A Single Center, Randomized and Controlled Clinical Study of Inverted Internal Limiting Membrane Insertion Combined with Air Tamponade in the Treatment of Macular Hole Retinal Detachment in High Myopia

Study Protocol

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Summary

1. Purpose

To evaluate the surgical outcomes of inverted internal limiting membrane insertion combined with air tamponade in the treatment of macular hole retinal detachment (MHRD) in high myopia, and also to compare the treatment efficacy between different surgical approaches of MHRD.

2. Design

Design: a prospective, single-centered, randomized, controlled clinical trial

3. Target

Patients with high myopia complicated by macular hole associated-retinal detachment.

4. Inclusion Criteria

Inclusion Criteria
1) Prior written informed consent should be obtained before any assessment is carried out; 2) Participants are more than 18 years of age, and less than 75 years of age, male or female Chinese patients; 3) Visual impairment is caused by macular hole associated with retinal detachment secondary to high myopia; 4) Axial length ≥ 26mm, or the refractive error ≥ -6.0D

5. Exclusion criteria

Exclusion Criteria
1) Failure to comply with research or follow-up procedures; 2) Diabetes with uncontrolled blood glucose (defined as fasting plasma glucose more than 7.0mmol/L or blood glucose more than 11.1mmol/ L 2 hours postprandial), and / or with diabetic retinopathy; 3) Poor control of blood pressure in hypertensive patients (defined as blood pressure >150/95mmHg, including antihypertensive medication);

4) With surgical contraindication due to other local or systemic conditions at screening or baseline;

5) With any active ocular or periocular infection or inflammation (e.g., blepharitis, conjunctivitis, keratitis, scleritis, uveitis, endophthalmitis) at screening or baseline;

6) With uncontrolled glaucoma at screening or baseline (IOP ≥ 30mmHg when receiving medical treatment or as judged by the researchers);

7) With the presence of iris neovascularization or neovascular glaucoma at screening or baseline;

8) With ocular diseases which may interfere the study results at screening or baseline, including severe vitreous hemorrhage, peripheral retinal hole, proliferative diabetic retinopathy, proliferative vitreoretinopathy (≥ Level C), choroidal detachment;

9) With other causes which may result in macular hole associated-retinal detachment at screening or baseline, except high myopia;

10) Previously underwent scleral buckling surgery;

11) With current or planned medication known to have toxic effects on the lens, retina or optic nerve, including hydroxychloroquine, chloroquine, hydroxychloroquine, tamoxifen, phenothiazine and ethambutol;

12) With laboratory abnormalities, such as ALT, AST, TB, GGT, LDH, exceeded the normal limit by more than 2 times, and CREA or blood urea nitrogen exceeded 1.2 times the normal limit;

13) With abnormal coagulation function (defined as more than normal prothrombin time for 3 seconds or more, more than 1.5 of the international standard ratio (INR), activated partial thromboplastin time of 10 seconds or longer than the upper limit of normal time);

14) Patients who participated in any clinical study of medication within 3 months prior to screening (excluding vitamins and minerals)

6. Exit criteria

Exit criteria

1) Due to adverse events, especially severe adverse events, the researchers consider withdrawal of patients based on concerns of safety and ethics;

2) Drop out;

3) The patients voluntarily withdraw the informed consent;

4) Serious violation of the study protocol due to the subjects or investigators' reasons;

5) Other reasons that the researchers believe for quitting the study

7. Treatment

Group 1: The patients in Group 1 are treated by the surgical method of standard 3-port 23 gauge pars plana vitrectomy + internal limiting membrane peeling + air-fluid exchange + silicone oil infusion

Group 2: The patients in Group 2 are treated by the surgical method of standard 3-port 23 gauge pars plana vitrectomy + internal limiting membrane peeling + inverted internal limiting membrane insertion + air-fluid exchange.

8. Inspection and observation schedule

Period / **Project**	**Screening period**	**Randomization period**	Follow up period[1]								
	Baseline	**Treatment**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**Termination**	**Unscheduled visit**
Visiting time	**-7~0d**	**0d**	**1d**	**1w**	**2w**	**4w**	**8w**	**12w**	**6m**	**12m**	**—**
Informed consent	×										
Inclusion and exclusion criteria	×	×[2]									

Demographic data	×										
Chief complaint and current medical history	×										
Medical history	×										
Previous surgery/ trauma history and ocular surgery history	×										
Diagnosis	×										
Vital signs [3]	×		×	×	×	×	×	×	×	×	×
General physical examination	×		×	×	×	×	×	×	×	×	×
Slit lamp examination [4] (binocular)	×										

Slit lamp examination [5] (study eye)			×	×	×	×	×	×	×	×	×
ECG and chest radiography[6]	×										
Laboratory examination [7]	×										
Auxiliary examination[8]	×		×	×	×	×	×	×	×	×	×
Low vision quality of life questionnaire [9]	×						×	×	×	×	
History change		×									
Randomization		×									
Surgical treatment		×									

Subject files	×										
Adverse events [10]		×	×	×	×	×	×	×	×	×	×
Previous / combined medication [11]	×	×	×	×	×	×	×	×	×	×	×
Quit in advance			×	×	×	×	×	×	×	×	
Statistical summary of major endpoints									×		
Summary of the study										×	
Unscheduled visits											×
Research statistics summary										×	

Remarks

(1) Visit Window: Visit 2 to visit 6; each visit has a window period of ±3 days; visit 7 and end visit allow a window period of ±7 days.

(2) If both the eyes meet the requirements in the screening, the eye with the poorer BCVA should be selected as the study eye, unless for medical reasons, the researchers believe that the other eye is more suitable for the research. The study eye will undergo surgical treatment according to the protocol. If the BCVA damage of the contralateral eye is caused by macular hole associated with retinal detachment secondary to high myopia, according to the

judgment of the researchers, the contralateral eye can also be recommended for surgical treatment. The contralateral eye was labeled as the contralateral eye for treatment. The treatment of bilateral eyes should not be performed on the same day.

(3) Vital signs, including blood pressure, pulse, respiration, armpit temperature, should be measured after sitting for 5 minutes.

(4) Slit lamp examination: Use “Slit Lamp Examination Form-I” (Attachment 1). Accept the examination results carried out before the informed consent signature during the same hospitalization.

(5) Slit lamp examination: Use “Slit Lamp Examination Form-II” (Attachment 2).

(6) ECG, chest radiography: Accept the examination results carried out before the informed consent signature during the same hospitalization.

(7) Laboratory examination includes routine blood test, blood biochemistry, routine blood coagulation, hepatitis B quantification, HCV antibody, TPPA+RPR and HIV antibody. Accept the examination results carried out before the informed consent signature during the same hospitalization.

(a) Routine blood test: white blood cell, neutrophil, lymphocyte, neutrophil ratio, lymphocyte ratio, red blood cell, hemoglobin, platelet.

(b) Blood biochemistry: alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, gamma glutamyltransferase, total bilirubin, direct bilirubin, total protein, albumin, urea, creatinine, uric acid, glucose, triglyceride, total cholesterol, potassium, sodium, chloride, calcium, phosphorus.

(c) Routine blood coagulation: prothrombin time, activated partial thromboplastin time, thrombin time, fibrinogen, prothrombin time -INR.

(8) Auxiliary examinations:

(a) Auxiliary examinations in the screening period include: BCVA OU, IOP OU, OCT of study eye, wide angle CP of study eye, the multifocal electroretinogram of study eye, microperimetry analysis of study eye, ocular axis measurement of study eye, B-scan ultrasound of study eye. Accept the examination results carried out before the informed consent signature during the same hospitalization.

(b) Auxiliary examinations in V1 and 2 include: BCVA OU, IOP OU, OCT of study eye, wide angle CP of study ocular axial measurement of study eye;

(c) Auxiliary examinations in V3 include: BCVA OU, IOP OU, OCT of study eye, wide angle CP of study eye, B-scan ultrasound of study eye;

(d) Auxiliary examinations in V4 include: BCVA OU, IOP OU, OCT of study eye, wide angle CP of study eye;

(e) Auxiliary examinations in V5, 6, 7, end visits, and unscheduled visits include: BCVA OU, IOP OU, OCT of study eye, wide angle CP of study eye, the multifocal electroretinogram of study eye, microperimetry analysis of study eye and B-scan ultrasound of study eye .

(9) The low vision quality of life questionnaire: Subjects were asked to self-rate according to the low vision quality of life questionnaire (Attachment 3);

(10) Adverse events: Adverse events were collected from the time the subjects sign informed consent until the end of the study.

(11) Previous/ combined medication: Collect relevant information from the time the subjects sign informed consent until the end of the study, including all the medication used for the treatment of AE or SAE.

9. Outcome Assessment

1) Primary Outcome Assessment:

Macular hole closure rate: Fundus examination combined with optical coherence tomography (OCT) are performed 3 months after surgery.

2) Secondary Outcome Assessment:

Best corrected visual acuity (LogMAR): 6 months after the surgery

Reattachment rate of retinal detachment: Use fundus examination combined with B-scan ultrasound, optical coherence tomography (OCT) to observe the reattachment rate of retinal detachment within 12 months after the surgery.(The reattachment rate assessment is performed 12 months after the first surgery among the patients with air tamponade. The reattachment rate assessment is performed 12 months after the first surgery among the patients with silicone oil tamponade, and the silicone oil removal is performed 6 months after the previous surgery.)

Postoperative complication rate

10. Adverse event

(1) Adverse events (AE) refer to any adverse event that occurs during clinical studies, but do not necessarily have causal relationship with the surgery.

Safety evaluation should be carried out from the signature of the informed consent until the end of the study, according to management requirements (Adverse events or serious adverse events should be reported).

(2) Severe adverse events (SAE) refer to the occurrence of hospitalization, prolonged

hospitalization, disability, incapacity, life-threatening or death, congenital malformations during the clinical trials.

(3) Record of adverse events

During the study, all adverse events should be recorded. Records should include the name of AE (using the standard medical terminology), the date of AE occurrence and disappearance / stablization, severity, impact on the surgery, relationship with the surgery, treatment measures and outcomes.

(4) Reports of serious adverse events

If serious adverse events occur, researchers must fill in the report of serious adverse events. The report should be signed and dated, and be reported to the ethics committee within 24 hours.

11. Target case load and sample size calculation

Target case load: 38

The study uses the superiority design. According to the references and the professional judgment, macular hole closure rate is 25% in the control group (group 1), while in the experimental group (group 2), macular hole closure rate is 65%. The significant level αis 0.05, and test performance (1- beta) is 0.80. The software of NCSS PASS 14 is used, and each group has 17 cases with the loss rate of 10%. The final sample size is 38.

12. Randomization

Stratified randomization is conducted according to the extent of retinal detachment [type 1 (within the arcade area), type 2 (beyond the arcade area)]. The software of NCSS PASS 14 will be used. The study includes 2 groups.

13. Masking method

In this study, the third party independent evaluation method is used to evaluate the results of the study. The analyzer is in the masking state, and the patients and the surgeons are in the non-masking state.

14. Statistical data processing

(1) Validity analysis: Descriptive statistical method is used to describe the research indicators. Univariate analysis of continuous variables is performed using ANOVA, and univariate analysis of categorical variables is performed using chi square test. The repeated measurement data are

analyzed by mixed effect model. The population of effectiveness analysis is the population of people with intention to be treated.

(2) Safety analysis: The safety assessment of clinical parameters (including adverse events, laboratory tests, vital signs, etc.) will be carried out. Descriptive statistics method is adopted. The safety analysis of the population is the population of all groups received treatment.

(3) Subgroup analysis: To determine whether the therapeutic effects of different subgroups are consistent, the component outcomes (and 95% confidence interval (CI)) are estimated for the major endpoints within the subgroup of the following categorical variables:

The type of retinal detachment [type 1 (within the arcade area), type 2 (beyond the arcade area)]

Gender (male and female)

15. Study implementation period (Anticipated)

April 7th, 2017 to April 6th, 2020

16. Quality Control

The researcher and laboratory personnel involved in this project must have the professional knowledge and experience required in the study protocol;

The researchers and other staff involved in the study perform their duties, and strictly follow the clinical trial plan and adopt standard operating procedures to ensure the implementation of the quality control and quality assurance system;

To ensure that the data is complete, accurate, authentic and reliable, all the relevant observation results and findings need to be verified in each phase of the clinical trials;

The researchers and other staff who participated in the study have sufficient time and reliable sources of subjects for the study;

For all examinations, examination room conditions must meet the requirements: clean, quiet, and no pollution; Pipeline arranged neatly; Safety management measures, emergency and first-aid facilities are all required; Instruments placed properly; Dustproof, shockproof, appropriate special ventilation and exhaust facilities are required; For the instruments sensitive with the change of temperature and humidity, there is a constant temperature and dehumidification device; The examination room responsible personnel with corresponding professional theory and practical

experience, can effectively organize, guide and carry out business, and be responsible for the study results; Different inspection instruments are operated by specially-assigned staff, and regular verification is required.

The specimen involved in the study are collected by specially-assigned staff;

The procedure is checked according to the standard operating procedures;

When the study protocol needs to be modified, ethical committees should be convened according to standard operating procedures, and the functions of the ethics committee should be fully applied to ensure the interests of the subjects to be protected;

Set up data files and keep all the original data according to the requirements of the scheme in chronological order for verification;

The inspectors regularly check the related activities and documents, to evaluate whether the study is operated according to the study protocol, standard procedures and relevant laws and regulations, and whether the test data is recorded timely, truly, accurately and completely. The inspection should be carried out by personnel not involved in the study, and the audit report shall be written. Meetings should be held with relevant personnel to discuss the problems found in the audit.

Specific Study Protocol

Overall objective

To evaluate the surgical outcomes of inverted internal limiting membrane insertion combined with air tamponade in the treatment of macular hole retinal detachment (MHRD) in high myopia, and also to compare the treatment efficacy between different surgical approaches of MHRD.

Main study contents

This study uses a new surgical method (vitrectomy combined with inverted internal limiting membrane insertion) to evaluate its effect on the prognosis of macular hole retinal detachment secondary to high myopia.

This study uses a new surgical method (intraocular sterilized air tamponade) to assess its effect on the prognosis of macular hole retinal detachment secondary to high myopia.

This study compares this new type of surgery with the current commonly used surgery (vitrectomy combined with internal limiting membrane peeling + silicone oil infusion) on the prognosis of macular hole retinal detachment secondary to high myopia.

Study protocol

Title:

A Single Center, Randomized and Controlled Clinical Study of Inverted Internal Limiting Membrane Insertion Combined with Air Tamponade in the Treatment of Macular Hole Retinal Detachment in High Myopia

Key word:

Surgical procedures, air tamponade, high myopia, macular hole retinal detachment

Study design:

Single center, randomized, controlled, interventional, prospective

Aim:

The aim of this study is to evaluate the effectiveness and safety of different surgical procedures for patients with macular hole retinal detachment secondary to high myopia.

Primary Outcome Measure:

To evaluate the effectiveness of different surgical procedures by evaluating the following indicators:

Macular hole closure rate: Fundus examination combined with optical coherence tomography (OCT) are performed 3 months after surgery.

Secondary Outcome Measure:

To evaluate the effectiveness and safety of different surgical procedures by evaluating the following indicators:

Best corrected visual acuity (LogMAR): 6 months after the surgery

Reattachment rate of retinal detachment: Use fundus examination combined with B-scan ultrasound, optical coherence tomography (OCT) to observe the reattachment rate of retinal detachment within 12 months after the operation.(The reattachment rate assessment is performed 12 months after the first surgery among the patients with air tamponade. The reattachment rate assessment is performed 12 months after the first surgery among the patients with silicone oil tamponade, and the silicone oil removal is performed 6 months after the previous surgery.)

Postoperative complication rate of ocular adverse events

Postoperative complication rate of the non ocular adverse events

Postoperative complication rate of severe adverse events

Key inclusion criteria

Prior written consent is required before any assessment.

Study eye selection criteria:

Age: ≥18 years old, ≤75 years old

Visual impairment is caused by macular hole associated with retinal detachment secondary to high myopia

Axial length ≥ 26mm, or the refractive error ≥ -6.0D

Key exclusion criteria

Exclusion criteria for general medical history:

Local or systemic surgical contraindications at screening or baseline

For both eyes:

With any ocular eye or periocular infection or inflammation (e.g., blepharitis, conjunctivitis, keratitis, scleritis, uveitis, endophthalmitis) at screening or baseline;

With uncontrolled glaucoma at screening or baseline (IOP ≥ 30mmHg when receiving medical treatment or as judged by the researchers);

With the presence of iris neovascularization or neovascular glaucoma at screening or baseline.

For research eye:

With ocular diseases which may interfere the study results at screening or baseline , including severe vitreous hemorrhage, peripheral retinal hole, proliferative diabetic retinopathy, proliferative vitreoretinopathy (≥ Level C), choroidal detachment;

With other causes which may result in macular hole associated-retinal detachment at screening or baseline, except high myopia;

Previously underwent scleral buckling surgery.

Exclusion criteria for past or current systemic drug use:

With current or planned medication known to have toxic effects on the lens, retina or optic nerve, including hydroxychloroquine, chloroquine, hydroxychloroquine, tamoxifen, phenothiazine and ethambutol.

Study design

This study is a prospective, randomized, controlled study, involving multiple visits within 12 months. The patients with macular hole retinal detachment secondary to hign myopia are randomly

divided into 2 treatment groups:

Group 1: The patients in Group 1 are treated by the surgical method of standard 3-port 23 gauge pars plana vitrectomy + internal limiting membrane peeling + air-fluid exchange + silicone oil infusion

Group 2: The patients in Group 2 are treated by the surgical method of standard 3-port 23 gauge pars plana vitrectomy + internal limiting membrane peeling + inverted internal limiting membrane insertion + air-fluid exchange

Sample size calculation

The study uses the superiority design. According to the references and the professional judgment, macular hole closure rate is 25% in the control group (group 1), while in the experimental group (group 2), macular hole closure rate is 65%. The significant level αis 0.05, and test performance (1- beta) is 0.80. The software of NCSS PASS 14 is used, and each group has 17 cases with the loss rate of 10%. The final sample size is 38.

Grouping method

Patients are assessed whether they meet the inclusion/exclusion criteria before inclusion. The clinical research center completes the compliance assessment form, preoperative consents and informed consent. Informed consent is a qualified standard, since it is agreed by the subjects to be selected, randomly assigned, and agreed to complete the regular follow-up after the surgery.

1) Informed consent of the subjects

In this study, researchers must explain the research purpose, process, possible profit and risk to the subjects (or the legal representative, or witnesses). Only when the subjects (or the legal representative, or witnesses) fully understand the study, and sign informed consent, can they be selected.

The informed consent form should be signed by the subjects (or their legal representatives or witnesses) and the researcher who executed the informed consent procedure in two copies, each of which has one copy.

2) Allocation of screening number of subjects

The subjects who signed the informed consent will be assigned to a screening number. The center will assign a number of 4 Arabia numbers to each subject, with individual uniqueness. Among them, the first number represents the clinical center number, and the second, third, fourth number is the ordinal number, which is assigned to each subject according to the chronological order of the informed consent agreement. The subjects name writing rules: When the name is consisted with two characters, fill in the first two letters of each phonetic alphabet; When the name is consisted with three characters, fill in the first letters of each phonetic alphabet and the second letter of the third phonetic alphabet; When the name is consisted with four characters, fill in the first letters of each phonetic alphabet; When the name is consisted with five or more than five characters, fill in the first letters of the first four phonetic alphabets.

Randomized controlled clinical trial design is used in this study.

Randomization: Stratified randomization is conducted according to the type of retinal detachment [type 1 (within the arcade area), type 2 (beyond the arcade area)]. The software of NCSS PASS 14 will be used. The study includes 2 treatment groups.

According to randomization procedures, the researchers assign ID numbers to patients. The ID number of the randomization group must be recorded together with the patient screening number in a random directory. Completed random directory should be signed and hand over to the data center by the researcher.

Masking method

In this study, the third party independent evaluation method is used to evaluate the results of the study. The analyzer is in the masking state, and the subjects and the surgeons are in the non-masking state.

Outcome evaluation

1) Primary Outcome Measures:

To evaluate the effectiveness of different surgical procedures by evaluating the following

indicators:

The difference between macular hole closure rate, closed type in each group from baseline to the 3rd month

2) Secondary Outcome Measures:

To evaluate the effectiveness and safety of different surgical procedures by evaluating the following indicators:

The difference of the reattachment rate of retinal detachment between each group from baseline to the 6th month

The difference of the reattachment rate of retinal detachment between each group from baseline to the 12th month

The change of BCVA relative to baseline and the difference between groups from baseline to the 6th month

The change of BCVA relative to baseline and the difference between groups from baseline to the 12th month

The number of people whose BCVA result improves by more than 1 row, 2 rows and 3 rows comparing to the baseline at a time.

The number of people whose BCVA result decreases by 3 rows comparing to the baseline at a time

The difference of multifocal ERG results between each group from 1 week to the 6th month after surgery

The difference of multifocal ERG results between each group from 1 week to the 12th month after surgery

The change of microperimetry analysis results from 1 week to the 6th month after surgery relative to baseline, and the difference between each group

The change of microperimetry analysis results from 1 week to the 12th month after surgery relative to baseline, and the difference between each group

The change of the extent of foveal ellipsoid zone damage from baseline to the 6th month after the surgery relative to baseline, and the difference between each group

The change of the external limiting membrane integrity of fovea from baseline to the 6th month after the surgery relative to baseline, and the difference between each group

The change of the extent of foveal ellipsoid zone damage from baseline to the 12th month after the surgery relative to baseline, and the difference between each group

The change of the external limiting membrane integrity of fovea from baseline to the 12th month after the surgery relative to baseline, and the difference between each group

Describe the number of retreatment and retreatment modalities for patients with different surgical procedures over a period of 12 months

Evaluate the safety of different surgical procedures by assessing the type, frequency and severity of ocular adverse events and non-ocular adverse events or severe adverse events during 12 months

Data analysis

(1) Validity analysis: Descriptive statistical method is used to describe the research indicators. Univariate analysis of continuous variables is performed using ANOVA, and univariate analysis of categorical variables is performed using chi square test. The repeated measurement data are analyzed by mixed effect model. The population of effectiveness analysis is the population of people with intention to be treated.

(2) Safety analysis: The safety assessment of clinical parameters (including adverse events, laboratory tests, vital signs, etc.) will be carried out. Descriptive statistics method is adopted. The safety analysis of the population is the population of all groups received treatment.

(3) Subgroup analysis: To determine whether the therapeutic effects of different subgroups are consistent, the component outcomes (and 95% confidence interval (CI)) are estimated for the major endpoints within the subgroup of the following categorical variables:

The type of retinal detachment [type 1 (within the arcade area), type 2 (beyond the arcade area)]

Gender (male and female)

CRC assistance

The study requires one to two clinical research coordinator (CRC)

Responsiblities:

(1) Contact the subjects before 3-7 days before a follow-up;

(2) Communicate with the director in advance, and make appointments for patient follow-ups;

(3) Arrange the relevant examination for the patients;

(4) Have good communication skills;

(5) Fill in Case Report Form.

Benefit status of subjects

The therapy in this study may help to further control the patient's condition, to optimize the treatment of the disease, to provide the necessary advice for the future treatment of patients, to provide useful information for treatment or disease;

If the subjects quit the study, the doctors will still perform the related examinations and treatments to ensure the safety of the subjects.

Risk supervision

The principal investigator and researchers should make full use of the informed consent when asking the patient to participate in the clinical trial. They should confirm that the patients fully understand its content, participate in this study based on the their free will, and sign the informed consent. The principal investigator, researchers and participants should sign on the informed consent form respectively.

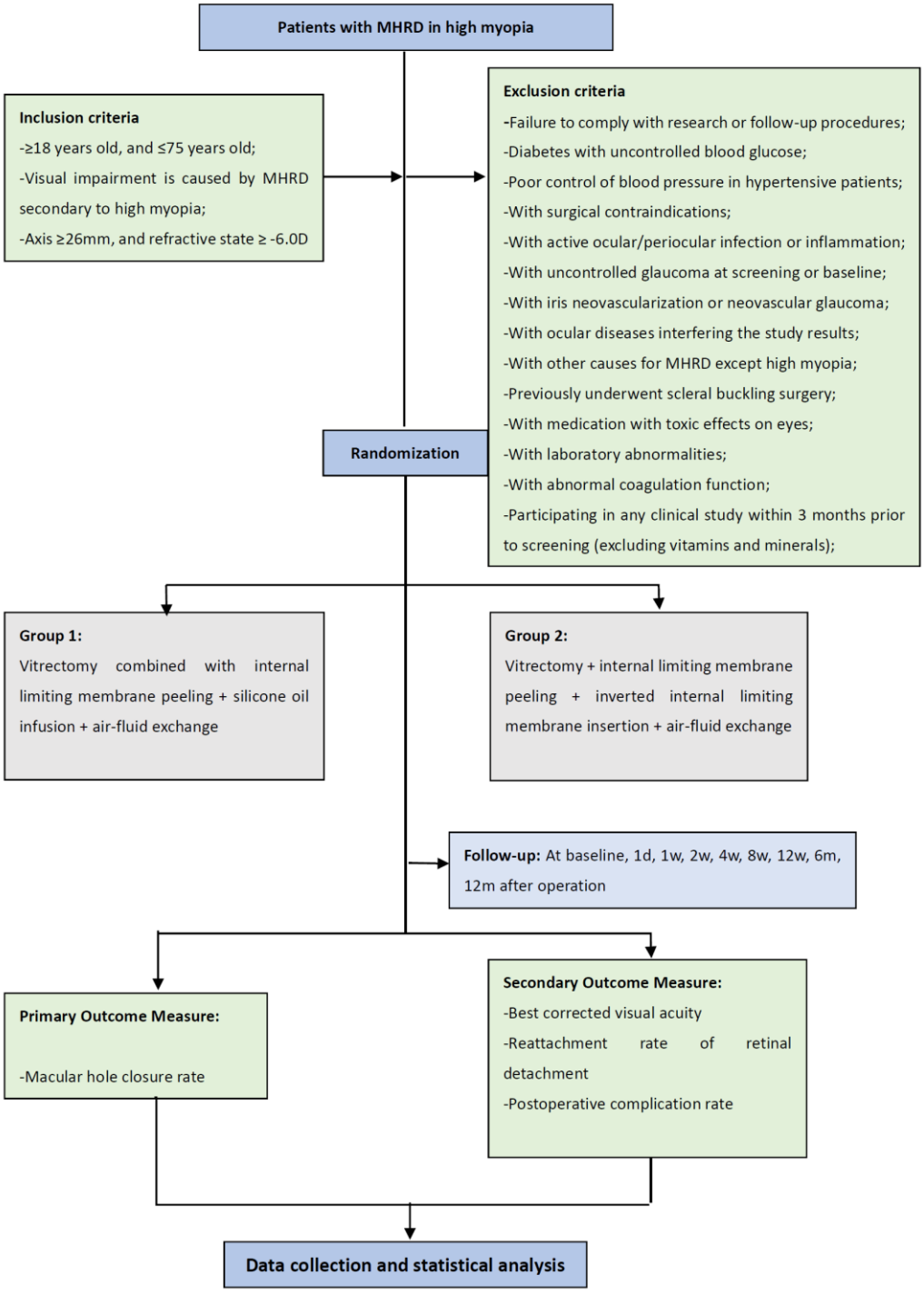
During the implementation process of the clinical trials, if serious adverse events (including the events such as the occurrence of hospitalization, prolonged hospitalization, disability, incapacity, life-threatenning or death, congenital malformation during the process of the clinical trial) occur, the events must be promptly reported to the center of clinical trials and the principal investigator.

When the subjects suffer any health impairment caused by the study, researchers undertake the cost of treatment and the corresponding economic compensation for clinical trial-related injury or death, except the impairment caused by medical accidents.

Research schedule

Time	Schedule
2017.4~2018.3	Enroll patients, observe patients, collect clinical data, complete international clinical trial registration (clinicaltrial.gov), and complete midterm summary of patients who completed the first year visit
2018.4~2019.3	Follow patients up and collect clinical data
2019.4~2020.4	Complete the visit of all patients, complete the analysis of clinical data, subject summary, and prepare acceptance.

Technology Roadmap



Attachment 1

Slit Lamp Examination Form (right eye)-I

Whether to have slit lamp examination (right eye)?: $_{1}$□Yes→Please record as follows, $_{0}$□No	
Other lesions of eyelid	$_{0}$□No $_{1}$□Yes, Please describe: _____
1. Conjunctiva (right eye)	
Congestion	$_{0}$□Normal. It may appear white or reddish pink, without peripheral congestion. The conjunctival or bulbar conjunctival vessels are easily observed $_{1}$□Slight redness, reddish color, mainly confined to the palpebral conjunctiva or bulbar conjunctiva $_{2}$□Mild redness, reddish color, mainly confined to the conjunctiva or bulbar conjunctiva $_{3}$□Moderate, palpebral conjunctiva or bulbar conjunctiva is bright red $_{4}$□Severe, palpebral conjunctiva or bulbar conjunctiva is deep diffuse bright red
Edema	$_{0}$□Normal, no swelling $_{1}$□Slight, beyond normal and regional $_{2}$□Mild, mild conjunctival swelling, beyond normal, regional $_{3}$□Moderate, conjunctival swelling moderately $_{4}$□Severe, large conjunctival swelling
Subconjunctival hemorrhage	$_{0}$□Nil, no bleeding $_{1}$□Slight, flat and less than 1 quadrant $_{2}$□Mild, bulging, and 1 quadrant, or flat and more than 1 quadrants $_{3}$□Moderate, bulging and >1 quadrant, but less than 2 quadrants $_{4}$□Severe, bulging and more than 2 quadrants

Other conjunctival lesions	0□No 1□Yes, Please describe: _____
2. Cornea (right eye)	
Edema	0□Nil, transparent and clear 1□Slight, micro and local epithelial haze 2□Mild, turbid vitreous appearance and may contain tiny droplets 3□Moderate, turbid vitreous appearance with a large number of vacuoles 4□Severe, bullous and / or stromal edema, localized or diffuse, with or without matrix streaks
Other corneal lesions	0□No 1□Yes, Please describe: _____

Slit Lamp Examination Form (right eye)-I

3. Anterior chamber (right eye)	
Cell number	0□Nil, no cells 1□Slight, 1-5 cells 2□Mild, 6-25 cells 3□Moderate, 26-50 cells 4□Severe, the number of cells is too large to count
Anterior chamber flare	0□Nil, no Tyndall effect 1□Slight, almost cannot distinguish the Tyndall effect 2□Mild, slight brightness 3□Moderate, strong brightness 4□Severe, very strong and aqueous humor is white or milky
Other lesions	0□No 1□Yes, Please describe: _____
4. Iris / pupil (right eye)	
Iris / pupil (right eye)	Clinically significant abnormality: 0□No1□Yes, Please describe:

	_____
5. Lens (right eye)	
Lens (right eye)	1□Complete 2□Artificial 3□Nil
Other lesions	0□No 1□Yes, Please describe: _____
Transparency	
Cortex	0□Nil 1□There are turbidity, but below standard pictures  2□There are turbidity, and the severity of the standard picture is the same or more serious  3□Not applicable
Nucleus	0□Nil 1□Turbid, but below standard pictures  2□Turbid, the same or more serious than standard pictures  3□Not applicable
Posterior capsule	0□Nil 1□Turbid, but below standard pictures  2□Turbid, the same or more serious than standard pictures  3□Not applicable

Slit Lamp Examination Form (right eye)-I

6. Vitreum (right eye)

Anterior vitreous cell count	0□Nil, no cells 1□Slight, 1-10 cells 2□Mild, 11-30 cells 3□Moderate, 30-50 cells 4□Severe, >50 cells
Other lesions	0□No 1□Yes, Please describe: _____
Vitreous / anterior retinal hemorrhage	0□Nil 1□Slight 2□Mild 3□Moderate 4□Severe
7. Macular and retina (right eye)	
Macular hole	0□Nil 1□Hole diameter≤1/3PD 2□Hole diameter>1/3PD, and≤1/2PD 3□Hole diameter>1/2PD, and≤1PD 4□Hole diameter>1PD
Retinal detachment	0□Nil 1□Yes, Please describe: 1□Within the arcade 2□Beyond the arcade, and within the equator 3□Beyond the equator
Peripheral retinal split holes	0□No 1□Yes, Please describe: _____
Posterior scleral staphyloma	0□No 1□Yes, Please describe: _____
Other lesions	0□No 1□Yes, Please describe with words or pictures:

	_____

Attachment 1

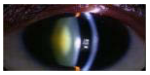
Slit Lamp Examination Form (left eye)-I

Whether to have slit lamp examination (left eye)?: 1□Yes→Please record as follows, 0□No	
Other lesions of eyelid	0□No 1□Yes, Please describe: _____
1. Conjunctiva (right eye)	
Congestion	0□Normal. It may appear white or reddish pink, without peripheral congestion. The conjunctival or bulbar conjunctival vessels are easily observed 1□Slight redness, reddish color, mainly confined to the palpebral conjunctiva or bulbar conjunctiva 2□Mild redness, reddish color, mainly confined to the conjunctiva or bulbar conjunctiva 3□Moderate, palpebral conjunctiva or bulbar conjunctiva is bright red 4□Severe, palpebral conjunctiva or bulbar conjunctiva is deep diffuse bright red
Edema	0□Normal, no swelling 1□Slight, beyond normal and regional 2□Mild, mild conjunctival swelling, beyond normal, regional 3□Moderate, conjunctival swelling moderately 4□Severe, large conjunctival swelling
Subconjunctival hemorrhage	0□Nil, no bleeding 1□Slight, flat and less than 1 quadrant 2□Mild, bulging, and 1 quadrant, or flat and more than 1 quadrants 3□Moderate, bulging and >1 quadrant, but less than 2 quadrants

	4□Severe, bulging and more than 2 quadrants
Other conjunctival lesions	0□No 1□Yes, Please describe: _____
2. Cornea (left eye)	
Edema	0□Nil, transparent and clear 1□Slight, micro and local epithelial haze 2□Mild, turbid vitreous appearance and may contain tiny droplets 3□Moderate, turbid vitreous appearance with a large number of vacuoles 4□Severe, bullous and / or stromal edema, localized or diffuse, with or without matrix streaks
Other corneal lesions	0□No 1□Yes, Please describe: _____

Slit Lamp Examination Form (left eye)-I

3. Anterior chamber (left eye)	
Cell number	0□Nil, no cells 1□Slight, 1-5 cells 2□Mild, 6-25 cells 3□Moderate, 26-50 cells 4□Severe, the number of cells is too large to count
Anterior chamber flare	0□Nil, no Tyndall effect 1□Slight, almost cannot distinguish the Tyndall effect 2□Mild, slight brightness 3□Moderate, strong brightness 4□Severe, very strong and aqueous humor is white or milky
Other lesions	0□No 1□Yes, Please describe: _____
4. Iris / pupil (left eye)	

Iris / pupil (right eye)	Clinically significant abnormality: 0□No1□Yes, Please describe: _____
5. Lens (left eye)	
Lens (right eye)	1□Complete 2□Artificial 3□Nil
Other lesions	0□No 1□Yes, Please describe: _____
Transparency	
Cortex	0□Nil 1□There are turbidity, but below standard pictures  2□There are turbidity, and the severity of the standard picture is the same or more serious  3□Not applicable
Nucleus	0□Nil 1□Turbid, but below standard pictures  2□Turbid, the same or more serious than standard pictures  3□Not applicable
Posterior capsule	0□Nil 1□Turbid, but below standard pictures  2□Turbid, the same or more serious than standard pictures  3□Not applicable

Slit Lamp Examination Form (left eye)-I

6. Vitreum (left eye)	
Anterior vitreous cell count	0□Nil, no cells 1□Slight, 1-10 cells 2□Mild, 11-30 cells 3□Moderate, 30-50 cells 4□Severe, >50 cells
Other lesions	0□No 1□Yes, Please describe: _____
Vitreous / anterior retinal hemorrhage	0□Nil 1□Slight 2□Mild 3□Moderate 4□Severe
7. Macular and retina (left eye)	
Macular hole	0□Nil 1□Hole diameter≤1/3PD 2□Hole diameter>1/3PD, and≤1/2PD 3□Hole diameter>1/2PD, and≤1PD 4□Hole diameter>1PD
Retinal detachment	0□Nil 1□Yes, Please describe: 1□Within the arcade 2□Beyond the arcade, and within the equator 3□Beyond the equator
Peripheral retinal split holes	0□No 1□Yes, Please describe: _____
Posterior scleral staphyloma	0□No 1□Yes, Please describe: _____

Other lesions	0□No 1□Yes, Please describe with words or pictures: _____

Attachment 2

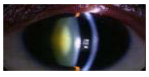
Slit Lamp Examination Form (study eye)-II

Whether to have slit lamp examination (study eye)?: 1□Yes→Please record as follows, 0□No	
Other lesions of eyelid	0□No 1□Yes, Please describe: _____
1. Conjunctiva (study eye)	
Congestion	0□Normal. It may appear white or reddish pink, without peripheral congestion. The conjunctival or bulbar conjunctival vessels are easily observed 1□Slight redness, reddish color, mainly confined to the palpebral conjunctiva or bulbar conjunctiva 2□Mild redness, reddish color, mainly confined to the conjunctiva or bulbar conjunctiva 3□Moderate, palpebral conjunctiva or bulbar conjunctiva is bright red 4□Severe, palpebral conjunctiva or bulbar conjunctiva is deep diffuse bright red
Edema	0□Normal, no swelling 1□Slight, beyond normal and regional 2□Mild, mild conjunctival swelling, beyond normal, regional 3□Moderate, conjunctival swelling moderately 4□Severe, large conjunctival swelling
Subconjunctival hemorrhage	0□Nil, no bleeding 1□Slight, flat and less than 1 quadrant 2□Mild, bulging, and 1 quadrant, or flat and more than 1 quadrants

	3□Moderate, bulging and >1 quadrant, but less than 2 quadrants 4□Severe, bulging and more than 2 quadrants
Other conjunctival lesions	0□No 1□Yes, Please describe: _____
2. Cornea (study eye)	
Edema	0□Nil, transparent and clear 1□Slight, micro and local epithelial haze 2□Mild, turbid vitreous appearance and may contain tiny droplets 3□Moderate, turbid vitreous appearance with a large number of vacuoles 4□Severe, bullous and / or stromal edema, localized or diffuse, with or without matrix streaks
Other corneal lesions	0□No 1□Yes, Please describe: _____

Slit Lamp Examination Form (study eye)-II

3. Anterior chamber (study eye)	
Cell number	0□Nil, no cells 1□Slight, 1-5 cells 2□Mild, 6-25 cells 3□Moderate, 26-50 cells 4□Severe, the number of cells is too large to count
Anterior chamber flare	0□Nil, no Tyndall effect 1□Slight, almost cannot distinguish the Tyndall effect 2□Mild, slight brightness 3□Moderate, strong brightness 4□Severe, very strong and aqueous humor is white or milky
Other lesions	0□No 1□Yes, Please describe: _____

4. Iris / pupil (study eye)	
Iris / pupil (study eye)	Clinically significant abnormality: 0□No1□Yes, Please describe: _____
5. Lens (studyeye)	
Lens (study eye)	1□Complete 2□Artificial 3□Nil
Other lesions	0□No 1□Yes, Please describe: _____
Transparency	
Cortex	0□Nil 1□There are turbidity, but below standard pictures  2□There are turbidity, and the severity of the standard picture is the same or more serious  3□Not applicable
Nucleus	0□Nil 1□Turbid, but below standard pictures  2□Turbid, the same or more serious than standard pictures  3□Not applicable
Posterior capsule	0□Nil 1□Turbid, but below standard pictures  2□Turbid, the same or more serious than standard pictures  3□Not applicable

Slit Lamp Examination (study eye)-II

6. Vitreum (study eye)	
Anterior vitreous cell count	0□Nil, no cells 1□Slight, 1-10 cells 2□Mild, 11-30 cells 3□Moderate, 30-50 cells 4□Severe, >50 cells
Other lesions	0□No 1□Yes, Please describe: _____
Vitreous / anterior retinal hemorrhage	0□Nil 1□Slight 2□Mild 3□Moderate 4□Severe
Air volume in vitreous cavity	0□Nil 1□≤30% 2□>30%, and≤50% 3□>50%, and≤70% 4□>70% 5□Not applicable
Silicone oil volume in vitreous cavity	0□Nil 1□>50%, and≤70% 2□>70%, and≤90% 3□>90% 4□Not applicable
7. Macular and retina (research eye)	
Macular hole	0□Nil 1□Hole diameter≤1/3PD 2□Hole diameter>1/3PD, and≤1/2PD 3□Hole diameter>1/2PD, and≤1PD

	4□Hole diameter>1PD
Retinal detachment	0□Nil 1□Yes, Please describe: 1□Within the arcade 2□beyond the arcade, and within the equator 3□Beyond the equator
Peripheral retinal split holes	0□No 1□Yes, Please describe: _____
Posterior scleral staphyloma	0□No 1□Yes, Please describe: _____
Other lesions	0□No 1□Yes, Please describe with words or pictures: _____

Attachment 3

Low vision quality of life questionnaire

5=Nil; 4-2=Moderate; 1=Severe; x=Unable to do.

How well do you know about your current vision? 5=Much, 1=Little

1. Because of your vision, in the following circumstances, do you feel difficult?.	
1. Feel tired (for example, only after a short time using eyes)	□5 □4 □3 □2 □1□x □Others
2. At home at night	□5 □4 □3 □2 □1□x □Others
3. Look at things in the right amount of light	□5 □4 □3 □2 □1□x □Others
4. Feel the light glare (such as car lamp or sun make you dazzle)	□5 □4 □3 □2 □1□x □Others
5. Look at road signs	□5 □4 □3 □2 □1□x □Others
6. Watch TV (or enjoy pictures)	□5 □4 □3 □2 □1□x □Others
7. Look at moving objects (such as cars on the road)	□5 □4 □3 □2 □1□x □Others
8. Determine the distance or depth of objects	□5 □4 □3 □2 □1□x □Others
9. See the stairs or railings	□5 □4 □3 □2 □1□x □Others
10. Walk outdoors (e.g., on an uneven sidewalk)	□5 □4 □3 □2 □1□x □Others
11. Cross the street when there is vehicles	□5 □4 □3 □2 □1□x □Others
12. Generally speaking	□5 □4 □3 □2 □1□x □Others
2. Because of your vision, so you	
1. Not satisfied with your current life	□5 □4 □3 □2 □1□x □Others
2. Be upset about not being able to do some work	□5 □4 □3 □2 □1□x □Others
3. Visiting relatives and friends is limited	□5 □4 □3 □2 □1□x □Others
4..How well do you know about your current vision	□5 □4 □3 □2 □1□x □Others
3. If you use visual aids or glasses, if there are difficulties when doing the following things	
1.Identify uppercase fonts	□5 □4 □3 □2 □1□x □Others
2. Read newspaper articles and books	□5 □4 □3 □2 □1□x □Others
3. Read labels (for example, on a bottle or kit)	□5 □4 □3 □2 □1□x □Others
4. Reading letters	□5 □4 □3 □2 □1□x □Others

5. Use some tools (such as sutures or scissors)	□5 □4 □3 □2 □1□x □Others
4. If you use visual aids or glasses, if there are difficulties when doing the following things	
1. Watch the clock to know the time	□5 □4 □3 □2 □1□x □Others
2. Sign or write cards	□5 □4 □3 □2 □1□x □Others
3. Identify your own handwriting	□5 □4 □3 □2 □1□x □Others
4. Do daily activities (such as housework)	□5 □4 □3 □2 □1□x □Others

Attachment 4

Abbreviations

Abbreviations and special terms	**Explanation**
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BCVA	Best corrected visual acuity
CREA	Serum creatinine
Wide angle CP	Wide angle fundus color photography
GGT	Glutamyl transferase
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
LDH	Lactate dehydrogenase
LogMAR visual acuity	Standard logarithmic visual acuity
MHRD	Macular hole complicated with retinal detachment
INR	International normalized ratio
IOP	Intraocular pressure
OCT	Optical coherence tomography

OD	Right eye
OS	Left eye
OU	Both eyes
PDR	Proliferative diabetic retinopathy
PVR	Proliferative vitreoretinopathy
TB	Total bilirubin
TPPA+RPR	Treponema pallidum antibody gelatin particle agglutination test + syphilis serum test
VA	Vision acuity