INFORMED CONSENT AND AUTHORIZATION TO DISCLOSE HEALTH INFORMATION

Sponsor /Protocol Title	**NeuroRx, Inc / "RLF-100 Expanded Access for the Treatment of Critical COVID-19 with Respiratory Failure"**
Protocol Number:	**RLF-100-EA1** **NCT04453839**
Principal Investigator: **(Protocol Doctor)**	**«PiFullName»**
Telephone:	**«IcfPhoneNumber»**
Address:	**«PiLocations»**

INTRODUCTION

You (or your legally authorized representative named below) are being offered participation in this protocol because you have been diagnosed with Critical COVID-19 and Respiratory Failure. This means that the virus infection has caused damage to lung tissue and decreased the ability of your lungs to bring oxygen to your blood. As a result, your doctors have determined that you need high flow oxygen by nose or mask or a mechanical ventilator in order to breath. The purpose of this expanded access program is to offer you the opportunity to be treated with an experimental drug, RLF-100 (Aviptadil) which might improve the chance of surviving Critical COVID-19 and help the lung transmit oxygen to your blood. RLF-100 might also decrease the need for mechanical ventilation, shorten the course of hospitalization, and otherwise improve the outcome of COVID-19 in ways that could be meaningful to you. RLF-100 is being examined in an FDA phase 2/3 clinical trial where patients are randomly assigned to be treated with drug or placebo. However, either because of your medical condition or your physical location, you are not a candidate for the clinical trial and the US FDA has given your doctors and NeuroRx the ability to offer RLF-100 treatment to you in an "Expanded Access Protocol" where there is no placebo.

Although this consent form is written to you as the patient, we recognize that given the nature of COVID-19 (patients) it may be necessary for your legally-authorized representative to sign on your behalf. In that case, pronouns “you” and “your” should be read as referring to you, the patient rather than the person (legally authorized representative) who is signing and dating this form for the patient. If your representative gives consent on your behalf, he/she will inform you about your participation in this program to the extent possible given your medical condition.

If this consent is initially signed and dated by a legally authorized representative and you regain the capacity to consent, this informed consent is being offered and explained to you so that you can make the decision to continue or discontinue participation in the protocol.

This consent document describes the purpose, procedures, benefits, risks, discomforts and precautions of the protocol. It also describes the alternative procedures that are available to you and your right to withdraw from the protocol at any time. You should consent to participate in this protocol only if you want to. No guarantees or assurances can be made as to the results of the protocol.

Before any protocol-related tests and procedures are performed, you will be asked to read, sign and date this consent document. If there are words or procedures in it that you do not understand, please ask protocol doctors or protocol staff to explain. Please ask as many questions as you need to. You should not sign and date this form if your questions have not been answered to your satisfaction.

BACKGROUND AND PURPOSE

The purpose of this protocol is to:

- Offer the potential medical benefits of RLF-100 – which are not yet proven – to you in the hope that RLF-100 will help you recover from acute respiratory failure, a condition which currently threatens you life and your health.
- To determine whether RLF-100 is safe and is tolerated by patients with Critical COVID-19 whose medical condition disqualifies them from participation phase 2/3 trials of RLF-100
- We will be comparing your progress and outcomes to patients with medical conditions similar to yours who did not receive RLF-100. However this is not a randomized research study where you might receive placebo instead.

Critical COVID-19 with respiratory failure is a life threatening condition. The SARS-CoV-2 coronavirus that causes COVID-19 attacks the air sacs in the lungs and damages the delicate cells that line those air sacs. Because of this damage, oxygen that is required to sustain life cannot pass from the lung to the blood. Therefore, the organs of the body, including the kidneys, heart, and brain, cannot get enough oxygen to work. People with Critical COVID-19 and respiratory failure cannot get enough oxygen from room air and require extra oxygen (ventilation), delivered either by a tube in the nose, a mask on the face, or a tube in the throat in order to survive. In many cases, Critical COVID-19

causes serious damage to other organs of the body – especially the kidney and the heart, which leads to death. Even with high oxygen ventilation, many people with Critical COVID-19 may die of the disease.

In a study of 45 patients conducted at a major US hospital, the 21 patients who received RLF-100 were statistically 9 times more likely to survive and to recover from respiratory failure than were the 24 comparison patients who received the standard of care in the same intensive care unit. However, some patients who received RLF-100 did not survive long term or recover from respiratory failure. There is no guarantee that if you are treated with RLF-100 it will achieve this benefit for you.

A previous research protocol showed that when Aviptadil was given to eight patients with Acute Respiratory Distress Syndrome (ARDS) caused by bacterial infection, seven patients showed improvement and six of those patients left the hospital alive. There were no serious side effects seen. Aviptadil has also been seen in studies of other lung disease to reduce signs of inflammation. Aviptadil is known to cause a lowering of blood pressure, which can be managed by either by reducing the dose or by giving medicines to raise blood pressure. Aviptadil is also known to cause facial flushing, diarrhea or uncontrollable bowel movements. Aviptadil (RLF-100) has not been approved by the U.S. Food and Drug Administration (FDA). Its use is experimental in this protocol.

A randomized placebo-controlled trial of Aviptadil is underway that has enrolled more than 130 patients. In that trial, no drug-related serious adverse effects were seen and an independent data safety board determined that the trial should continue with a clear possibility that a difference between RLF-100 and placebo will be seen.

There is a large amount of information from studies in animals and in human patients that Aviptadil is safe. Aviptadil is a manmade form of “Vasoactive Intestinal Peptide” or VIP that is made normally in the human body and in the body of all warm-blooded animals. It has been proven safe for both short term and long term use in mice, rats, dogs, and monkeys. It has been given to many human volunteers and used in five prior studies of patients with other lung diseases without harm to patients. Aviptadil is sold as a registered drug in Europe for a different medical condition.

In this protocol, patients who test positively for the SARS-CoV-2 corona virus and have a diagnosis of Critical COVID-19 with respiratory failure will be treated with IV (intravenous, or into a vein) RFL-100 (Aviptadil) while receiving either high flow oxygen by nose, high pressure oxygen by mask, or mechanical ventilation with an endotracheal tube (in the throat).

Because there is no placebo arm, you will be certain to receive treatment with Aviptadil. The FDA may allow NeuroRx to charge its costs of making and distributing Aviptadil, without making any profit. If so, a charge for Aviptadil may appear on your hospital bill.

INDEPENDENT DATA MONITORING COMMITTEE

The safety of the patients in this protocol will be reviewed by an independent committee, not connected to the pharmaceutical company or the hospital whose only concern is for the your safety and the safety of all patients in this protocol. The members of this committee have no financial connection to NeuroRx.

PROCEDURES

Only after you have agreed (consented) to participate in this protocol, Aviptadil will be given to you through the intravenous tubes already in place so there is no additional discomfort to you from administration of the protocol drug.

An infusion of Aviptadil will be given each day for 3 days. Your doctor might decide to give less drug, based on your medical response.

All patients in the protocol will receive the best standard of care, with monitoring of oxygen levels, electrolytes, vital signs, heartbeat and other measurements that are part of normal care in the hospital.

Informed Consent for Patients

You may be asked to sign and date this consent on paper, electronically, or by speaking your consent in front of a witness.

RISKS, SIDE EFFECTS AND/OR DISCOMFORTS

The protocol procedures are designed to limit risks to the patient's health and limit discomfort as much as possible. Your safety is monitored closely throughout the protocol.

But we need to state that there is a possibility that symptoms may not improve and could even worsen if you consent for the patient to take part in this protocol.

Known risks of Aviptadil

Aviptadil is a naturally-occurring substance that is made in your lungs and has now been given to more than 10,000 patients for various medical conditions both within protocols supervised by FDA and/or European regulatory authorities and in some cases when prescribed by doctors and dispensed by pharmacies under US State laws.

Two side effects are well known when high doses of Aviptadil are administered for treatment of COVID-19 Respiratory Failure:

1. Aviptadil is known to lower blood pressure. This is a side effect that your doctors are well-aware of and there are various medicines that they may give in the intensive care unit to address this issue. Reduced blood pressure has not been seen to cause adverse events in the phase 2/3

trials of Aviptadil.

2. Aviptadil is known to cause diarrhea (loose bowel movements) in some patients. This side effect is similarly well known to your doctors and the standard care in the ICU is able to address this side effect if it occurs.

PREGNANCY

If you are pregnant and choose to participate in this protocol, you must understand that the potential risks to a pregnant woman, an embryo, fetus (unborn baby) or nursing infant are simply not known for Aviptadil. Therefore, if you are pregnant, you are consenting both on your behalf and on behalf of your unborn child because of the known serious nature of your respiratory failure and the lack of other alternative treatment.

ALTERNATIVE TREATMENT

If you do not consent to this protocol, you will receive the best available standard of intensive care.

NEW FINDINGS

Any important new information that is discovered during the protocol which may change your willingness to allow the patient to continue participation in the protocol will be provided to you.

BENEFITS

You may derive medical benefit as a result of your participation in this protocol. There is, however, no guarantee that Aviptadil will be effective in helping to relieve your acute Respiratory Failure. Results from this protocol may benefit others in the future.

COMPENSATION FOR PARTICIPATION

There is no compensation for participation in this protocol.

CONFIDENTIALITY

Records of the patient's participation in this protocol will be strictly confidential and your will never be retained by anybody in the pharmaceutical company or connected research organizations. The protocol doctor, the sponsor or persons working on behalf of the sponsor, and under certain circumstances, the United States Food and Drug Administration (FDA) and the Institutional Review Board (IRB) will be able to inspect and copy confidential protocol-related records which identify you by name. However, US law requires such personnel to comply with all privacy provisions of the Health Insurance Portability and Accountability Act and the National Institutes of Health regulations regarding the protection of human patients. Copies of these laws will be given to you if you request.

COMPENSATION FOR INJURY

The expanded access protocol is being offered to you for your benefit and you are not an experimental subject as part of this protocol. Therefore, treatment under this protocol is at your own risk.
So far, no patient is known to have been injured or otherwise harmed by Aviptadil. If you are injured or otherwise harmed as a result of taking Aviptadil under this expanded access protocol drug or from procedures done for the purpose of this protocol, NeuroRx Inc. will not pay compensation for any injury or other harm.

By agreeing to the above, you are not waiving any of your legal rights or releasing NeuroRx, the Investigator, the protocol staff, or protocol site from liability for mistakes or intentional misconduct.

A new public health declaration, called the Public Readiness and Emergency Preparedness Declaration (PREP), was issued by the Department of Health and Human Services on March 10, 2020. This declaration limits the legal rights of a subject participating in a COVID-19 clinical protocol that uses a drug, device or vaccine designed to treat, diagnose, cure or prevent COVID-19. This includes the protocol Aviptadil (RLF-100) used in this protocol. Subjects using Aviptadil (RLF-100) in this protocol will have limits on their right to sue the manufacturers, the protocol sponsor, healthcare providers and others for significant injuries and adverse reactions.

COSTS

The FDA may allow NeuroRx to charge its costs of making and distributing Aviptadil, without making any profit. If so, a charge for Aviptadil may appear on your hospital bill.

WHOM TO CONTACT ABOUT THIS PROTOCOL

During the protocol, if you experience any medical problems, suffer a research-related injury, or if you have questions, concerns or complaints about the protocol, please contact the protocol doctor at the telephone number listed on the first page of this consent document.

An institutional review board (IRB) is an independent committee established to help protect the rights of research subjects. If you have any questions about the subject's rights as a research subject, and/or concerns or complaints regarding this research protocol, contact:

- By mail:
  Protocol Subject Adviser
  Advarra IRB
  6940 Columbia Gateway Drive, Suite 110
  Columbia, MD 21046
- or call **toll free**: 877-992-4724

- or by **email**: adviser@advarra.com

Please reference the following number when contacting the Protocol Subject Adviser: Pro00043143.

A description of this expanded access protocol will be available on http://www.ClinicalTrials.gov, as required by U.S. Law This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

VOLUNTARY PARTICIPATION / WITHDRAWAL

Your decision to consent for the subject to participate in this protocol is voluntary. You may choose for the subject to not participate, or you may withdraw the subject from the protocol for any reason without penalty or loss of benefits to which the subject is otherwise entitled and without any effect on the subject's future medical care.

The Investigator or the sponsor can stop your participation at any time without your consent for the following reasons:

- If it appears to be medically harmful to you;
- If you decide to withdraw your consent;
- If it is discovered that you do not meet the protocol requirements;
- If the protocol is canceled; or
- If there is a temporary unavailability of RLF-100 or logistical failure in delivering it to your site of care.

If you leave the protocol for any reason, the Investigator may ask you to have some end-of-protocol tests for your safety.

PRIMARY CARE PHYSICIAN / SPECIALIST NOTIFICATION OPTION

Please indicate below whether you want us to notify the subject's primary care physician or their specialist of their participation in this protocol.

_____ Yes, I want the Investigator to inform the subject's primary care physician/specialist of the subject's participation in this protocol.

_____ No, I do not want the Investigator to inform the subject's primary care physician/specialist of the subject's participation in this protocol.

_____ The subject does not have a primary care physician/specialist.

_____ The Investigator is the subject's primary care physician/specialist.

CONSENT

I have read and understand the information in this informed consent document. I have had an opportunity to ask questions and all my questions have been answered to my satisfaction. I voluntarily agree to participate in this protocol until I decide otherwise. I do not give up any of my legal rights by signing and dating this consent document. I will receive a copy of this signed and dated consent document.

_____
Subject's Printed Name

_____ _____
Subject Signature Date

_____
Printed Name of Person Conducting the Consent Discussion

_____ _____
Signature of Person Conducting the Consent Discussion Date

CONSENT for Legally Authorized Representatives

Since the person for whom you are consenting is not able to give consent, the law allows us to ask you to consent as the Legally Authorized Representative (LAR). During the COVID-19 epidemic non-patients are barred from hospital grounds. Therefore, we may provide you with an electronic form to use in giving consent or the entire Consent Form may be read to you over the phone. Your signature may be obtained via an SMS text message, special electronic systems such as REDCap, or DocuSign. Consent will be documented by a witness who signs and dates the consent form, to be kept on file together with telephonic signature or DocuSign.

If it is not possible to obtain a digital image of the signed and dated page, the protocol team will document that an imaging device was not available and have a witness to the consent process. The entire consent process will be documented in the protocol records.
Under these circumstances, having a witness to the consent process will be part of the consent process.

_____
Subject's Printed Name

_____
Printed Name of Legally Authorized Representative

_____ _____
Signature of Legally Authorized Representative Date

_____
Printed Name of Person Conducting the Consent Discussion

_____ _____
Signature of Person Conducting the Consent Discussion Date

IF No Physical Record of consent by Legally Authorized Representative

_____
Printed Name of Witness to Consent by Legally Authorized Representative

_____ _____
Signature of Witness Date

AUTHORIZATION TO USE AND DISCLOSE PROTECTED HEALTH INFORMATION

This form is for use in a research protocol that may involve subjects who may or may not have the capacity to consent to take part in the protocol. When the subject cannot legally consent to take part, pronouns “you” and “your” should be read as referring to the subject rather than the person (legally authorized representative) who is signing this form for the subject. In cases where the subject’s representative gives consent or authorization, the subject should be informed about the protocol to the extent possible given his/her understanding. During the course of the protocol, if the subject regains the capacity to consent, informed consent will be obtained from the subject and the subject offered the ability to leave the protocol if desired.

During your participation in this research protocol, the Investigator and protocol staff will collect or create personal health information about you (for example, medical histories and results of any tests, examinations or procedures you undergo while in the protocol) and record it on protocol documents. The Investigator will keep this personal health information in your protocol-related records (that we will refer to as "your protocol records"). In addition, the Investigator may obtain, and include in your records, information regarding your past, present and/or future physical or mental health and/or condition. Your Investigator may ask you to sign a separate authorization to obtain some or all your medical records from your doctor. Your protocol records may include other personal information (such as social security number, medical record numbers, date of birth, etc.), which could be used to identify you. Health information that could identify you is called "Protected Health Information" (or "PHI").

Under federal law (the "Privacy Rule"), your PHI that is created or obtained during this research protocol cannot be "used" to conduct the research or "disclosed" (given to anyone) for research purposes without your permission. This permission is called an "Authorization". Therefore, you may not participate in this protocol unless you give your permission to use and disclose your PHI by signing this Authorization. By signing, you are agreeing to allow the Investigator and staff to use your PHI to conduct this protocol. Information may include psychiatric, medical, psychological or neuropsychological evaluations, reports, consultations, recommendations and treatments that include medication, social, educational and family

history, and pharmacy records to be reviewed for the purpose of determining protocol eligibility and ongoing treatment for your physical and mental health condition(s).

By signing and dating this Authorization, you also are agreeing to allow the Investigator to disclose PHI as described below:

- The sponsor of this protocol and anyone working on behalf of the sponsor to conduct this protocol (referred to as "the sponsor"). The sponsor will analyze and evaluate the PHI and may use it to develop new tests, procedures and commercial products. The protocol staff will assign a code number and/or letters to your records, which means that you will not ordinarily be identified in the records sent to the sponsor. The sponsor may, however, look at your complete protocol records that identify you. In addition, the sponsor may visit the protocol site to oversee the way the protocol is being conducted and may review your PHI during these visits to make sure the information is correct.
- The Institutional Review Board ("IRB") may have access to your PHI in relation to its responsibilities as an Institutional Review Board.
- Your insurance company
- The U.S. Food and Drug Administration (FDA)
- Other regulatory agencies

The Investigator or sponsor may disclose your PHI to the United States Food and Drug Administration ("FDA") or similar regulatory agencies in the United States and/or foreign countries.

These disclosures also help ensure that the information related to the research is available to all parties who may need it for research purposes.

Except for the disclosures described above, your PHI will not be shared with others unless required by law. If your PHI is given to the parties listed above and/or to others who are not required to comply with the federal law, your PHI will no longer be protected by this law and could possibly be used or disclosed in ways other than those listed here.

You have a right to see and make copies of your PHI. You are agreeing, however, by signing and dating this document, not to see or copy some or

all your PHI until the sponsor has completed all work related to this protocol. At that time, you may ask to see your records.

This Authorization will expire 50 years from the date you sign it unless you revoke (cancel or withdraw) it sooner.

You have a right to revoke your Authorization at any time. If you revoke it, your PHI will no longer be used for this protocol, except to the extent the parties to the research have already acted based upon your Authorization or need the information to complete analysis and reports for this research. To revoke your Authorization, you must write to the Investigator, stating that you are revoking your Authorization to Use and Disclose Protected Health Information. If you revoke this Authorization, you will not be allowed to continue to be in this protocol.

You will receive a copy of this Authorization after you have signed and dated it.

_____
Printed Name of Subject

_____ _____
Subject Signature Date

_____
Printed Name of the Person Obtaining the Authorization

_____ _____
Signature of Person Obtaining the Authorization Date

Authorization for Legally Authorized Representatives

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Subject's Printed Name

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Printed Name of Legally Authorized Representative

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Signature of Legally Authorized Representative Date

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Printed Name of Person Conducting the Consent Discussion

_____ _____
Signature of Person Conducting the Consent Discussion Date

IF No Physical Record of consent by Legally Authorized Representative

_____

Printed Name of Witness to Consent by Legally Authorized Representative

_____ _____

Signature of Witness Date