX06, intensive care

Introduction

Since the outbreak of the COVID-19 epidemic in 2019-2020, the European Union (EU) has supported a number of research projects in the Horizon 2020 and Horizon Europe research programmes as a part of the one billion euros pledge for coronavirus research [1]. The COVend project [2], funded by the Horizon Europe programme is one of these projects, with a 9.9 million euros funding from the European Commission.

The initial good results with the Fibrin-derived peptide Bβ15-42 (FX06) in treating critically ill patients with COVID-19 [3] called for a start of a wider clinical trial to study the effectiveness of FX06 in COVID-19 therapy to be able to bring this drug to wider availability in the treatment of the millions of patients suffering from this disease. The COVend project (8/2021-7/2024) carries out this clinical trial, the IXION study, registered under EudraCT number 2021-005059-35. Nine of the 17 project partners are European hospitals administering the drug to the patients fulfilling the inclusion criteria of the study. The project is coordinated by the Goethe University Frankfurt am Main, Germany.

Although the main objective of the project is to study the effectiveness of the FX06, the extensive data collection of the study subjects offers the

possibility to study the effects of the drug in more detail depending on the characteristics of the patients. Moreover, if significant patterns and variations of treatment results are found from the data, this would offer the possibility to provide decision support for planning and guidance of FX06 treatment of the patients with the help of artificial intelligence. This paper focuses on the artificial intelligence part of the COVend project with the objective to produce a prototype decision support tool for the treatment of COVID-19 patients in hospitals.

Material and methods

According to the published study protocol [4], 306 hospitalised patients will be included to the placebo-controlled, double-blinded, parallel, randomized (2:1), phase II clinical study of the FX06 drug. The inclusion and exclusion criteria of the study patients exclude those COVID-19 patients who have serious and/or uncontrolled diseases with a bad prognosis that are likely to interfere with the evaluation of the patient's safety and with the study outcome [4]. The main objective is to compare the progression/worsening disease state of the patients in the intervention and control groups of the patients at the end of the 28-day study period.

Many variables are measured from the subjects during the study. These are also related to the secondary objectives such as overall disease progression, lung function, systemic inflammation, survival, capillary refill time, duration hospital stay, and drug accountability [4]. In addition to the traditional measurements of vital signs and the information in the patient data management systems, OMICS analysis of the samples from the subjects is also to be performed. This includes proteomics, metabolomics, and lipidomics.

Data protection is important in these kinds of studies, and it has to fulfil the requirements of the EU data protection regulation (GDPR) [5], including documentation, consent forms, and contracts. It would be easiest for the researchers to process anonymised data to which GDPR does not apply, but the nature of the study is such that pseudonymized data needs to be processed to allow actually meaningful data-analysis method development. The required ethical approvals of the study have been obtained and the study subjects have the right to stop participation in the study any time.

The analysis of the data begins with an exploratory phase. As the number of input variables is large and the formats and properties of different data modalities are highly diverse, dummy data in the correct format is delivered to the AI researchers first. This data with its documentation will help the AI researchers to prepare for the arrival of the real data from patients and start designing the data processing pipeline. The dummy data is used to tune the analysis software to read data in correct format and analyse its variability and set limitations and requirements to the potential AI methods that can be used. Interaction between the providers of the data and the AI researchers is necessary to understand the data sufficiently. The exploratory phase studies the main statistical properties of the highly multidimensional data, and possible correlation/association of individual parameters to the outcome of the patients first. Since this is unlikely to reveal the full truth of the disease progression and recovery, the combinations of the parameters need to be studied, as well.

As a result of the exploratory study, the relationship of the variables with outcomes is expected to be brought forward, in addition to possible clusters and similarities/dissimilarities in the patient data. The study aims also at finding out most beneficial treatment patterns depending on patient types. This can be used to develop a model-based

personalised decision support module to treat COVID-19 patients. Machine learning can be attempted if the sample size is large enough to allow this. Traditional machine learning approaches such as Random Forest, Logistic Regression and Support Vector Machines can be benchmarked. In addition, various deep learning architectures can also be implemented such as Convolutional Neural Networks (CNN) and Long Short-Term Memory (LSTM). An alternative to machine learning based model is to apply expert originated rules for the decision support module. If enough data will be available, these models will also be validated during the project. Additionally, a hybdrid approach may be explored if sample size is somewhat lacking for fully training a complex supervised model. A combination of rules presented as a priori distribution for bootstrapping a Bayesian inference model and then evolving the model with the data that was collected may bring clinically meaningful insight and use the power of modern Bayesian samplers to make use of hard to collect data for patient benefit.

Openness of the research data is a principle of the Horizon Europe research program. This is phrased 'as open as possible as closed as necessary' [6]. One of the tasks of the artificial intelligence work package is to determine how much of the collected patient data can be made open through an appropriate anonymisation process. The final decision on the composition of the open data set cannot be done by the AI researchers alone, but meetings are needed with the clinical partners to come up with an acceptable compromise.

Results

At the time of writing (February 2023), everything is ready to include patients to the randomised control study. The course of the epidemic has been unpredictable and the number of COVID-19 patients who need intensive care has decreased from the top of the epidemic. This has resulted in difficulties finding the patients who fulfil the inclusion criteria of the IXION study.

The EU funded projects relating to the COVID-19 epidemic Envision [7], COVirna [8] and COVend have begun co-operation. The report of the joint webinar of these projects "Addressing unmet clinical needs, practices and patient outcomes: the impact of EU-funded projects" is available in [9].

Dummy data has been obtained and its contents have been analysed. It turned out that the available documentation has not yet been sufficient to fully specify the data analysis pipeline and that the documentation needs to be more detailed for this specific purpose. The use of dummy data has thus been useful for the development of the research process within the project.

The regular monthly meetings of the project have increased mutual understanding of the goals of the project and understanding of the specific needs of the work packages in the project. In future, more targeted, smaller group international meetings are necessary to bring the AI work package to a successful conclusion.

Discussion

The unpredictable course of the COVID-19 epidemic has surprised the project consortium to some extent. As the project has not met its timetable target in patient inclusion, discussions have been conducted to widen the inclusion criteria. It is, however, a relatively large undertaking to change the inclusion criteria as it would require changes in the study protocol which would require additional approvals of the project in ethical committees etc. delaying the project significantly. By the time all this has been accomplished, the epidemic can have

taken another route again. For these reasons this step has not been taken.

The AI development work package has suffered from the lack of real patient data in this initial phase of the project. It may turn out that there will be little time to actually analyse the data and generate the AI models when the study data codes revealing the patients with verum and placebo are opened. It remains to be seen what can be finally accomplished in this time frame but the good preparation ensures that at least the exploratory analysis of the relationships between the variables, clustering and unsupervised and semi-supervised learning will be possible. The positive side of the delay is that more and more literature will become available about applying AI in COVID-19 and we can learn from past mistakes [10,11]. The designed multi-modal AI-driven data analysis pipeline may also be useful in future projects to come.

The opening of the research data will also be a challenge in the project. For example, the OMICS data may be difficult to open in a substantial amount.

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Conflict of interest statement

The authors are researchers in the project that is described here but they have no conflicts of interests with the producers of the equipment or producers of the data used in this study.

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