RUTGERS
New Jersey Medical School

Department of Neurological Surgery
Rutgers, The State University of New Jersey
90 Bergen Street, Suite 8100
Newark, NJ 07103

CONSENT TO TAKE PART IN A RESEARCH STUDY

Title of Study: Aggrenox in Treatment of Patients with COVID-19: A Randomized Controlled Trial.

Principal Investigator: Amit Singla, MD, FAANS

STUDY SUMMARY: This consent form is part of an informed consent process for a research study and it will provide information that will help you decide whether you want to take part in this study. It is your choice to take part or not.

The **purpose of the research** is to: explore the efficacy of Aggrenox (Aspirin-Dipyridamole) in patients with SARS-CoV-2 infection with symptoms consistent with COVID-19.

If you take part in the research, you will be asked to be a part of one of the 2 groups based on randomization; one group, the treatment group, will be given Aggrenox capsule twice a day in addition to standard care for COVID treatment and other group, the Standard care Comparator group will not be getting any additional drug apart from the standard care for COVID infection.
The patients in the treatment group will receive Aggrenox (Dipyridamole ER 200mg/ Aspirin 25mg orally), 2 times daily (FDA–recommended dose) starting on the day of enrollment for a total of 2 weeks + standard care. You will be given this medication for a total of 2 weeks after enrollment. During the hospital stay, you will be checked by the research coordinator to follow your symptoms and will get the labs and swabs done, which are part of your care for COVID infection. Once discharged, you will be called on day 15 and day 28 by the research coordinator to follow up on your symptoms. This intervention for COVID patients is experimental, based on the literature evidence that COVID patients have higher tendency to form clots in blood vessels, and can also have an overblown response to the COVID infection call an inflammatory response. This medication is designed to prevent inflammation and blood clots.
Patients in the Standard care Comparator group will receive standard care starting on the day of enrollment for a total of 2 weeks.

Possible harms or burdens of taking part in the study may be increased risk of bleeding, Gastrointestinal (GI) Side Effects such as nausea, vomiting, painful or difficult digestion, ulcer, GI bleeding. Chest pain could occur in patients with existing diseases of the blood vessels of the heart, low blood pressure, or an allergy to the drug You may feel discomfort and/or pain during some of the tests or procedures in the study. Your condition may not improve and could even worsen if you take part in this study.
Possible benefits of taking part may be that the group that receives Aggrenox (Aspirin-Dipyridamole) could do better, such as having a decreased risk of death, cut down the chance of needing the ventilator, a machine that helps you breathe, and less time in the hospital.
Information learned from the study may help other people in the future. However, it is possible that you will not receive any direct personal benefit from taking part in this study.

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An alternative to taking part in the research study: Your alternative to taking part in the research study is not to take part in it.

The information in this consent form will provide more details about the research study and what will be asked of you if you choose to take part in it. If you have any questions now or during the study, if you choose to take part, you should feel free to ask them and should expect to be given answers you completely understand. After your questions have been answered and you wish to take part in the research study, you will be asked to sign this consent form. You are not giving up any of your legal rights by agreeing to take part in this research or by signing this consent form.

Who is conducting this study?
Amit Singla, MD is the Principal Investigator of this research study. A Principal Investigator has the overall responsibility for the conduct of the research. However, there are often other individuals who are part of the research team.

Amit Singla, MD may be reached at
Address:
DOC 8th Floor
90 Bergen Street, Newark, NJ
07013
Phone: 9739725633

The Principal investigator or another member of the study team will also be asked to sign this informed consent. You will be given a copy of the signed consent form to keep.

Sponsor of the Study: Amit Singla, MD is the sponsor-investigator (the physician in charge) of this research study. He works at the New Jersey Medical School. **Boehringer Ingelheim Pharmaceuticals Inc.** (BIPI) is the funding source for the study and supplying Aggrenox (Aspirin-Dipyridamole) (study drug) for this study and may request access to study records.

Why is this study being done?
Coronavirus disease 2019 (COVID-19) is a lung illness that can spread from person to person. The virus that causes COVID-19 is a novel coronavirus that was first identified during an investigation into an outbreak in Wuhan, China. There is currently no FDA approved treatment for COVID-19.
The purpose of the research is to determine if the addition of Aggrenox (Aspirin-Dipyridamole) to your standard of care treatment can improve symptoms in patients with COVID-19. The use of Aggrenox (Aspirin-Dipyridamole) has not been approved by the FDA for treatment of COVID-19 and is experimental in this study.

Since we do not know which study treatment is better, we will compare the study groups. A computer will assign you to one of two groups in the study. This is called randomization and is done by chance like the flipping of a coin. One group will receive Aggrenox (Aspirin-Dipyridamole) and the other will not. Neither you nor the study doctor will choose the group you get.

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Aggrenox (Aspirin-Dipyridamole) is approved by the Food and Drug Administration (FDA) to reduce the risk of having a stroke in people who have already had a “mini-stroke” or a stroke because of a blood clot.

Who may take part in this study and who may not?

Inclusion Criteria:

1. You are 18 years of age or older
2. You are hospitalized for SARS-CoV-2 infection and exhibiting symptoms of COVID-19
3. Positive lab test for SARS-CoV-2 infection within 3 days of hospitalization.
4. Lab test results that are pending along with a high suspicion for SARS-CoV-2, such as having a fever and cough, an abnormal chest x-ray, or suffering from a lack of oxygen.
5. Willing and able to provide consent.

Exclusion Criteria:

1. Pregnancy.
2. History of G-6PD deficiency (an inherited disorder in which a person does not have enough of an enzyme called **G6PD** that helps red blood cells work the way they should).
3. Use of medicines that prevent blood clots from forming.
4. Extremely low blood pressure.
5. Patient with known ongoing chest pain, recent heart attached and defects of the heart.
6. Active ulcers or any bleeding disorder or kidney problems
7. Lab results the show low red blood cells, or low that your blood does not clot quickly.
8. A lung infection that has lasted more than 10 days.
9. Known allergy to medications that make-up Aggrenox, Dipyridamole and/or Aspirin.
10. Severe liver problems
11. Uncontrolled high blood pressure.
12. History of chronic, heavy alcohol use
13. Patients with known allergy to Advil or Motrin or similar medication
14. Patients enrolled in other COVID treatment clinical trials.

Why have I been asked to take part in this study?
You have been asked to participate in this study because you have been diagnosed with COVID-19 infection or are highly suspicious for COVID-19 infection while the swab test results are pending.

How long will the study take and how many subjects will take part?
Participants will be screened, enrolled, receive treatment and followed for 28 days. Study participants in the treatment group will be treated for fourteen (14) days and will then remain on follow-up for up to 4 weeks (28 days) after the completion of treatment.

The study will be conducted over approximately 24 months: 6-8 months for enrollment (anticipated) and follow-up/data collection (anticipated) and 18 months for specimen processing and analysis, and data analysis.

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What will I be asked to do if I take part in this study?

Study Procedures:

Day 0 – Screening Visit – many of the screening procedures will have been performed as part of your regular hospital inpatient care:

- Obtain informed consent for trial enrollment
- From your medical record we will obtain:
  - Information about you, such as race, ethnicity, gender, age
  - Medical history
  - Physical examination
  - Vital signs (blood pressure, heart rate, temperature)
  - An Electrocardiogram (ECG) (An ECG is a test which activity of your heart to show whether or not it is working normally)
  - Labs: including complete blood count, chemistry, clotting time, and blood tests that indicate how your heart is functioning
- If the "Screening Visit Procedures" show you are eligible to enter this study and you agree to take part, you will be randomized (like the flipping of a coin) to one of two of the Arms (groups). Either the treatment group to receive Aggrenox (Aspirin-Dipyridamole) plus the standard COVID treatment, or the standard care comparator group which will receive the standard COVID treatment.
- For research purposes we will collect samples for SARS-CoV-2 PCR laboratory testing, including saliva, an oral swab, a nasal swab, and a pharyngeal swab, and sputum, which is mucus coughed up from your lungs

Treatment Period –Days 1 - 14

Treatment Group:

- You will receive Aggrenox (Aspirin-Dipyridamole) twice per day, one capsule in the morning and one capsule in the evening, for 14 days
- During this period, we will meet with you to discuss any side-effects that you might experience from taking Aggrenox (Aspirin-Dipyridamole)

Treatment and Standard care comparator groups:

- We will meet with you to discuss how you are doing.
- From your medical record we will obtain:
  - Review of daily temperatures
  - Review of medications and treatments
  - Labs: including complete blood count, chemistry, clotting time, and blood tests that indicate how your heart is functioning
- For research purposes we will collect samples for SARS-CoV-2 PCR laboratory test on Day 7 and Day 14; including
  - saliva, an oral swab, a nasal swab, and a pharyngeal swab, and sputum
  - Urine samples will be collected on day 1 and day 14.

Follow-up Period Days 15 - 28

- If you are still in the hospital, we will:
  - Meet with you to discuss how you are doing.
  - We will collect from your medical record:
    - Review of daily temperatures
    - Review of medications and treatments
- If you have been discharged, we will call you throughout the period to ask how you are doing.

What are the risks of harm or discomforts I might experience if I take part in this study?
You may have side effects while on this study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors do not know all the side effect that may happen. Side effects may be mild or very serious. Your study doctor may give you medicines to help lessen side effects. Your study doctor may also decide that it is necessary to delay or stop the study treatment. Many side effects go away soon after you stop taking the drugs. In some cases, side effects can be serious, long lasting, or never go away. You should talk with your study doctor about any side affects you may have while taking part in the study.

- **Risk of Bleeding**
  AGGRENOX (Aspirin-Dipyridamole) (the study drug) increases the risk of bleeding.
  If you are on other blood thinner drugs such as Coumadin/Warfarin, therapeutic Heparin, Plavix/Clopidogrel, Brilinta, Eliquis, the risk of bleeding from Aggrenox (Aspirin-Dipyridamole) increases. This risk is less than 5% based on the studies.
- **Gastrointestinal (GI) Side Effects**
  You can have GI side effects such as stomach pain, heartburn, nausea, vomiting, and gross GI bleeding. Minor upper GI symptoms, such as dyspepsia, are common and can occur anytime during therapy; if they happen and can be tolerated with or without the addition of anti-acidity medications such as Pepcid, you will be requested to continue to be in the study group. You will be monitored closely for signs of ulceration and bleeding, even in the absence of previous GI symptoms. If the serious GI bleeding happens or the GI ulcer is diagnosed during the study, the study drug will be discontinued. This risk is less than 5% based on the studies.
- **Peptic Ulcer Disease**
  If you have a history of gastric/ intestinal ulcer, please let the study team know and you will not be included in the study due to a higher risk of bleeding.
- **Alcohol Warning**
  Due to the bleeding risk involved, if you have a history of chronic, heavy alcohol use, you will not be included in the study as a study participant.
- **Coronary Artery Disease**
  The study drug component Dipyridamole has a vasodilatory effect and it may precipitate chest pain if you have an underlying disease of the blood vessels of the heart. If you have a recent/recurrent heart attack or unstable angina (recurrent chest pains related to heart), you will not be included in the study as a study participant.
- **Hypotension**
  If you have a history of low blood pressure, the study drug may worsen pre-existing hypotension (low blood pressure). You will be closely watched for the change in blood

pressure after starting the study drug and if your blood pressure becomes too low and if deemed significant by the study team, you will be removed from the study as a study participant.

- **Stress Testing with Intravenous Dipyridamole and Other Adenosinergic Agents (e.g. adenosine, regadenoson)**

If while you are taking Aggrenox (Aspirin-Dipyridamole), you should need to have a stress test, we will temporarily stop your Aggrenox (Aspirin-Dipyridamole) treatment 48 hours prior to your scheduled stress test.

Risk of Harm from an Intervention on a Subject with an Existing Condition

- **Renal Failure**
  If you have a history of severe kidney failure you will not be included in the study as a study participant.
- **Liver Insufficiency**
  If you have a history of severe liver failure you will not be included in the study as a study participant.

Other Foreseeable Risks of Harm
One potential risk from being a study participant is loss of confidentiality of your health information. We have taken several steps to minimize the probability of this risk to you.

Reproductive Risks of Harm

Available data from published studies and post marketing experience with AGGRENOX (Aspirin-Dipyridamole) use during pregnancy have not identified a clear association between AGGRENOX (Aspirin-Dipyridamole) use and major birth defects, miscarriage, or adverse maternal or fetal outcomes.
All women of child bearing potential involved in the study must use one of the approved methods of contraception or be abstinent from sexual intercourse for the duration of study. Likewise, for men with partners of child bearing potential should notify their partners about taking study drug and either be abstinent from sexual intercourse for the duration of study or use one of the approved methods of contraception.

Other risks/ cautions:
You should not take any new over-the-counter medicines, herbal products, vitamins or food supplements while taking part in this study, unless you tell the study doctor and get permission from the study doctor to go on taking these medicines. You will follow the instructions of the study doctor about the use of any of these products.

You should also tell the study doctor about all medicines that other doctors may have prescribed for you to take.

Are there any benefits to me if I choose to take part in this study?
The benefits of taking part in this study may be better clinical outcomes in the group which receive Aggrenox (Aspirin-Dipyridamole) such as decreased risk of mortality, decreased risk of needing the ventilator, reduced hospital stay. Dipyridamole has been shown to have some

benefit in a small series of COVID-19 patients in an unpublished study from China. However, it is possible that you may not receive any direct benefit from taking part in this study.

Data gathered from this study may allow us to identify an effective treatment for COVID-19 that could result in benefit to the patients or society as whole in the future.

What are my alternatives if I do not want to take part in this study?
There are no alternative treatments available. Your alternative is not to take part in this study. You may receive supportive care outside of this study.

How will I know if new information is learned that may affect whether I am willing to stay in the study?
During the study, you will be updated about any new information that may affect whether you are willing to continue taking part in the study. If new information is learned that may affect you after the study or your follow-up is completed, you will be contacted.

Will I receive the results of the research?
In general, we will not give you any individual results from the study except the details that pertain to your condition. You will receive the COVID-19 results. If we find something of urgent medical importance to you, we will inform you, although we expect that this will be a very rare occurrence. For example, 'unusual findings on the blood test that we think you should discuss with your doctor.

Will there be any cost to me to take Part in this study?
The drugs used in this study are commercially available. The study drugs will be provided at no charge by the BI pharmaceutical company. You and/or your health insurance company will not be billed for the cost of any research procedures, which are conducted as part of this study.

If you are hospitalized and being treated for COVID-19 symptoms, this is standard of care. You and/or your health insurance will be responsible for the cost of the hospitalization, standard of care tests and/or procedures and any co-pays related to your hospitalization or emergency department visit.

Will I be paid to take part in this study?
You will not be paid to take part in this study.

How will information about me be kept private or confidential?
All efforts will be made to keep your personal information in your research record confidential, but total confidentiality cannot be guaranteed.

Information about your condition and treatment will be collected from your medical record for the study. The information will be with a study identification number and stored in a secured electronic file. The electronic file is password protected and accessible only to authorized study personnel.

If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

A description of this clinical trial will be available on ClinicalTrials.gov, as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

What will happen to my information or biospecimens collected for this research after the study is over?
All specimens including oral-nasopharyngeal swabs, saliva, sputum and urine will be used to address the study objectives. The specimens will be collected and analyzed during your treatment, and some samples will be stored for the duration of the study. The study will be conducted over approximately 24 months: 6-8 months for enrollment (anticipated) and follow-up/data collection (anticipated) and 18 months for specimen processing and analysis, and data analysis.

Any unused specimens will be discarded at the conclusion of the study.

If you decide to withdraw from the study, your specimens will be discarded as per the laboratory policy.

What will happen if I am injured during this study?
Subjects in this study may be exposed to certain risks of personal injury in addition to those associated with standard forms of treatment. In addition, it is possible that during the course of this study, new adverse effects that result in personal injury may be discovered.
If you get ill or are injured as the direct result of being in this study inform your study doctor as soon as possible. The Institution will make appropriate referrals for treatment. The Study Sponsor shall reimburse all the reasonable and necessary costs of diagnosis and treatment of any Study subject injury, including hospitalization, if it:

(a) Is not a medical condition that you had before you started the study;
(b) Is not the result of the natural progression of your disease or condition;
(c) Is not caused by your failure to follow the study plan; and
(d) Is not proved to be directly caused by the Institution's negligence or misconduct.

There are no other plans for the University to provide other forms of compensation (such as lost wages) to you for research related illnesses or injuries.

What will happen if I do not wish to take part in the study or if I later decide not to stay in the study?
It is your choice whether to take part in the research. You may choose to take part, not to take part or you may change your mind and withdraw from the study at any time.

If you do not want to enter the study or decide to stop taking part, your relationship with the study staff will not change, and you may do so without penalty and without loss of benefits to which you are otherwise entitled.

You may also withdraw your consent for the use of data already collected about you, but you must do this in writing to

Amit Singla, MD
Address:
DOC 8th Floor
90 Bergen Street, Newark, NJ
07013
Phone: 9739725633

Any data that has already been sent to the Data Coordinating Center cannot be withdrawn because there may not be any identifiers with the data.

If you decide to withdraw from the study for any reason, you may be asked to return for at least one additional visit for safety reasons.

If you decide to withdraw from the study, with your permission, your specimens will be discarded as per the laboratory policy.

Who can I contact if I have questions?
If you have questions about taking part in this study or if you feel you may have suffered a research related injury, you can contact the Principal Investigator:
Amit Singla, MD
Address:
DOC 8th Floor
90 Bergen Street, Newark, NJ
07013
Phone: 9739725633

If you have questions about your rights as a research subject, you can contact the Rutgers IRB Director at Newark HealthSci IRB, 65 Bergen St., SSB 511, Newark, NJ 07107, (973)-972-3608.

PERMISSION (AUTHORIZATION) TO USE OR SHARE HEALTH INFORMATION THAT IDENTIFIES YOU FOR A RESEARCH STUDY

The next few paragraphs tell you about how investigators want to use and share identifiable health information from your medical record in this research. Your information will only be used as described here or as allowed or required by law. If you sign this consent form, you agree to let the investigators use your identifiable health information in the research and share it with others as described below. Ask questions if there is something you do not understand.

What Is The Purpose Of The Research And How Will My Information Be Used?
You are being invited to take part in this research study which is described at the beginning of this form. The purpose of collecting and using your health information for this study is to help investigators answer the questions that are being asked in the research.

What Information About Me Will Be Used?

- All information in your medical record
- Hospital discharge summaries
- Medical history or treatment
- Medications and their effects
- Consultations
- Laboratory/diagnostic tests or imaging
- EKG/ echocardiogram reports
- Pathology/ Microbiology reports
- Emergency Medicine reports

Who May Use, Share or Receive My Information?

The research team may use or share your information collected or created for this study with the following people and institutions:

- Rutgers University Investigators Involved In The Study
- The Rutgers University Institutional Review Board and Compliance Boards
- The Office for Human Research Protections in the U.S. Dept. of Health and Human Services
- Hospital Personnel as Necessary For Clinical Care:
    - University Hospital
- Non-Rutgers Investigators On the Study Team: Your protected health information will not be shared with someone outside of Rutgers. However, the data of the study will be shared with the sponsor of the study and with the other investigators of the study team.
- The Food and Drug Administration— (For studies involving drugs or biologics, etc.)

Other organizations not affiliated with Rutgers University:

- Boehringer Ingelheim- the sponsor of the study: No protected health information will be shared with them.
- Data safety monitoring board.
- National Institutes of Health.

Those persons or organizations that receive your information may not be required by Federal privacy laws to protect it and may share your information with others without your permission, if permitted by the laws governing them.

Will I Be Able To Review My Research Record While The Research Is Ongoing?

No. We are not able to share information in the research records with you until the study is over. To ask for this information, please contact the Principal Investigator, the person in charge of this research study.

Do I Have To Give My Permission?

No. You do not have to permit use of your information. But, if you do not give permission, you cannot take part in this study. (Saying no does not stop you from getting medical care or other benefits you are eligible for outside of this study.)

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If I Say Yes Now, Can I Change My Mind And Take Away My Permission Later?
Yes. You may change your mind and not allow the continued use of your information (and to stop taking part in the study) at any time. If you take away permission, your information will no longer be used or shared in the study, but we will not be able to take back information that has already been used or shared with others. If you say yes now but change your mind later for use of your information in the research, you must write to the researcher and tell him or her of your decision:

Amit Singla, MD may be reached at
Address:
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Phone: 9739725633

How Long Will My Permission Last?
Your permission for the use and sharing of your health information will last until: “There is no set date when your permission will end. Your health information may be studied for many years.”

AGREEMENT TO PARTICIPATE

Subject:

I have read this entire consent form, or it has been read to me, and I believe that I understand what has been discussed. All of my questions about this form and this study have been answered. I agree to take part in this study.

Subject Name (Print):_____

Subject Signature:_____ Date:_____

Signature of Investigator/Individual Obtaining Consent:

To the best of my ability, I have explained and discussed all the important details about the study including all of the information contained in this consent form.

Investigator/Person Obtaining Consent (Print):_____

Signature:_____ Date: _____