Dear guardian,

The person whose legal guardian you are has been diagnosed with severe COVID-19 (infection with the “novel coronavirus”), and must receive mechanical ventilation as well as be stabilised with an additional lung support technique referred to as ECMO (extracorporeal membrane oxygenation). We would hereby like to inform you that the person whose legal guardian you are can take part in the research project stated in the heading. Participation is voluntary and the person whose legal guardian you are will not suffer any drawbacks if you refuse.

The following contains information about the research project "Cytokine Adsorption in Patients With Severe COVID-19 Pneumonia Requiring Extracorporeal Membrane Oxygenation - Randomized, Controlled, Open-label Intervention, Multi-center Trial (CYCOV II-study)". In this study, we want to investigate whether the adsorption of cytokines in a special adsorber (CytoSorb®) in patients with severe COVID-19 and lung failure has a positive impact on clinical stabilisation and thus also the patients’ recovery.

You receive this “Information for the Legal Guardian” in addition to the verbal informed consent discussion during which the study schedule, the study objectives and risks will be explained in detail and where you will be able to ask questions. The following pages explain the research project once more, and possible risks and discomforts for the patients taking part will be outlined. This is done in the form of providing answers to frequently asked questions. Should anything still be unclear to you, please do not hesitate to contact the study team at the hospital treating your relative at any time.

As the person whose legal guardian you are currently cannot decide about the study participation themselves, we would like to ask you to decide about the participation in the study on their behalf, taking into account the person’s presumed will regarding taking part in the study.

1. What is the objective of the research project?

In the Chinese city Wuhan, a series of patients who suffered from respiratory disorders and pneumonia was discovered in December 2019; some of the patients died from this. In virological analyses of samples from the patients’ deep respiratory tract, a novel coronavirus was isolated (SARS-CoV-2). The disease
(COVID-19) spread rapidly in the city of Wuhan at the beginning of 2020 and soon beyond in China and, in the coming weeks, around the world. A small number of the particularly severely ill patients required not only highly invasive ventilation therapy but also extracorporeal membrane oxygenation (ECMO) to supply the patient's blood with sufficient oxygen. Even under maximum intensive care treatment, a very high mortality rate of was observed in this patient group. In addition, high levels of substances (so-called cytokines) known from other severe infectious diseases could be detected in the blood of these severely ill patients. From experience in the therapy of patients with severe infections, we know that treatment with a CytoSorb® Adsorber can lead to a reduction of these substances, but it is so far unclear whether this also improves the further course of the disease and the likelihood of the patients’ recovery. The aim of the research project is to transfer the experience from treatment with other severe infectious diseases to treatment of patients with severe COVID-19. Use of CytoSorb® Adsorber is intended to lower significantly increased cytokine levels in patient blood; we want to find out whether this can contribute to stabilising the patients.

2. **What will the schedule of the research project look like?**

There will be two groups: In the one group (control group), the patients will receive the usual standard treatment as set forth in the relevant therapy recommendations and guidelines. As a large number of studies is currently being conducted, in particular about COVID-19, treatment recommendations — and thus also the standard treatment in both groups — may change during the course of the study. The treatment in the other group (study group) is different only in that the patients’ blood will in addition to the usual standard treatment be guided through a specific adsorber (similar to a filter); a large amount of the messenger substances released as part of the severe infection will remain in the adsorber and thus be removed from the circulatory system. The adsorber can be integrated into the miniaturised life support machine (ECMO) while the latter is running, and it must be exchanged every 24 hours. During the research project, the adsorber will be exchanged twice. In addition to routine diagnostics, 4 additional blood collections of approx. 10 mL each (a total of approx. 40 mL) will be required over a time period of 72 hours. When considered in relation to the routine blood collections of approx. 130 mL of blood over this time period, this amount is small and safe. No additional vessel punctures will be required for these blood collections because the blood can be collected via indwelling catheters. If you agree to the study participation of the person whose legal guardian you are, these samples will be analysed within the context of the study. If you do not agree, the study participation of the person whose legal guardian you are will end, and the sample results will not be used for this study.

Provided that you agree, we will contact you around 30 days after study enrolment if the person whose legal guardian you are has by then been discharged from in-patient treatment or been transferred to a different hospital in order to enquire about the further course of the disease in the person whose legal guardian you are after discharge from in-patient treatment.

3. **When does the informed consent discussion for the research project take place?**

Our objective is to always have the the informed consent discussion before the start of the research project. In patients who require extracorporeal lung support due to severe COVID-19, however, a medical coma must be induced, and informing them is thus not possible during the acute phase. The first few hours after the start of the ECMO treatment are particularly important because the uncontrolled release of messenger substances is particularly strong during this time period. Integrating the adsorber in order to remove these messenger substances from the circulatory system therefore cannot be delayed for long. For that reason, it may happen that, at the time the informed consent discussion takes place, the patient has by way of precaution already been enrolled in the study, has been assigned to either the study group or the control group, and if applicable an adsorber may already have been integrated and blood samples may already have been collected.

During primary emergency care, the treating physicians and the study team already try to quickly contact relatives, or, if available a legal guardian, in order to enquire about the patient’s presumed will regarding participation in the study. Since you act as legal guardian, we would like to ask you to agree to the study...
participation of the person whose legal guardian you are, provided that this is in line with that person’s presumed will. If the person whose legal guardian you are regains consciousness before the end of the investigational period, the person themselves will also be informed and asked for their agreement.

4. **Are therapeutic procedures performed before the informed consent discussion?**
   Yes. An increased amount of messenger substances may be released into the patient’s circulatory system as early as during the first few hours after initiating extracorporeal life support, and the decision about using a CytoSorb® adsorber should therefore be taken just as rapidly. For patients assigned to the study group, the adsorber will usually be integrated into the system before connecting it to the patient’s circulatory system as part of preparing the miniaturised life support machine (ECMO). If no legal patient representative has been reached by this time, assignment to one of the two groups (study group or control group) and the integration of the adsorber takes place without obtaining consent beforehand.

5. **Why are there two groups, and how are patients assigned to the groups?**
   Assigning the study patients to two different groups allows investigating the impact of the adsorber on the therapy in an isolated manner. Patients will be assigned to one of the two groups based on chance, immediately after the decision to enrol them in the study has been taken. Both groups have the same size, and there is the same likelihood of being assigned to either of them. It is not possible to switch between the groups; likewise, it is impossible to enrol a patient in one of the two groups in a targeted manner – this is decided solely by chance (so-called randomisation).

6. **Which risks are associated with taking part in the research project?**
   The CytoSorb® Adsorber has been used in the therapy of different diseases for multiple years. To date, no relevant complications have been described, so that we do not expect any specific risks due to using the adsorber in our research project. The CytoSorb® Adsorber adsorbs molecules of a specific size and does not differentiate based on the effects these molecules have. It can therefore be expected that not only “harmful” molecules will be adsorbed and removed from the circulatory system, but also beneficial messenger substances and medicines. As it is known that some medicines are adsorbed, these may possibly need to be replaced by alternative drugs with the same or similar effects. The possible risk of beneficial substances and medicines being removed from the patient’s blood applies only to those patients treated with the CytoSorb® Adsorber; for those in the control group, the risks are no different to those of the standard treatment.

7. **How will the blood samples be processed and used?**
   The blood samples are collected using an arterial catheter that is already in place. No additional vessel puncture is necessary. Thus, no risks or pain can be expected from the collection. Under no circumstances will a medical procedure be affected or delayed by a blood collection. The first study-related blood collection takes place 1 hour after the CytoSorb® Adsorber has been integrated. Further collections take place 24, 48 and 72 hours after the integration. In the control group, collections take place 1 h, 24 h, 48 h and 72 h after the start of ECMO therapy.

8. **Which investigations are planned?**
   For the planned investigations, the blood samples and the blood cells, salts, proteins and messenger substances contained in it will be analysed. No other study-related investigations take place; however, some additional data obtained during routine treatment will be analysed as part of the study (e.g. survival time, ventilation time, dosage of medicines supporting the circulatory system etc.).

9. **What are the benefits of taking part in this research project?**
   We want to find out whether using the CytoSorb® Adsorber in patients with severe COVID-19 and ECMO contributes to the patients’ clinical stabilisation and thus also recovery. Treatment with the CytoSorb® Adsorber may improve patients’ survival - some research results indicate this. However, it is also possible that standard treatment results in better outcomes. Therefore, it cannot be predicted whether patients will individually benefit from taking part in the study.
No direct personal advantage or benefit for the patients can be expected from the planned analyses of blood samples and data. The results of these analyses are intended solely for research purposes and will not have any consequences for the person whose legal guardian you are or their treatment.

10. **Are there treatment alternatives?**

   Patients who require life support (ECMO) due to COVID-19 experience a very severe course of disease. The decision to use ECMO is taken only if invasive ventilation is insufficient to supply the patients’ blood with enough oxygen. As described under 9., patients may in this situation benefit from the additional treatment with the CytoSorb® Adsorber. As this is, however, still unclear, it is to be investigated in this study. Due to this uncertainty, use of the CytoSorb® Adsorber is planned to be investigated in patients with severe COVID and ECMO at our hospital as part of this study. Treatment with a CytoSorb® Adsorber is thus an addition to ECMO therapy; there are no established therapy alternatives.

11. **Is the confidentiality of the patient’s data ensured?**

   Yes. The data and analysis results recorded as part of this project will be scientifically analysed and archived pursuant to the applicable legal provisions, without making reference to the patients’ names. The personal data of the person whose legal guardian you are will be pseudonymised. Pseudonymisation of the personal data makes it significantly harder to identify data subjects, which is only possible with any certainty by using a list which links the pseudonym and the patient’s name. Pseudonymisation is performed directly on the raw data before any processing, so that only the pseudonyms can be found in all analyses. The decryption table will be stored under separate protection; only authorised study staff at the hospital treating the person whose legal guardian you are has access to this list.

   All study-relevant data are collected at the hospital treating the person whose legal guardian you are and processed and stored on this hospital’s PCs and servers. These servers are professionally protected from unauthorised access by way of multiple layers of security. Only authorised persons directly involved in this research project have access to this data.

   The data relevant for the study will subsequently be entered into the study database. The personal (medical) data regarding the person whose legal guardian you are is solely entered into the study database in pseudonymised form. This means that no unambiguous identifiers, such as the name or date of birth of the person whose legal guardian you are, are entered into the study database.

   The study database is located on a server at Freiburg University Hospital. The study coordinator at Freiburg University Hospital (Dr. Alexander Supady), his deputy as well as the staff of the Clinical Studies Centre responsible for conducting and analysing the study have access to the database and the coded (pseudonymised) patient data, but cannot decrypt the pseudonymous patient codes nor link them to the person whose legal guardian you are. Only the treating study staff at your hospital knows that this code is linked to the person whose legal guardian you are. All persons involved in data entry and analysis are bound by medical confidentiality.

   After the study has been completed, the results are planned to be (statistically) analysed and published in medical journals. The publications will not contain any data such as names or characteristics that might allow disclosing your relative’s identity.

   Furthermore, the study coordinator (Dr. Supady) may also, together with further research colleagues – possibly also from abroad – join the data from this study with data from other, similar studies, and analyse them together (so-called pooled analyses or meta-analyses of multiple studies). The goal of this would be to obtain even more reliable scientific findings, based on a larger number of patients. In that case, legislation on data protection will also be complied with, and solely pseudonymised or anonymised data will be used, i.e. the name of the person whose legal guardian you are will never be stated, and, outside of the treating hospital, no conclusions as to their identity can be drawn.

12. **Information about data protection rights**

   The data collected as part of the research project described herein is solely used for the implementation of this research project. The purpose of the research project is to investigate the use of the CytoSorb®
Adsorber for stabilising patients with severe COVID-19 requiring extracorporeal membrane oxygenation (ECMO).

The legal foundation for processing the data regarding the person whose legal guardian you are as part of this study is the consent provided by either the patient or you, which has been documented in writing in the Informed Consent Form (see also sections 3. and 4. for further information regarding informed consent). A further legal foundation for processing the data is the public interest in the area of public health (Art. 9 Para. 2 lit. i) GDPR [General Data Protection Regulation]).

Freiburg University Hospital acts as data controller as defined in legislation on data protection. The study coordinator at Freiburg University Hospital (Dr. med. Alexander Supady) as well as the study doctor at your site, [placeholder local site (placeholder local study doctor)] are jointly responsible as defined in data protection legislation for the data of the person whose legal guardian you are.

**Data controller’s name and contact details:**

<table>
<thead>
<tr>
<th>Freiburg location</th>
<th>Local site location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr. med. A. Supady</td>
<td>[placeholder local site]</td>
</tr>
<tr>
<td>Freiburg University Hospital</td>
<td></td>
</tr>
<tr>
<td>Department of Internal Medicine III</td>
<td></td>
</tr>
<tr>
<td>Hugstetter Str. 55,</td>
<td></td>
</tr>
<tr>
<td>79106 Freiburg i. Br.</td>
<td></td>
</tr>
<tr>
<td>Tel.: 0761 270-34010</td>
<td></td>
</tr>
</tbody>
</table>

**Storage duration**

The data collected during the study will be stored for 10 years after the completion of the study and will be deleted then.
Your data protection rights:
In the following, you will find information about the data protection rights of the person whose legal guardian you are pursuant to the EU General Data Protection Regulation (abbreviated as EU-GDPR) and the local legislation in Germany/Baden-Württemberg.

Right to information:
You have the right to request to be informed about the data regarding the person whose legal guardian you are that is processed as part of this clinical trial and to receive a copy of the data free of charge.

Right to rectification of data:
You have the right to request the rectification of the personal data regarding the person whose legal guardian you are if it should be incomplete or inaccurate.

Right to restriction of processing:
You have the right to request that the processing of the personal data regarding the person whose legal guardian you are be restricted.

Right to object (right of withdrawal pursuant to legislation on data protection):
You have the right to withdraw consent to the processing of the personal data regarding the person whose legal guardian you are, without stating any reasons.

Right to erasure of data:
You have the right to request that the personal data regarding the person whose legal guardian you are be erased.

The right to erasure of data and the right to object to the processing of already collected data are restricted because the loss of a patient’s data is not acceptable in view of the small sample size and the public interest in quick and reliable results (Art. 17 Para. 3c GDPR and Sec. 13 Para. 4 LDSG B-W [Data Protection Act of the State of Baden-Württemberg]).

Data protection officer’s contact details:
In case of any questions regarding data protection, please contact the competent data protection officer in writing or by email, using the following address:

Freiburg location
Freiburg University Hospital
Data Protection Officer
Breisacher Straße 153
79110 Freiburg i. Br.
Email: datenschutz@uniklinik-freiburg.de

Local site location
[placeholder local site’s data protection officer]

You furthermore have the right to lodge a complaint with a supervisory authority if you think the processing of the personal data regarding the person whose legal guardian you are violates the EU-GDPR. If applicable, you can lodge a complaint with the supervisory authority responsible for Freiburg University Hospital (study coordinator’s location) and for the [placeholder study site].
a. The supervisory authority responsible for the study coordinator at Freiburg University Hospital:

<table>
<thead>
<tr>
<th>State Officer for Data Protection and Freedom of Information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Street address:</strong> Königstrasse 10 a 70173 Stuttgart</td>
</tr>
<tr>
<td><strong>Postal address:</strong> PO box 10 29 32 70025 Stuttgart</td>
</tr>
<tr>
<td><strong>Tel.:</strong> 0711 61 55 41-0</td>
</tr>
<tr>
<td><strong>Fax:</strong> 0711 61 55 41-15</td>
</tr>
<tr>
<td><strong>Email:</strong> <a href="mailto:poststelle@lfdi.bwl.de">poststelle@lfdi.bwl.de</a></td>
</tr>
<tr>
<td><strong>Internet:</strong> <a href="http://www.baden-wuerttemberg.datenschutz.de">http://www.baden-wuerttemberg.datenschutz.de</a></td>
</tr>
</tbody>
</table>

b. The supervisory authority responsible for your study site:

13. **Will I be informed about the results of the research project?**
The results of the analysis are only used for research purposes. Therefore, the overall results of the research will be published as per the information provided in section 14. You can, of course, at any time receive information and findings about the treatment of the person whose legal guardian you are, provided this does not conflict with patient confidentiality.

14. **Can I end the participation of the person whose legal guardian I am in the research project early?**
You can at any time and without stating reasons end the participation of the person whose legal guardian you are without this resulting in any drawbacks for them. In case of a withdrawal, you can decide whether the stored data should be deleted.

15. **Scientific and commercial use of the research results**
The results of this research project will be published in scientific journals and at conferences. These publications will not contain any personal data that allow drawing conclusions as to the patients’ identities. The results may furthermore be used commercially; they may for instance be patented. The patients will not have any stake in a possible commercial profit.

16. **Further information**
If you have any further questions or requests regarding this research project, do not hesitate to contact your study doctor and their staff as well as the study coordinator at Freiburg University Hospital. You can reach us by phone or email using the contact details below.

Name of contact person: [placeholder contact details local study site]
xxx
xxx@xxx.de
Tel. xxx

Name and contact details of study coordinator at Freiburg University Hospital:
Dr. Alexander Supady
Study Coordinator, Consultant
alexander.supady@universitaets-hirzzentrum.de
0761 270-34010

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Informed Consent Form

I have read and understood the written information for legal guardians about the research project “CYCOV II study”. I have had the opportunity to receive further advice and information from a study staff member.

On behalf of the person whose legal guardian I am, I agree to their participation in the CYCOV II study.

Once the patient has regained their capacity to consent, the study team will have the conclusive informed consent discussion with the patient.

I have been informed about the data protection rights. I agree to the collection, processing and storage (in a special research database) of the data regarding the person whose legal guardian I am. I have been assured that the data will not be shared with third parties (except, if applicable, for the purpose of pooled analyses / meta-analyses as explained in section 11 of this Information Leaflet for Legal Guardians). It will be deleted at least 10 years after the completion of the research project.

Name of the legal guardian: ............................................................................................................

Patient’s name: ..............................................................................................................................

☐ Yes, I agree to the participation of the person whose legal guardian I am in the above-named research project.

☐ No, I do not agree to the participation of the person whose legal guardian I am in the above-named research project.

☐ Yes, the study team may contact me to enquire about the course of disease in the person whose legal guardian I am outside the hospital if the person whose legal guardian I am by then cannot be contacted themselves.

☐ No, I do not want to be contacted by the study team for questions regarding the course of disease in the person whose legal guardian I am after discharge from in-patient treatment.

Place, date Signature of the legal guardian

Place, date Informed consent discussion conducted by

Place, date Signature of the study doctor
Informed Consent Form

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Patient’s name: .................................................................................................................................

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Place, date Signature of the legal guardian

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Informed consent discussion conducted by .................................................................
Place, date Signature of the study doctor