Please read carefully

For Patient Reference

Vascular Regeneration Therapy for Lower Limb Ischemia by Autologous Peripheral Blood CD34 Positive Cell Transplantation

Explanatory Document and Consent Form

Shonan Kamakura General Hospital Ver.2.2
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1. Introduction

This document is an explanation of the regenerative therapy called ″Lower Limb Vascular Regeneration Therapy by Autologous Peripheral Blood CD34 Positive Cell Transplantation,″ which is being performed at our hospital.

Please listen to the doctor's explanation regarding this therapy and after fully understanding the contents of this document, please decide whether or not to undergo this therapy using your own free will. If you feel that you are willing to undergo this treatment, please sign the ″Consent Form″.

Even if you decide to not undergo this particular therapy, you will not face any disadvantages in finding or receiving other forms of treatment that you will determine to be best for you.

Furthermore, even if you agree to undergo this therapy, you may stop treatment at any time. In such cases, other treatments considered to be best for you will be provided, and you will not suffer any disadvantages.

The treatment plan for this regenerative therapy reviewed by the Certified Special Committee for Regenerative Medicine (Shonan Kamakura General Hospital Certified Committee for Regenerative Medicine see page 31 for details), which is accredited by the Ministry of Health, Labour and Welfare, to ensure that there are no problems in terms of the protection of human rights, the safety of the participants, and the scientific nature of the regenerative therapy in accordance with the laws established by the government (Act on Securing Safety of Regenerative Medicine, etc.) and related notifications. Based on the results of the review, the plan was submitted to the Ministry of Health, Labour and Welfare through the Regional Health and Welfare Bureau. In addition, the plan was also approved by the Director of Shonan Kamakura General Hospital.

If you wish, we will do our best to provide you with additional materials regarding the plans for administration and treatment methods of this regenerative therapy. We will also provide you with information about the effects and conditions of this regenerative therapy. If you are interested in such materials, please contact the listed in the contact information on page 30.

2. Explanation of Regenerative Therapy

2.1. About your disease

Your disease has been diagnosed as critical limb ischemia.

This disease is a chronic condition with symptoms such as pain in the lower limbs and ulceration/necrosis of the skin.

2.2. Conventional treatment methods

To date, the following treatments have been used to treat critical limb ischemia.

◇◆Conventional treatment◆◇

1） Medical treatment: vasodilators and antiplatelet agents (drugs that prevent the formation of blood clots)

2） Angioplasty: Balloon dilation (widening of blood vessels with balloons) and stenting (placement of a metal tube in a narrowed or blocked blood vessel)

3） Surgical bypass surgery: surgery using arterial or venous grafts (surgery to improve blood flow by connecting another blood vessel (called a graft) to a narrowed or blocked blood vessel)

4） Gene therapy: Intramuscular administration of a gene that promotes angiogenesis at the site of ischemia.

The above treatments are effective for patients with mild symptoms, but for patients with severe cases such as yourself, treatment 1) cannot be expected to show sufficient effects, and treatments 2) and 3) are also deemed insufficient due to surgical limits regarding the maximum number of blood vessels that can undergo operation. Additionally, these treatments cannot be performed in case of the occlusion of small peripheral vessels. As for 4), this treatment became covered by insurance in September 2019, but its approval is subject to conditions and time limits.

2.3. About the method of regenerative therapy

This new method of regenerative therapy aims to treat critical limb ischemia by regenerating blood vessels using your own cells.

◇◆New treatments◆◇

This is a treatment to regenerate blood vessels by removing cells from the patient's blood, isolating the cells that produce blood vessels (autologous peripheral blood CD34 positive cells) from the rest of the cells and transplanting them into the lower limbs.

This type of cell transplantation therapy is called cell therapy. The CD34 positive cells to be transplanted are undifferentiated cells found in bone marrow and blood, and are thought to have the ability to become blood vessel-forming cells when transplanted into organs or tissues with impaired blood flow.

Several studies have been conducted on the improvement of critical limb ischemia by transplantation of CD34 positive cells, and animal studies as well as actual patient studies have shown that the transplantation of CD34 positive cells creates new blood vessels, which may be effective in preventing the progression of necrosis of lower limb muscles and eventual lower limb amputation.

However, this treatment may cause side effects due to the medication used during cell harvesting, as well as side effects from the manipulation of cell harvesting (apheresis) (see 5. Anticipated benefits and risks).

2.4. About this regenerative therapy

This regenerative therapy will provide transplantation of the patient's own peripheral blood CD34 positive cells to patients with critical limb ischemia (peripheral artery disease) whose symptoms have not been improved by conventional medical therapy, angioplasty, surgical bypass surgery. After the treatment, we will confirm the efficacy of the treatment and the safety of the patient for up to 24 weeks.

3. Method of Regenerative Treatment

3.1. Eligible patients

Patients who meet all of the following criteria 1)-6) are eligible.

1) Patients with lower limb ischemia (peripheral artery disease) who have an occlusion or significant stenosis (internal diameter stenosis rate of 70% or more) confirmed by lower limb arteriography, CT angiography, or MRA, or those who are judged to have pain or ulcer/ necrosis due to foot ischemia even if no occlusion or significant stenosis is confirmed by these imaging diagnostics.
2) Patients with lower limb ischemia whose pain at rest or ulceration/necrosis has appeared more than 12 weeks prior to the date of consent.
3) Those who feel pain in the lower limbs at rest due to ischemia of the lower limbs, or those who have ulcers or necrosis of the lower limbs and have no other effective means of wound treatment.
4) Those for whom angioplasty or bypass surgery is not administered (i.e., cases where stenosis is too diffuse or in small peripheral arteries, making angioplasty or bypass surgery inappropriate), or those who are seriously ill and fall under criterion 3) (above) in spite of having received these prior treatments.
5) Aged 20 years or older at the time of consent.
6) Those who can provide written consent themselves.

However, those who meet any of the following conditions are not eligible.

1) Patients with severely impaired heart function.
2) Those who have a history of serious hypersensitivity or side effects to medications or reagent components used in this regenerative therapy.
3) Patients with a malignant tumor(s) or a history of a malignant tumor(s) within the past 5 years※1
4) Patients with diabetic proliferative retinopathy (neo-Fukuda classification BII to BV)
5) Patients with unstable angina pectoris or myocardial infarction, or patients who have suffered the onset of a stroke within the past 12 weeks.
6) Patients with leukemia, myeloproliferative disorders, myelodysplastic syndromes, or sickle cell disease.
7) Patients with liver cirrhosis.
8) Patients with complications concerning, or a history of interstitial pneumonia.
9) Patients with cerebral artery aneurysms that require treatment.

10) Those who have or have already contracted hepatitis B virus, hepatitis C virus, or human immunodeficiency virus (HIV).
11) Patients with rest pain, ulceration, or necrosis of the lower extremities due to spinal canal stenosis, joint diseases, vasculitis, etc. (Even if a patient has these diseases, it is not a disqualifying criterion if the rest pain or ulceration necrosis is determined to be caused by ischemia of the lower limbs)
12) Patients with osteomyelitis, osteonecrosis, exposure of bone or tendon due to ulceration or necrosis, or complications of sepsis, for whom major amputation of the lower extremity (amputation at the ankle joint or more centrally) is inevitable regardless of the success of vascular regeneration therapy.
13) Pregnant women, lactating women, women who may be pregnant, and women who plan to become pregnant by the end of the treatment period.
14) Those who are participating in other clinical trials or clinical studies.
15) Those who are otherwise judged by the assigned physician to be ineligible for participation in this regeneration therapy.

※1 In the search for malignant tumors, the following tests are performed: CT scan (chest, abdomen), head MRI (if the doctor in charge determines that an MRI is not appropriate, other tests such as a CT or angiography may be substituted), urine cytology (only for those who maintain urine), human hemoglobin test via stool samples, colonoscopy (only for those who are positive in the stool test; if the colonoscopy shows no abnormalities, an upper gastrointestinal endoscopy will be performed), and serum PSA (men only), cervical Papanicolaou test (women only), and breast examination and mammography (women only).

3.2. Treatment Schedule

First, you will be tested to determine if you are an eligible candidate for this treatment. If it is determined that you are eligible, you will be enrolled in the treatment, and treatment will begin within four weeks from the date of enrollment.

3.2.1. Attendance at regular intervals

The planned period of participation is the treatment period (approximately one week from the start of G-CSF [granulocyte colony-stimulating factor] preparation administration to cell therapy) and the observation period (24 weeks) for the progress of the treatment. Cell harvesting (apheresis) is performed on the fifth day after the start of treatment (start of G-CSF administration), cell transplantation is performed on the next day (the sixth day), and tests and observations are performed on the next day of transplantation (the seventh day), as well as one week after transplantation. Therefore, patients will be hospitalized for about two weeks from the day before the start of treatment to one week after the transplantation. The rest of the time, the patient will be seen as an outpatient.

In addition, the period from the start of treatment to the end of the observation period is approximately six months after registration.

For details regarding the test items and schedule at each point, please refer to ″Main test items and schedule″ on page 14.

A diagram of the process from consent to registration, cell therapy, observation, etc. is shown on the next page.

3.2.2. What takes place before registration

◆Screening phase (before registration)

After you agree to undergo this treatment, we will assess your general health conditions and check for the presence of malignant tumors before performing the cell transplantation. Other tests will be conducted to determine whether or not you are a suitable candidate for this treatment.

If any of the same, required medical tests were performed recently before you consented to this treatment, we may use their results in order to reduce the number of tests scheduled.

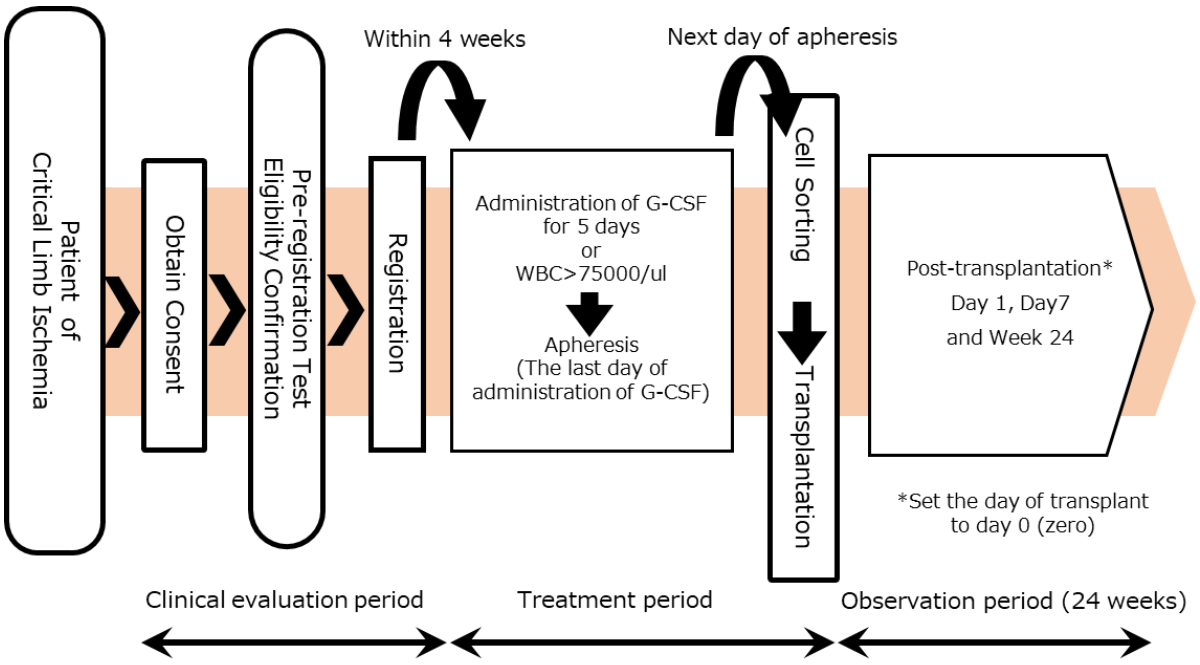
Within 16 weeks prior to registration: Background interview (gender date of birth, date of consent, age on date of consent, information on

lower limb ischemic disease, medical complications/history, smoking history, dialysis information), lower limb angiography or CT angiography or MRA, head MRA* chest and abdominal CT, malignancy search (chest and abdominal CT, cerebral MRA*, maintain urine cytology only for those who maintain urine, stool test colonoscopy only for those who test positive in the stool test, serum PSA only for male patients, cervical Papanicolaou test only for female patients, breast examination and mammography only for female patients,) ocular fundus test, and echocardiography.

※If the physician in charge determines that MRI or MRA is not appropriate, other tests such as CT or angiography may be substituted.

Within 2 weeks prior to registration : Physical examination, lower limb physiological function tests, blood tests, infectious disease tests, electrocardiogram, evaluation of pain due to lower limb ischemia, lower limb ulceration/necrosis findings, transplanted limb information, pretreatment information, and minor amputation schedule after registration.

Angiography, MRI, MRA, CT, etc. take about 1 to 2 hours each, including waiting time. Lower limb physiological function tests take less than one hour. If various tests are performed at a hospital(s) other than our hospital (such as your regular hospital), the results of those tests can be used.



3.2.3. What happens from cell transplantation phase - after transplantation

◆Treatment period

① Treatment to deliver bone marrow cells to blood (subcutaneous injection of G-CSF preparation.)

CD34 positive cells are usually found in large numbers in bone marrow, and only a small number in the blood. G-CSF, a medication that helps deliver the necessary amount of CD34 positive cells from the bone marrow into your bloodstream, is injected subcutaneously at a dose of 400 μg/m^2 once a day for up to 5 days. The dose will be administered on the same day that hematological test and blood biochemistry test are performed and after the results are confirmed.

The G-CSF preparation also increases the number of neutrophils (a type of white blood cell) in the blood. If the white blood cell count reaches 75,000/μL or higher, the administration of the G-CSF preparation would be stopped and apheresis would be performed on the same day. In such cases, the administration period of the G-CSF preparation will be shortened to less than 5 days.

② Procedure to collect mononuclear cells including CD34 positive cells from blood (Apheresis)

On the fifth day of G-CSF administration（or the day the white blood cell count reaches 75,000/μL or higher）, "Apheresis" will be performed. To collect sufficient number of cells needed for transplantation (mononuclear cells), percutaneous catheter insertion into jugular or inguinal vein is necessary. Then, blood will be drawn through catheter, and mononuclear cells for transplantation will be separated using a cell separator. The other blood components will be returned to your body. (The inserted catheter will also be used as a route for fluid infusion. Catheter will be removed on day 7 [the day after cell transplantation] otherwise specified).

During apheresis, blood pressure and electrocardiogram will be monitored for your safety. Hematological tests will be performed just before the start and just after the end of apheresis, and blood biochemical tests will be performed just after the end of apheresis.

The method of cell extraction（①Subcutaneous injection of G-CSF preparation & ②Apheresis） described above has been established as a

general method.

Please note that apheresis takes around 3 hours.

③ CD34 positive cells magnetic sorting

On the next day of "②Apheresis", CD34 positive cells are separated from mononuclear cells extracted during "②Apheresis" using a magnetic cell separator*.

If the purity, survival rate, and cell count of the isolated cells meet the specified conditions, cell therapy is performed.

〔Guideline for transplanted cells〕
Purity : 25% or more
Survival rate : 70% or more
Cell count : 1 x 10^5 per kg of body weight or more
However, even if any of the rates are less than the above values, cell transplantation can still be performed with the patient's consent.

*Magnetic cell separator : Uses CliniMACS (Miltenyi Biotec).
This is a medical device that has not yet been approved in Japan, but it was developed for the purpose of separating cells for hematopoietic stem cell transplantation for leukemia patients, and its safety has been approved in the United States, the European Union, South Korea, Singapore, and a number of other countries.

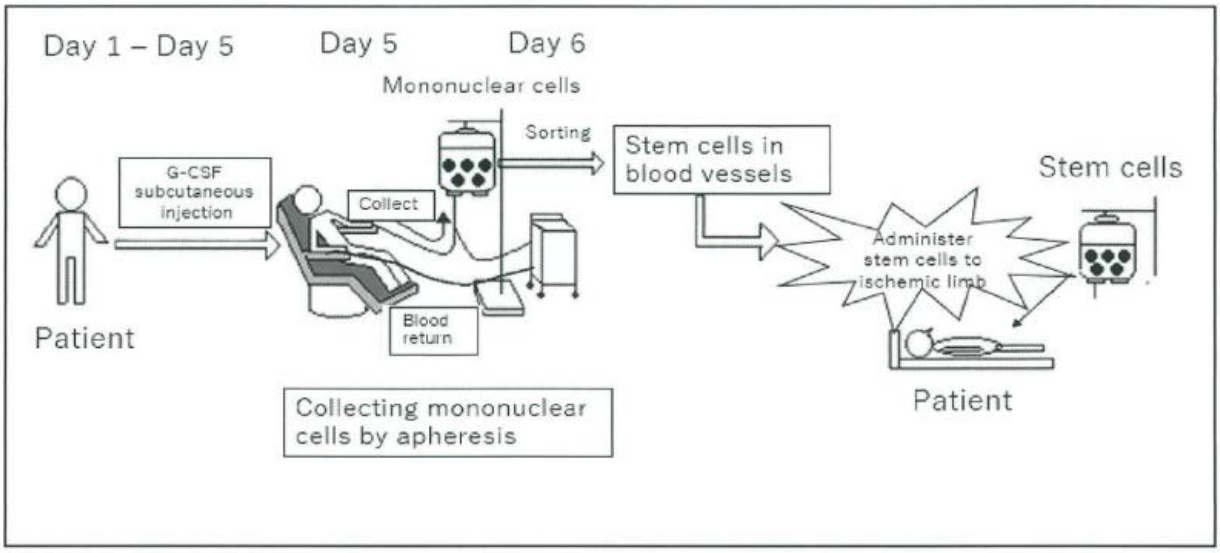
④ Cell therapy (Transplantation)

The isolated cells (CD34 positive cells) are transplanted into the patient's lower limbs by intramuscular injection. The amount of cell suspension to be transplanted per site is 0.25 mL, and 40 sites are transplanted per lower limb where transplantation therapy is performed. The maximum number of cells to be transplanted is 2 x 10^6 cells (2 million cells) per kg of body weight per day, regardless of whether the transplant treatment is performed on one or both lower limbs. In the case of transplantation to both lower limbs, the timing of the transplantation may be staggered and the cell therapy treatment for each lower limb may be performed separately instead of transplanting the cells to both limbs at the same time. Also, if the number of CD34 positive cells collected is low,

less than 1 x 10^5 cells per kilogram of body weight (100,000 cells per limb), transplantation can still be performed with the patient's consent.

Anesthesia （General anesthesia, transfer anesthesia, or surface anesthesia） will be administered during the transplantation process in order to relieve any pain during the procedure.

Please note that cell transplantation takes about 1-1.5 hours（for unilateral affected limbs only） from the start of anesthesia to the end of the transplantation.



Some of the isolated CD34 positive cells are also used for quality testing and storage. Further tests may also be performed to examine the characteristics/conditions of the transplanted cells. However, genetic testing will be never performed.

◆Observation period

1 day, 7 days, and 24 weeks after transplantation, observation and examination will be conducted to evaluate the safety of the patient and the efficacy of the treatment. When the observation is discontinued for any reason, an assessment of patient safety and feasible efficacy is also made. For information regarding the discontinuation of therapy, please refer to ″12. Discontinuation of therapy.

24 weeks of medical examinations and tests can be completed in about

half a day, so in principle it should be possible to make outpatient visits for your appointments. However, please note that it may take additional time if you have to receive eye examinations. It is also possible to implement the program at a hospital other than our hospital (e.g., your primary care clinic).

For details regarding the test items and each's schedule, please refer to "Main Test Items and Schedule" on page 14.

If you have any questions about any of the tests, please contact your doctor. Other medical procedures may be performed depending on your medical conditions.

3.2.4. Main test items and schedule

The main test items and schedule are shown on the next page.

For hematological and biochemical tests, about 10 mL of blood will be drawn at a time. Also, before starting treatment, there will be a coagulation system and infection test, and about 10 mL of blood will be drawn separately for this purpose. Hematological and blood biochemical tests will be performed a total of 12 times, beginning from the pre-registration examination before the start of treatment, carrying through the period of G-CSF preparation administration, and continuing until the end of the 24-week observation period after cell transplantation. Please understand that the total amount of blood collected over a period of about six months will be about 120 mL.

Main test items and schedule

〔Before registration～At the time of cell transplantation〕

Date of tests / Test Items	Pre-registration test period※1		Treatment period		
	Within 16 weeks prior to registration	Within 2 weeks prior to registration	G-CSF administration	Apheresis performance	Cell transplantation
Subject background	○※2				
Lower limb angiography※3	○				
Urine cytology	○※4				
Stool test	○				
Lower or upper endoscopy	○※5				
MRI and MRA of head	○※6				
Chest CT, Abdominal CT	○				
Malignant tumors search※7	○				
Ocular fundus test	○				
Echocardiogram	○※2				
Abdominal echo			○※8		
Physical findings		○	○※9		○※9
Lower limb physiological function test		○			
Hematological test and blood biochemistry test		○※10	○※11	○	○
Coagulation system test		○			
Infectious disease test		○			
Electrocardiogram		○			
Lower limb ischemia severity classification		○※12			
Severe degree of pain due to lower limb ischemia		○			
Ulceration findings		○			
Lower limb MRI		○※13			
Transplanted limb		○			

information					
Concomitant treatment and medication		○	○	○	○
G-CSF preparation administration record			○		
Apheresis record				○	
Transplanted cell information					○
Adverse events/outcomes			◄	―	►
Magnetic cell separator malfunction					○
Allowed test date	―	―	±0 days	±0 days	±0 days

※1：Pre-registration test period: Previous test data collected prior to obtaining consent for this procedure will be used if additional consent is obtained from the patient.

※2：Patients suspected of having coronary artery disease based on electrocardiogram, echocardiogram, medical history, etc. will undergo a thorough examination using myocardial scintigraphy, coronary CT, and/or coronary angiography, etc.

※3：This test is performed using direct angiography, CT angiography or MR angiography.

※4：This is only performed for patients who have urine output.

※5：A colonoscopy will be performed when the fecal hemoglobin test is positive. If the colonoscopy shows no abnormalities, an upper gastrointestinal endoscopy will be performed.

※6：For patients with contraindications or ineligibility for MRI or MRA, a CT or angiography, etc. will be used instead.

※7：The following tests will be performed.
CT scan (chest, abdomen), MRI of head (for patients with contraindications or ineligibility for MRI, a CT etc. will be used instead), urine cytology, fecal hemoglobin test, colonoscopy (only when the fecal hemoglobin test is positive), serum PSA (only for male patients), Cervical Papanicolaou test (only for female patients), breast exam and mammography (only for female patients)

※8：Abdominal echocardiography will be performed on either day 3 or 4 of the G-CSF administration period.

※9：Only body temperature and weight will be measured.

※10：Test of HbA1c, glycohemoglobin (only for diabetic patients).

※11：Blood biochemistry tests will be performed only on days 1, 3, and 5.

※12：Evaluation of both limbs.

※13：This is performed only for patients belonging Rutherford Classification category 5 or 6.

〔During the observation period〕(Observation schedule for each target limb) #

Inspection period / Inspection Items	Period of observation			Discontinued※14
	Day 1 after transplantation	Day 7 after transplantation	24 Weeks after transplantation	
Lower limb ischemia severity classification			○	○
Severe degree of pain due to lower limb ischemia			○	○
Ulceration findings			○	○
Lower limb physiological function test			○	○
Physical findings	○※9	○※9		
Hematological test and blood biochemistry test	○	○	○※10	○※10
Electrocardiogram			○	
Ocular fundus test			○※15	○※15
Concomitant treatment and medication	○	○	○	○
Adverse events/outcomes	←	—	—	→
Allowance of inspection period	±0 days	±3 days	±14 days	—

#: If both limbs have been affected and thereby treated separately with transplantation therapy, the observation for each target limb will be performed according to each's own observation schedule as described above..

※9 : Only body temperature and weight will be measured.

※10 : Test of HbA1c, glycohemoglobin (only for diabetic patients).

※14 : If treatment is discontinued during the therapeutic period, safety tests and studies will be conducted at the time of discontinuation. Tests for efficacy will also be conducted if possible.

※15 : Only for diabetic patients.

3.3. Concomitant therapy and medications

◆Contraindicated medications and treatments

The following treatments are prohibited within 24 weeks of cell transplantation as they may affect the evaluation of this treatment. However, we do not limit the following treatments to those who show intensified pain or ulceration after cell therapy, if they wish to do so.

- Other cell transplantation therapies
- Gene therapy
- Sympathetic ganglion block
- Angioplasty of the lower extremities, bypass operation
- LDL apheresis
- Other medication from clinical trials and clinical trial equipment

◆Limited medication

1) With a limited period of use

(Your physician(s) may reduce the dose of or suspend the use of the following medications depending on your condition.)

- Warfarin Potassium（Product name：Warfarin etc.）

4. Planned Duration of Treatment

This treatment will be conducted at one facility, Medical Corporation Tokushukai Shonan Kamakura General Hospital.

The total duration of treatment will last approximately five years from the time the treatment is approved for implementation.

5. Anticipated Benefits and Risks

5.1. Anticipated benefits

Several clinical studies have been conducted on the effects of CD34 positive cell transplantation in patients with critical limb ischemia. It has been reported that the treatment may be effective in reducing ulcers and necrosis of the lower limbs and preventing amputations of the lower limbs. Transplantation of CD34 positive cells into patients with critical limb ischemia

on maintenance hemodialysis, which is difficult to treat, may help create new blood vessels and improve pain, ulcers and necrosis of the lower limbs.

5.2. Anticipated risks

Your doctor will also closely monitor you for any unfavorable symptoms or signs (called adverse events) that occur after treatment.
If an adverse event occurs, you will be informed and appropriate action will be taken accordingly. If necessary, treatment may be discontinued.

The following are examples of possible symptoms, which may vary from patient to patient. Please contact your doctor if you notice any changes in your physical condition.

1）Side effects of the G-CSF products used in this treatment

In this treatment, a G-CSF preparation is administered at 400 μg/m^2.
Past reports show high frequency incidences where doses that were administered higher than 10 μg/kg (similar to this treatment's dose) were accompanied by bone pain, headache, and general malaise.

The following is what is described in the prescribing information of the G-CSF products

＜Serious side effects＞

Shock, Anaphylaxis（Frequency unknown）, interstitial pneumonia[*1]（Frequency: unknown）, acute respiratory distress syndrome[*2]（Frequency: unknown）, increased number of blasts（Frequency unknown）, splenomegaly(Frequency unknown), rupture of the spleen（Frequency: unknown）, capillary leakage syndrome（0.01% of cases）, large vessel vasculitis（inflammation of the aorta, common carotid artery, subclavian artery, etc.）（Frequency unknown）

＜Other side effects＞

Skin：(Frequency unknown) skin disorder with neutrophilic infiltration, painful erythema, and fever (Sweet Syndrome, etc.) [*3] (Less than 1%) rash, redness of skin

Muscles and bones：(1%-less than 5%) bone pain, back pain, (Less than 1%)

chest pain, joint pain, muscle pain, (Frequency: unknown) pain in extremity

Digestive organs : (Less than 1%) nausea and vomiting

Liver : (Less than 1-5%) increase in ALT (GPT), (Less than 1%) hepatic function abnormal, increased AST (GOT)

Blood : (Frequency unknown) platelet decreased, leukocytosis

Kidney : (Frequency unknown) glomerulonephritis

Other : (Frequency unknown) Edema, (Higher than 5%) DH elevation, (1%-less than 5%) fever, increased Al-P(Less than 1%), headache, fatigue, palpitations, elevated uric acid, elevated serum creatinine, elevated CRP

*1 interstitial pneumonia : Inflammation of the interstitial tissue of the lungs causes symptoms such as coughing, shortness of breath, and fever.

*2 Acute respiratory distress syndrome : This is an acute lung injury with a variety of causes. Symptoms include difficulty breathing and hypoxia.

*3 Skin disorder with neutrophilic infiltration, painful erythema, and fever （Sweet Syndrome, etc.) : This is a type of skin condition that is accompanied by redness, pain, itching and burning.

2) Side effects of apheresis

Side effects that may be caused by apheresis are as follows

platelet decreased（higher than 50%）, general malaise（about 30%）, numbness of extremities（citric acid poisoning by ACD solution used as anticoagulant）, vomiting vasovagal reflex*4, dehydration, bradycardia, ascites accumulation

*4 Vomiting vasovagal reflex : Symptoms such as dizziness, nausea, and vomiting may occur due to anxiety and fear of blood sampling and injection.

Vasovagal reflex is very rare, but in severe cases it can lead to bradycardia, loss of consciousness, and even cardiac arrest. For the safety of the patient, we will monitor the patient with an electrocardiogram during apheresis and be prepared to respond in the case of an emergency.

3) Side effects of cell transplantation (CD34 positive cell transplantation)

No side effects have been reported with autologous CD34 positive cell

transplantation. However, possible risks include the following:

① Risk of bacterial or viral infection of isolated transplanted cells, and the transplantation of such already-infected cells to you

Transplant cells are separated by aseptic manipulation, but the risk of bacterial (e.g., syphilis, tuberculosis), viral (e.g., hepatitis B, hepatitis C, HIV), or mycoplasma infection of the cells cannot be completely ruled out.
To ensure your safety, a portion of the cells obtained during separation (CD34 negative cells) will be tested for the presence of these infections. （The results of the test will be known after the cell transplantation.） If the test confirms any infection, a specialist will provide the appropriate treatment（for example, the administration of globulin products, antiviral drugs, antibiotics, etc.）.

② Risks associated with drugs used during cell separation.
〔Risks depending on the antibody used〕

When separating the cells, it is necessary to use antibodies made from mouse proteins, and very small amounts of mouse proteins may enter your body along with the transplanted cells. As a result, your body may produce antibodies against the mouse proteins. Please note that if antibodies to the mouse protein are produced in the body, allergic reactions and anaphylactic symptoms[*5] may occur, and there may be restrictions on future treatments using similar mouse proteins.

[*5] allergic reactions and anaphylactic symptoms : The most common symptoms of allergic reactions are skin symptoms such as hives, redness, and itching. Other symptoms include respiratory symptoms such as sneezing, coughing, wheezing, and breathlessness; mucosal symptoms such as itchy eyes, swelling, and swollen lips; gastrointestinal symptoms such as abdominal pain and vomiting; circulatory symptoms such as low blood pressure. Anaphylaxis is the rapid onset of these multiple symptoms throughout the body.

〔Risks arising from the manufacturing process of the antibodies used〕

In the manufacturing process of the antibody used to isolate CD34 positive cells, no components of human or animal origin are used other than the mouse-derived cells that produce the antibody.

In the production of antibodies using mouse-derived cells, safety measures have been taken to reduce the risks of infection. However, when using of biologically-derived raw materials, the risk of infectious diseases cannot be completely eliminated.

〔Risk depending on the human serum albumin used〕

Human serum albumin, which is commercially available as medicine, is used during the isolation of CD34 positive cells. Therefore, allergic reactions to human serum albumin and anaphylactic symptoms may occur.

This human serum albumin is a medicine derived from domestic human blood components, and has been tested negative for hepatitis B virus, hepatitis C virus, and human immunodeficiency virus in infectious disease-related tests. Although the risk of infection cannot be completely eliminated, safety measures are in place to prevent associated risks during its production.

③ Risks associated with general anesthesia during transplantation

The possible side effects of general anesthesia when transplanting cells into the muscles of the lower limb are as follows:

Sore throat, hoarseness, nausea, headache, damage to vital organs (brain, heart, lungs, liver, kidneys, etc.), abnormal reactions to medications (allergies, malignant hyperthermia, etc.), teeth falling out, teeth breaking, nerve damage (numbness, paralysis)

4) Other information concerning side effects

According to the Donor Adverse Event Report of the Japan Society for Hematopoietic Cell Transplantation, there have been no reports of donor deaths in Japan so far, but there have been 8 deaths overseas after granulocyte-stimulating factor injection and apheresis administered to stem cell donors for patients with blood disorders（as of November 2014）. However, the relationship between death and the procedure is not clear. In addition, in a study of 1,780 donors who had been followed up for five years out of 3,264 donors registered between April 2000 and March 2005 in the Peripheral Hematopoietic Stem Cell Donor Follow-up Project for Blood

Relatives conducted by the Japan Society for Hematopoietic Cell Transplantation, 12 persons (0.7%) developed nonhematologic tumors and 1 person (0.06%) developed hematologic tumors. In addition, one donor (0.06%) developed a hematologic tumor, but a causal relationship to peripheral blood stem cell donation could not be denied but not clarified (reported in August 2010). In this regenerative therapy, the patient will undergo the same procedure as the donor mentioned above.

In addition, the intravenous injection of CD34 positive cells obtained from the patient's own blood has been used for about 20 years in the treatment of blood diseases and cancer. In a clinical trial for the treatment of non-Hodgkin's lymphoma, two cases of pneumonia (4.9%) and one case of vomiting (2.4%) were reported as side effects after CD34-positive cell transplantation, but the symptoms disappeared with appropriate administration of the drug.

In the domestic clinical trials conducted by the company in charge of the development of the CD34 positive cell isolation device, adverse reactions (including abnormal changes in clinical laboratory values) were reported in 16 (35.6%) persons of non-Hodgkin's lymphoma out of 45 persons (41 persons of non-Hodgkin's lymphoma and 4 persons of breast cancer).
The most common adverse reactions were 8 cases (17.8%) of increased C-reactive protein[*1], 8 cases (17.8%)[#1] of cytomegalovirus infection[*2], 7 cases (15.6%)[#2] of decreased lymphocyte count, fever in 3 cases (6.7%), and pneumonia in 3 cases (6.7%). In these trials, chemotherapy as an anticancer drug was used in combination.

However, since this regenerative therapy targets a different disease from the above and does not involve the use of anticancer drugs, this information regarding side effects does not directly apply to the regenerative therapy at hand.

	5% and more	Less than 5%
Digestive	none	abdominal enlargement, vomiting
Respiratory organs	none	cough, pleurisy, rhinorrhea, increased sputum production, upper respiratory tract inflammation, hypoxia
Skin	none	dermatitis, bullous dermatitis, pruritus
Urinary organs	none	proteinuria, hematuria, increased creatinine in blood
Blood	decreased lymphocyte count[*1)]	decreased white blood cell count, decreased neutrophil count, decreased platelet count, decreased hemoglobin, increased white blood cell count, increased neutrophil count
Other	increased C-reactive protein, cytomegalovirus infection[*2)] , fever, pneumonia	herpes simplex, shingles, cystitis

#1) Including 1 case of lymphopenia

#2) Including 2 cases of cytomegalovirus antigen positive

*1 C-reactive protein : A protein that appears in the blood when there is an inflammatory reaction or tissue destruction in the body.

*2Cytomegalovirus infection : Cytomegalovirus is a member of the herpes virus family, and although it rarely causes symptoms in healthy people, it can cause a variety of symptoms such as fatigue, fever, sore throat, swollen lymph nodes in the neck, enlargement of the liver and spleen, and abnormal liver function in people with weakened immune systems.

5) Non-efficacy and inapplicability

Improvement of critical limb ischemia may not be provided by this cell transplantation therapy. If you have any symptoms that concern you after the start of treatment, please do not hesitate to consult your doctor at any time about anything. We will do as many tests and treatments as possible if necessary. In such cases, we may ask for your cooperation in investigating the cause(s) of the symptom(s).

6. Other Treatments for Critical Lower Limb Ischemia

Other treatments for critical lower limb ischemia include angioplasty, bypass surgery, and treatment with peripheral vasopressors. However, angioplasty and bypass surgery may not be sufficiently effective due to surgical limits regarding the maximum number of blood vessels that can undergo operation, and also due to the inability of the procedures to treat occlusions of peripheral small blood vessels. Gene therapy, another alternative, has not yet been studied in comparison to this treatment, so it is still unknown which treatment would be more effective. (Please refer to "2.2. Conventional treatment methods").

Finally, it is important to note that patients who undergo treatment using CD34 positive cell transplantation can continue to receive medication(s) they have been taking before this treatment.

7. Potential Health Hazards

This treatment is scientifically planned and carefully administered. However, if you experience any side effects or other health problems at any time from the start of treatment to the post-treatment observation period, please contact your doctor immediately. Your physician will provide you with appropriate medical care and treatment.

Specific measures to address health hazards are as follows:

- We will provide treatment and other necessary measures for health damages.
- Medical expenses will be paid by the hospital.
- Compensation for death and disability will be paid in accordance with the rules of the hospital's insurance policy. However, no monetary compensation will be paid for other health damages.

Please note that the following cases are not eligible for compensation:

- If the health problem turns out to be unrelated to this treatment.
- If the health hazard was caused by your intentional or negligent act.

● If cell transplantation is not effective.

8. Protection of Personal Information

All hospital staff, including doctors, nurses, and pharmacists, are obligated to maintain confidentiality regarding what they learn in the course of their duties during normal medical treatments, and the same obligation of confidentiality applies to this treatment.

The handling of personal information is reviewed in advance by a Certified special committee for regenerative medicine. When the compiled information is published in academic conferences or medical journals, care is taken to ensure that individuals are not identified.

As such, your personal information is strictly controlled, so there is no need to worry about your own or your family's personal information being leaked to a third party by undergoing this treatment.

By signing this consent form, you agree to the provision of information to organizations other than this hospital*, the publication of results, and the inspection of medical records.

* organizations other than this hospital : Certified special committee for regenerative medicine and the Ministry of Health, Labor and Welfare and its related staff.

9. Records and Sample Handling

9.1. Use, storage, and disposal of samples and information

The record of this treatment will be kept for 10 years after the end of the treatment and some of your samples(cells) will be kept for 5 years. In case of infection or other problems, the cells may be used to investigate the cause of the infection, but no genetic tests or other tests unrelated to the treatment will be performed. We may also investigate the causes of side effects and other problems that occur in patients after transplantation. When disposing of these records, we will shred or incinerate them to prevent the leakage of personal information.

The cells will be anonymized (then a way that attached a registration number that is coded in a format that does not identify the individual. and stored within our hospital. At the end of the storage period, the cells will be disposed of appropriately as medical waste.

When records are destroyed at the end of the retention period for this study, they will be shredded or incinerated, taking care to protect the patient's personal information.

9.2. Secondary use of information

The information collected in this treatment may be used for secondary purposes for analysis in the future, but this will be done only after a new research plan is prepared and approved by the Research Ethics Review Committee.

10. Cost of Treatment

By this treatment, the following expenses will be incurred: hospitalization expenses during the treatment period after the start date of G-CSF administration; drug, medical material, and laboratory expenses during G-CSF administration, apheresis, CD34-positive cell isolation, and cell transplantation; hospitalization expenses for post-transplant examinations* during the observation period (1 day, 7 days, and 24 weeks) and laboratory expenses, etc. The standard co-payment amount is approximately 6.6 million yen with consumption tax (the same hereinafter). The patient will also be responsible for the cost of extra bedding, as well as any other expenses incurred at his or her request.

If you wish to have a pre-registration examination at our hospital, the maximum amount will be 220,000 yen for the examination within 16 weeks prior to the registration. The maximum amount will be 88,000 yen for the examination within 2 weeks prior to the registration. In addition, hospitalization expenses for the number of days required for the examination will be charged.

※The day of transplantation is considered day 0.

11. Communication of Information that Influences the Intention to Implement Treatment

During the observation period after the start of treatment, your doctor will promptly inform you of any new information that may affect your decision to continue undergoing treatment. At that time, you will be asked to reconsider whether you wish to continue treatment or not, and you may cancel the treatment.

12. Discontinuation of therapy

Your doctor may ask you to stop the treatment after you have agreed to it and/or after it has already started.

◆Reasons for discontinuation related to the individual patient's condition:

1) When it is difficult to continue treatment due to illness, etc.
2) In the event that you request discontinuation (withdrawal of consent) after giving consent.
3) In case of death.
4) If, after enrollment, it is found that the conditions for implementing the treatment are not met.
5) If your post-transplant observation cannot be continued due to reasons such as hospital transfer.
6) If the transplantation could not be performed due to malfunction of equipment, deterioration of your condition, or if the cells collected are not suitable for transplantation.
7) Failure to start cell therapy within 4 weeks of enrollment.
8) In other cases where the person in charge of the treatment or your doctor judges that the treatment cannot be continued.

◆Reasons for discontinuation related to overall treatment:

1) If it is judged that there is a problem with the safety or effectiveness of the treatment.
2) If it is determined that the continuation of treatment is no longer meaningful during the course of treatment.

3) When instructed by the hospital director or the Ministry of Health, Labor and Welfare to discontinue treatment.

If you cancel the treatment midway, we will ask you to undergo an examination to check your health status for your safety. We appreciate your cooperation.

Finally, it is important to note that once the CD34 positive cells are transplanted during this treatment, the procedure cannot be undone and they cannot be removed.

13. Withdrawal of Consent

Once you have given your consent to this treatment, you may withdraw your consent at any time. If you feel that you want to cancel the treatment, please tell your doctor at any time. Even if you do withdraw your consent, you will not be treated unfavorably.

The data collected from the time you agree to the treatment until you cancel the treatment will be treated as treatment data. If you do not want your data to be used, please inform your doctor or other health care provider.

14. Follow-up after Completion of Treatment

Adverse events observed during the course of this treatment will be followed up with periodic health checks as frequently as possible until improvement or stabilization, and safety information will be collected. If any sort of infection is suspected, the patient will be retested every 3 months and followed up until diagnosed as negative. This information will be stored in the same manner as the data during treatment.

15. Requests for Your Cooperation

If you agree to undergo this treatment, we kindly ask that you please observe the following:

1) Please come to the hospital according to your schedule. If you are

unable to come to the hospital according to schedule for any reason, please inform your doctor as soon as possible.

2) If you are receiving treatment for other illnesses etc. from a doctor other than your own, please be sure to inform your doctor of this. Please also let us know if you are taking any medication(s) prescribed by another doctor or purchased at a pharmacy. If there are any changes in the type or dosage of the medication(s) you are taking, please contact your doctor as far in advance as possible.
3) During the post-treatment observation period, if you wish to see another doctor for a cold etc., please consult with your doctor as far in advance as possible. Also, please be sure to let the new doctor know that you are also participating in this treatment.
4) There is no information yet on the safety of G-CSF products during pregnancy and lactation. Women who are pregnant, lactating, or may become pregnant should not receive this treatment. Women receiving this treatment should also be advised not to become pregnant during the observation period following the start of treatment.
5) Please follow the instructions of the hospital staff when undergoing medical examinations and measures.

Please note that your doctor may ask you to stop the treatment if you do not follow the above instructions.

16. Handling of the Results

The results of this treatment may lead to some new insights. Any patent or other intellectual property rights (patent rights) that may arise will belong to the medical institution that participated in the treatment or to the treating physicians. This does not refer to the data provided, rather to the new ideas that emerged as a result of the treatment as well as the application of the results by the treating physicians. Therefore, the patient right belongs to the medical institution or treating physicians who participated in the treatment. Patients may not claim any financial benefits from the patent right.

17. For Inquiries

If you have any concerns or questions about this treatment, or if you notice anything unusual, please do not hesitate to contact your doctor or the consultation desk at any time.

Medical Institutions and Administrators	Medical Corporation okushukai Shonan Kamakura General Hospital Director Shuzo Kobayashi Address: 1370-1 Okamoto, Kamakura, Kanagawa 247-8533, Japan Phone: 0467-46-1717
Department in Charge	Regenerative Medicine and Kidney Disease and Transplant Center
Physician Responsible for Treatment	Name of Physician：Takayasu Ohtake M.D.
Attending Physician	Name of Physicians：Sumi Hidaka M.D., Kunihiro Ishioka M.D., Yasuhiro Mochida M.D. Machiko Oka M.D., Ayaka Mitomo M.D. Contact：Shonan Kamakura General Hospital Phone：0467-46-1717
Consultation Service	Contact: Shonan Kamakura General Hospital Regenerative Medicine,or Kidney Disease and Transplant Center Phone：0467-46-1717 Physicians：Takayasu Ohtake M.D. Yasuhiro Mochida M.D.,
Service for Medical travel support company	Contact: International Department, Tokushukai Medical Group Phone：0467-46-9931 FAX：0467-46-9932 Person in charge：Masaki Watanabe
Emergency Contact during Evening and Holidays	Contact: Shonan Kamakura General Hospital Phone：0467-46-1717

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If you have any complaints, please contact the Clinical Research Center at Shonan Kamakura General Hospital (0467-46-1717).

In addition, please refer to the following website for the list of the committee members, committee rules, outline of committee meetings, and other information pertaining to the. Certified Committee for Regenerative Medicine Complaints and inquiries are also accepted at the following e-mail address.

Name of Certified Review Board	Shonan Kamakura General Hospital Certified Committee for Regenerative Medicine
Accreditation Number of the Certified Committee	NA8150013
Address	1370-1 Okamoto, Kamakura, Kanagawa
Department in Charge	Shonan Kamakura General Hospital Certified Committee for Regenerative Medicine Secretariat
Phone Number of Department in Charge	03-3265-4804
FAX Number of Department in Charge	03-3263-4802
Email Address of Department in Charge	rm_committee2@shonankamakura.or.jp
Website	https://www.shonankamakura.or.jp/about/sp-regeneration-medicine/

The above is the explanation of the contents of this therapy. If you understand and agree to this treatment, please sign the following consent forms.

Consent form

For Hospital

To: Director of Medical Corporation Tokushukai Shonan Kamakura General Hospital

1. Consent Form for Cell Collection

Name of treatment: Vascular Regeneration Therapy for Lower Limb Ischemia by Autologous Peripheral Blood CD34 Positive Cell Transplantation

- ☐ Introduction
- ☐ Other treatments for critical limb ischemia
- ☐ Protection of personal information
- ☐ Cost of treatment
- ☐ Communication of information that influences the intention to implement treatment
- ☐ Withdrawal of consent
- ☐ Requests for your cooperation
- ☐ Contact information
- ☐ About the treatment
- ☐ How to do this treatment
- ☐ Anticipated benefits and risks
- ☐ In case of health hazards
- ☐ Retention and disposal of records and samples
- ☐ Discontinuation of treatment
- ☐ Follow-up after completion of the treatment
- ☐ Management of treatment results

I received a full explanation of the above items in written form. I understand the details of this treatment and agree to have my cells collected. However, it should be noted that consent may be withdrawn prior to the cell collection.

Date : _____ Signature : _____

☐ I have received the explanation document and consent form (copy).

The above treatment was explained based on the explanation document.

Date : _____

Explaining Physician : Department of _____

Signature : _____

Date : _____

Attending Coordinator Department of _____

Signature : _____

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Consent form

For Patient

To: Director of Medical Corporation Tokushukai Shonan Kamakura General Hospital

1. Consent Form for Cell Collection

Name of treatment: Vascular Regeneration Therapy for Lower Limb Ischemia by Autologous Peripheral Blood CD34 Positive Cell Transplantation

- ☐ Introduction
- ☐ Other treatments for critical limb ischemia
- ☐ Protection of personal information
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- ☐ Communication of information that influences the intention to implement treatment
- ☐ Withdrawal of consent
- ☐ Requests for your cooperation
- ☐ Contact information
- ☐ About the treatment
- ☐ How to do this treatment
- ☐ Anticipated benefits and risks
- ☐ In case of health hazards
- ☐ Retention and disposal of records and samples
- ☐ Discontinuation of treatment
- ☐ Follow-up after completion of the treatment
- ☐ Management of treatment results

I received a full explanation of the above items in written form. I understand the details of this treatment and agree to have my cells collected. However, it should be noted that consent may be withdrawn prior to the cell collection.

Date : _____ Signature : _____

☐ I have received the explanation document and consent form (copy).

The above treatment was explained based on the explanation document.

Date : _____

Explaining Physician : Department of _____

Signature : _____

Date : _____

Attending Coordinator : Department of _____

Signature : _____

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Consent form

For Hospital

To: Director of Medical Corporation Tokushukai Shonan Kamakura General Hospital

2. Consent Form for Cell Transplantation Treatment

Name of treatment : Vascular Regeneration Therapy for Lower Limb Ischemia by Autologous Peripheral Blood CD34 Positive Cell Transplantation

- ☐ Introduction
- ☐ Other treatments for critical limb ischemia
- ☐ Protection of personal information
- ☐ Cost of treatment
- ☐ Communication of information that influences the intention to implement treatment
- ☐ Withdrawal of consent
- ☐ Requests for your cooperation
- ☐ Contact information
- ☐ About the treatment
- ☐ How to do this treatment
- ☐ Anticipated benefits and risks
- ☐ In case of health hazards
- ☐ Retention and disposal of records and samples
- ☐ Discontinuation of treatment
- ☐ Follow-up after completion of the treatment
- ☐ Management of treatment results

I received a full explanation of the above items in written form. I understand the details of this treatment and agree to have my cells collected. However, it should be noted that consent may be withdrawn prior to the cell collection.

Date : _____ Signature : _____

☐ I have received the explanation document and consent form (copy).

The above treatment was explained based on the explanation document.

Date : _____

Explaining Physician : Department of _____

Signature : _____

Date : _____

Attending Coordinator : Department of _____

Signature : _____

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Date of Creation : March 30, 2023

Consent form

For Patient

To: Director of Medical Corporation Tokushukai Shonan Kamakura General Hospital

2. Consent Form for Cell Transplantation Treatment

Name of treatment：Vascular Regeneration Therapy for Lower Limb Ischemia by Autologous Peripheral Blood CD34 Positive Cell Transplantation

- ☐ Introduction
- ☐ Other treatments for critical limb ischemia
- ☐ Protection of personal information
- ☐ Cost of treatment
- ☐ Communication of information that influences the intention to implement treatment
- ☐ Withdrawal of consent
- ☐ Requests for your cooperation
- ☐ Contact information
- ☐ About the treatment
- ☐ How to do this treatment
- ☐ Anticipated benefits and risks
- ☐ In case of health hazards
- ☐ Retention and disposal of records and samples
- ☐ Discontinuation of treatment
- ☐ Follow-up after completion of the treatment
- ☐ Management of treatment results

I received a full explanation of the above items in written form. I understand the details of this treatment and agree to have my cells collected. However, it should be noted that consent may be withdrawn prior to the cell collection.

Date： _____ Signature：_____

☐ I have received the explanation document and consent form (copy).

The above treatment was explained based on the explanation document.

Date： _____

Explaining Physician： Department of _____

Signature：_____

Date： _____

Attending Coordinator： Department of _____

Signature：_____

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For Hospital

Consent Withdrawal Form

To: Director of Medical Corporation Tokushukai Shonan Kamakura General Hospital

Name of treatment : Vascular Regeneration Therapy for Lower Limb Ischemia by Autologous Peripheral Blood CD34 Positive Cell Transplantation

I agreed to undergo the treatment, but I withdraw my consent.

☐I have received the consent withdrawal form (copy).

Date : _____

Signature : _____

Signature of the representative※ : _____

(Relationship:)

※ When the person's intention to withdraw consent cannot be confirmed.

Date of confirmation by physician
or person in charge of the treatment : _____

Signature of confirmation by physician
or person in charge of the treatment : _____

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For Patient

Consent Withdrawal Form

To: Director of Medical Corporation Tokushukai Shonan Kamakura General Hospital

Name of treatment : Vascular Regeneration Therapy for Lower Limb Ischemia by Autologous Peripheral Blood CD34 Positive Cell Transplantation

I agreed to undergo the treatment, but I withdraw my consent.

☐I have received the consent withdrawal form (copy).

Date : _____

Signature : _____

Signature of the representative※ : _____

(Relationship:)

※ When the person's intention to withdraw consent cannot be confirmed.

Date of confirmation by physician
or person in charge of the treatment : _____

Signature of physician
or person in charge of the treatment : _____

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変更対比表

作成年月日：2023 年 3 月 30 日

治療課題名：『自家末梢血 CD34 陽性細胞移植による下肢血管再生療法（治療）』

以下に、「1-5 再生医療等を受ける者に対する説明文書及び同意文書の様式」（インバウンド用同意説明文書英語版/For Patient Reference）における修正箇所について修正・追加を下線、削除を、二重取消線として示す。

訂正箇所	Ver. 2.1	Ver. 2.2	変更理由
フッター	Shonan Kamakura General Hospital Ver.~~2.1~~ Date of Creation: ~~February 24~~, 2023	Shonan Kamakura General Hospital Ver.2.2 Date of Creation: March 30, 2023	版の更新
p.30 17. For Inquiries Attendinf Physician	Name of Physicians：Sumi Hidaka M.D., Kunihiro Ishioka M.D., Yasuhiro Mochida M.D. Machiko Oka M.D., ~~Toshihiro Shimizu M.D., Naoki Fujiwara M.D.,~~ Ayaka Mitomo M.D. Contact：Shonan Kamakura General Hospital Phone：0467-46-1717	Name of Physicians：Sumi Hidaka M.D., Kunihiro Ishioka M.D., Yasuhiro Mochida M.D. Machiko Oka M.D., Ayaka Mitomo M.D. Contact：Shonan Kamakura General Hospital Phone：0467-46-1717	医師削除による変更

以上