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Title {1}: A protocol for a parallel assignment prospective, randomized, comparative trial to evaluate the safety and efficacy of intense pulsed light (IPL) combined with 3% diquafosol (DQS) ophthalmic solution in dry eye syndrome.

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ABSTRACT

Background: Evaporative dry eye (EDE) is common and can lead to ocular pain, decreased visual quality, and reduced quality of life. Intense pulsed light (IPL) and 3% diquafosol ophthalmic solution have been found to be beneficial in reducing signs and symptoms of dry eye.

Methods: A randomized clinical trial was performed at He Eye Specialty hospital in Shenyang. 150 DED patients were randomly equally divided into IPL group, DQS group, and IPL+ group (IPL combined with 3% diquafosol eye drops). All groups follow up for four weeks. The primary outcome measure was the non-invasive tear breakup time (NIBUT), Ocular Surface Disease Index (OSDI) change from baseline. The secondary outcome measures included the conjunctival and cornea staining (CFS) with fluorescein and lissamine, meibomian gland function and secretion quality, tear film lipid layer score (TFLL), Tear meniscus height (TMH), conjunctival hyperemia (RS score) change from baseline for improvement in ocular symptoms. Adverse events also were monitored and documented.

Discussion: This study aimed to assess whether the combination of IPL with 3% diquafosol ophthalmic solution (study group) is more effective than IPL (active control group) or 3% diquafosol ophthalmic solution (active control group) in participants with evaporative dry eye.

Trial registration {2a, 2b}: Registration number: Clniicaltrials.gov NCT05694026. Name of the trial registry: Management of dry eye with Intense Pulsed Light combined with 3% diquafosol ophthalmic solution, registered on Jan 10, 2023.

Keywords: Dry eye, intense pulsed light, diquafosol ophthalmic solution, RCT

Note: The numbers in curly brackets in this protocol refer to the SPIRIT checklist item numbers. The order of the items has been modified to similar group items (see http://www. equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/).

Protocol version {3}: 2023, version 2

Funding {4}: This study was entirely funded by He Eye Specialist Hospital, Shenyang, China. No support was received for the publication of this article.

Trial sponsor {5b}: Department of Ophthalmology, He Eye Specialist Hospital, Shenyang 110034, China.

Roles and responsibilities {5c}: The study was sponsored and funded entirely by He Eye Specialist Hospital, Shenyang, China.

Composition of the coordinating center and trial Steering Committee {5d}: The subject leader and the project manager will form the Steering Committee (SC). The SC accountable for managing the whole project. The Monitor Group's (MG) inspectors are appointed by the SC. The MG will oversee the entire research procedure in compliance with the GCP requirements. The inspector analyses the investigator's adherence to the protocol, the protection of participants' rights and interests, the quality of the CRF form, and the investigators' understanding of different standards before submitting inspection reports to the SC.

INTRODUCTION

Background and rationale {6a, 6b}

Evaporative dry eye (EDE) has been reported to be the most prevalent form of dry eye disease (DED), [1–3]which is primarily caused by meibomian gland hypofunction or meibomian gland dysfunction (MGD).[4–6] MGD is defined as ‘‘a chronic, diffuse anomaly of the meibomian glands, often characterized by terminal duct blockage and/or qualitative/quantitative alterations in glandular secretion’’ by the International Workshop on MGD.[1,7] These glands are modified sebaceous glands that release meibum directly onto the ocular surface. Signs and symptoms of EDE and MGD can be addressed by improving the quality and quantity of meibum secretion.[8]

Diquafosol ophthalmic sodium is a P2Y2 receptor agonist, which can promote the secretion of mucin and lipid. It also improves the tear film composition and stability[9–

11]. It has a corneal epithelial-repairing effect and can be used to treat ocular surface damage caused by dry eye[5,12,13]. By targeting the inflammation involved in the pathogenesis of dry eye, it can inhibit the expression of inflammatory pathways and inflammatory factors that are involved in the pathogenesis of dry eye[14–16].

Intense pulsed light (IPL) is widely used to treat dermatological conditions[17], and its noncoherent polychromatic light source with a wide wavelength range of 500–1200 nm has been reported to stimulate facial sebaceous glands[18,19]. The photothermal effect of IPL is postulated to relieve inflammation by removing aberrant surface microvasculature and enhancing meibomian gland function[20–22]. Furthermore, an increase in fibroblast proliferation, collagen formation, and local blood flow has been associated with the application of IPL on the skin[23,24]. Several studies have documented the benefits of IPL in alleviating signs and symptoms of DED on the periocular skin[25–27] and combined it with other therapies such as heated eye mask (HEM) [28,29], 0.1% sodium hyaluronate eye drops [22], and blood extract eye drops[30]. Therefore, an RCT is warranted to assess the safety and efficacy of combining IPL with DQS for patients suffering from DED.

OBJECTIVES {7}

The primary objective of this study is to assess whether the combination of intense pulsed light with 3% diquafosol ophthalmic solution is more effective than intense pulsed light and 3% diquafosol ophthalmic solution in alleviating signs and symptoms of DED.

Trial design {8}

This is a prospective, randomized controlled trial performed at He Eye Specialist Hospital (HESH). The study adheres to the tenets of the Declaration of Helsinki and is registered at ClinicalTrails.gov (NCT05694026) using the SPIRIT reporting guidelines[31]. Randomization will be performed using a web-based, online, sealed envelope-based system (https://www.sealedenvelope.com). Specific study information sheets will be provided to patients prior to taking consent. Following a dedicated screening and randomization visit for eligible patients, participants will be randomized to one of three trial arms.

Study setting {9}

This study will be conducted between Mar 1, 2023, and Nov 30, 2023. Participants will be recruited at the Department of Ophthalmology, He Eye Specialist Hospital (HESH).

Eligibility criteria {10}

Inclusion criteria:

1. Age ≥18 years
2. Consenting participants
3. Able and willing to comply with the treatment/follow-up schedule
4. Bilateral signs and symptoms of dry eye disease: (i) Ocular Surface Disease Index (OSDI) questionnaire ≥13, (ii) Non-invasive tear breakup time (NITBUT) ≤ 5

seconds, (iii) conjunctival staining score (CS) ≥3 points. The presence of two or more criteria was used to establish a positive DE diagnosis, based on the 2016 Asia Dry Eye Society criteria

Exclusion criteria:

1. A recent history (past 30 days) of topical ophthalmic medication use, including antibiotics, steroids, non-steroidal anti-inflammatory drugs, or required the chronic use of topical ophthalmic medications
2. Eyelids or intraocular tumors that should not put pressure
3. Active allergy or infection or inflammatory disease that may have prevented the subjects from completing the study at the ocular surface
4. Any structural change in lacrimal passage
5. Glaucoma
6. Diabetes or other systemic, dermatologic, or neurologic diseases that affect the health of ocular surface
7. Use of any systemic anti-inflammatory drugs or medication that may interfere with tear production, such as antianxiety, antidepressive, and antihistamine medications within 3 months

Interventions {11a, 11b, 11c, 11d}

After enrollment in the study, Treatments were initiated after randomization immediately. None of the patients included were undergoing any topical or systemic agent for DE or MGD during this study; other treatments related to DED and any other dry eye systemic or topical medication, treatment, or therapy will be prohibited. If dry

eye signs and symptoms worsen, participants will be stopped and advised to use the designated device. Adverse events (AE) will be continuously monitored. In case of an AE, participants will be informed about the severity of the event, and PI will decide if participants can continue further. If participants consent and agree, they will be reminded daily regarding the administration of eye drops, recording their exposure to mobile phones or computer time, and any queries regarding the study will be answered by trailed clinical staff at HESH.

Participants in DQS group and IPL+ group will be used 1 drop of 3% DQS (Diquas; Santen Pharmaceutical Co., Ltd., Osaka, Japan) 6 times per day for 4 weeks (28 days), whereas participants in the IPL+ group and IPL group will undergo two IPL treatment sessions of M22 (Lumenis Ltd., Yokneam, Israel) IPL system, 2 weeks apart. IPL treatment utilizes a noncoherent polychromatic light source with a wavelength spectrum of 500–1200 nm on the cutaneous facial sebaceous glands.

OUTCOMES {12}

All patients are assessed at baseline, 14, and 28 days. We plan to use primary and secondary outcomes measures symptoms, corneal and meibomian gland improvement were compared between the three groups.

Primary Outcome

Ocular Surface Disease Index (OSDI): OSDI is a questionnaire consisting of 12 questions for evaluating the effects of dry eye syndrome on vision, ocular symptoms

and any condition associated with DED[32]. The patient will answer each question on a scale ranging from 0 to 4, with 0 indicating 'none of the time' and 4 indicating 'all of the time'. If a certain question is deemed irrelevant, it will be marked as 'not applicable (N/A)' and excluded from the analysis. The OSDI total score is calculated according to the following formula. The scale ranges from 0 to 100, with higher scores representing more severe cases of dry eye syndrome[33,34].

Non-invasive tear breakup time (NIBUT): Non-invasive initial tear film breaking time will be assessed using the Keratograph 5M (Oculus, Germany) topographer. Three sequential readings will be captured, and the median value will be included in the final analysis. The median value will be recorded[35,36].

Secondary outcomes

Fluorescein and lissamine conjunctival and cornea staining (CFS): Fluorescein and lissamine staining of the ocular surface will be divided into three zones comprising nasal conjunctival, corneal, and temporal conjunctival areas. The staining score ranged from 0 to 3 for each zone, yielding a total score of 0-9 for the ocular surface[37,38].

Tear meniscus height (TMH): Non-invasive first tear film breakup time using the Keratograph 5M (Oculus, Germany) topographer will be measured three times consecutively and the median value was recorded[35,39].

Conjunctival hyperemia (RS score): Conjunctival hyperemia (RS score) will be assessed by Keratograph image (Oculus, Germany) of 1156*873 pixels, redness score (RS) (accurate to 0.1 U) was displayed on the computer screen that ranged from 0.0

(normal) to 4.0 (severe)[36,40].

Meibomian gland function and secretion quality: Meibum quality will be assessed under a slit-lamp[41]: Five meibomian gland in the middle parts of the eyelid will be assessed using a scale of 0 to 3 for each gland (0 represented clear meibum; 1 represented cloudy meibum; 2 represented cloudy and granular meibum; and 3 represented thick, toothpaste-like consistency meibum)[42,43].

Tear Film Lipid Layer Score (TFLL): Tear Film Lipid Layer interferometry will be assessed using DR-1 (Kowa, Nagoya, Japan). The results will be graded as follows: grade 1, somewhat gray color, uniform distribution; grade 2, somewhat gray color, nonuniform distribution; grade 3, a few colors, nonuniform distribution; grade 4, many colors, nonuniform distribution; grade 5, corneal surface partially exposed[44–46].

Participant timeline {13}

The schedule for data collection and visits is shown in table 1. After registration for this study, the assigned treatment intervention will be administered for 4 weeks. Furthermore, the effect will be examined during the 2-week follow-up period of 4 weeks (**Figure 1**).

Sample size {14}

On the basis of a non-inferiority margin of 7.3, it was anticipated that 106 participants per treatment group would give 90% power to establish non-inferiority of IPL+ group compared IPL group and DQS group in mean change from baseline in

OSDI score at day 28. With the inclusion of the multidose treatment groups, about 350 individuals is estimated to be enrolled. The intended-to-treat population comprised all randomized individuals and was utilized for all efficacy studies.

The primary and secondary efficacy analyses utilized a two-way analysis of variance that accounted for treatment and baseline OSDI score stratification in order to compare treatment differences. Using paired t-tests, within-treatment differences from baseline were evaluated (alpha level 0.05). Using analysis of variance, additional analyses of OSDI subgroups and questionnaire data were conducted. Using descriptive statistics, safety data were summarized.

Recruitment {15}

This clinical study will be done in a single site, with participants blinded to the treatment assignment. This research is open to patients diagnosed with DED at He Eye Specialist Hospital's Department of Ophthalmology. Participants will be recruited using adverts in the distribution pamphlets, the website, and social media postings. Each participant's demographic information (including ocular diseases and current/previous usage of drugs and/or lubricating eye drops) will be collected during the first (screening) appointment. Participants will not be limited based on age, gender, or ethnicity (Table 1).

	STUDY PERIOD					
	Enrolment	Allocation	Post-allocation			Close-out
TIMEPOINT:	**Jan 2023**	**2023**	**DAY 0**	**DAY14**	**DAY28**	**End-2023**
ENROLMENT:						
Eligibility screen	×					
Informed consent	×					
Allocation		×				
INTERVENTIONS:						
[IPL+DQS]			←	—	→	
[IPL]			←	—	→	
[DQS]			←	—	→	
ASSESSMENTS:						
[The baseline variables]	×	×				
[The primary outcome]			×	×	×	×
[The second outcome]			×	×	×	×

243 **Table 1.** The schedule of enrolment, interventions, and assessments of this trial

METHODS

Assignment of interventions (for controlled trials) {16a, 16b}

A web-based randomization application will be used (https://www.project-redcap.org/). Allocation will be carried out using block randomization and stratified according to age (allocation factor: age <80 years or ≥80 years).

Implementation {16c}

Random allocation will be conducted after the enrolment. Random numbers with corresponding participants will be determined in the order of the time of the visit and divided into 3 groups (IPL+, IPL, or DQS group). The allocation result will not be announced to the participants until the end of the data collection phase of the trial. Researchers collecting and analyzing data related to this trial will be blinded to the participant allocation results.

Blinding (masking) {17a, 17b}

The treatment assignment for the study will be triple-masked. Participants in the research would be unable to recognize the contents. A masked examiner for all clinical assessments will not be involved in the data collection or group allocation procedure for this research. The investigator will not be aware of the three groups. Participants will be randomly assigned to one of three treatment groups and underwent IPL

treatment with 12 homogeneously spaced pulsed light to both eyes and sham treatment to both eyes. The box containing the ampoules is labeled with a batch number, study reference number, participant ID, contact number, investigator name, site address, the expiration date of the eye drops, storage instructions, and a statement informing the participant that the eye drops are for use only in clinical trials and should not be ingested. The circumstances and procedures under which unblinding is permissible will be determined and performed by the PI.

Data collection methods and management {18a, 18b, 19}

Data administration is the responsibility of Jiayan Chen, HESH, Department of Clinical Research, as chosen by the principal investigator (Emmanuel Eric Pazo). This research collects data using a proprietary EMR case report form and management application. The individual responsible for statistical analysis will get the locked data following the database lock. The data management handbook specifies the specifics. After the study has been finished, a report on the implementation and status of data management will be compiled and sent to the PI with the locked research data.

Statistical methods {20a, 20b, 20c}

Statistical Analysis in Social Sciences (SPSS) for MacOS software was used to analyze the data (version 26, IBM Corp.). Data from both eyes were collected at baseline, first follow-up at week 2, and second follow-up at week 4 for all patients participating in the treatment. Repeated measures analysis allowed for comparisons

across time periods, while paired analyses allowed for comparisons of pre-and post-treatment data at specific time periods. The Kolmogorov-Smirnoff test will be used to determine the normality of variables. The background of the study's subjects will be tabulated by calculating the mean and standard deviation for continuous variables and the frequency and percentage for categorical variables. Analysis of variance will be used to analyze ordinal variables and those having nonnormal distributions (ANOVA). The primary outcome measures for this study are NITBUT OSDI scores before and after treatment. For the main endpoint, between-group comparisons using baseline as a covariate and an analysis of covariance will be made to produce the adjusted mean, its 95% confidence interval, and the p value.

METHODS

Monitoring

Data monitoring {21a, 21b}

Due to the projected low frequency of adverse events and the modest numbers in each location, no data monitoring committee has been convened for this trial. The database will be constructed using Excel (Microsoft, USA 2022 version), and regular data monitoring will be undertaken in accordance with the sponsor's standard operating procedures. The steering committee (SC) will have oversight and access to the trial under the supervision of the trial manager (TM) at any time during the study.

Harms {22}

Adverse events are unanticipated indications, symptoms, or illnesses seen during a clinical study, regardless of their relationship to the treatment. There may be local, general, and psychological harmful effects. Local symptoms may include corneal epithelium disorder (filamentary keratitis, superficial keratitis, corneal erosion, etc.), conjunctivitis, eye irritation, eye discharge, conjunctival hyperemia, eye pain, eye itching, ocular foreign body sensation, visual discomfort, hyposphagma, abnormal sensation in the eye (dry eye sensation, strange eye sensation, sticky eye sensation), blurred vision, photophobia, and lacrimation. If major adverse events occur, HESH Certified Review Board will be notified; experimental treatments will be discontinued promptly, and appropriate therapies will be offered.

Auditing {23}

The study will be reviewed and evaluated weekly by an independent supervisor not related to the PI and sponsors.

DISCUSSION

DQS is a dinucleotide polyphosphate which is a purinoceptor agonist; when administered to the ocular surface, it binds to P2Y2 receptors and stimulates mucin and tear secretion.[47–49] At present, multi-center clinical trials have proved the advantages and efficacy of diquafosol sodium drops in the treatment of dry eyes, and the Asian Dry Eye Work Shop identifies it as the current first-choice treatment for aqueous tear deficiency dry eyes and as one of the first choices for the treatment of

mucin deficiency dry eyes.

Literature review shows that intense pulsed light (IPL) is a relatively new method for the treatment of lipid-abnormal dry eye caused by MGD, which can relieve the symptoms and signs of MGD-related dry eye by reducing eyelid inflammation, thermal effect, sterilization, and acariasis, and light regulation[50,51]. This result should allow us to assess the effectiveness of the combination of intense pulsed light with 3% DQS ophthalmic solution. In future studies, we will further expand the sample size and conduct a deeper study on the mechanism of symptom improvement in the hope of providing clinicians with more treatment options.

ETHICS AND DISSEMINATION

Research ethics approval {24}: This study will be conducted in compliance with the tenets of the Declaration of Helsinki and the Institutional Review Board of He Eye Specialist Hospital, Shenyang, China.

Protocol amendments {25}

If there are modifications to eligibility criteria, outcomes, or analyses, a revised protocol will be submitted for approval to the HESH Medical Ethics Committee.

Consent or assent {26a, 26b}

Trained and experienced clinicians will seek informed permission from prospective

participants.

Confidentiality {27}

Participant's personal information will be kept confidential in the same way as their medical histories in the hospital before, during, and after the trial.

Declaration of interests {28}: None

Access to data {29}: Not applicable.

Ancillary and post-trial care {30}: Not applicable.

Dissemination policy {31a, 31b, 31c}: The results of the trial will be reported and disseminated regardless of the direction of the effect. Trial findings will be disseminated to the patients and doctors. This will take the form of papers in peer-reviewed open-access medical journals and presentations at conferences

Trial Status

Recruitment began in April 2023 and the approximate date when recruitment will be completed is June 2023. Protocol version 2.0 was approved on December 2022.

APPENDICES

Informed consent materials {32}: Not applicable

Biological specimens {33}: Not applicable.

Author Contributions

Conception and design of the research: JC, GQ, LL, YQ, HC, HH, YX, QZ, YW, LY, SM, JEM, LX, WH, SY, XH, and EEP; analysis and interpretation of the data: JC, GQ, EEP; writing original draft preparation: JC; critical revision of the manuscript (reviewing and editing): JC and EEP; supervision: XH, SY, and EEP.

Disclosures

JC, GQ, LL, YQ, HC, HH, YX, QZ, YW, LY, SM, JEM, LX, WH, SY, XH and EEP have no disclosures.

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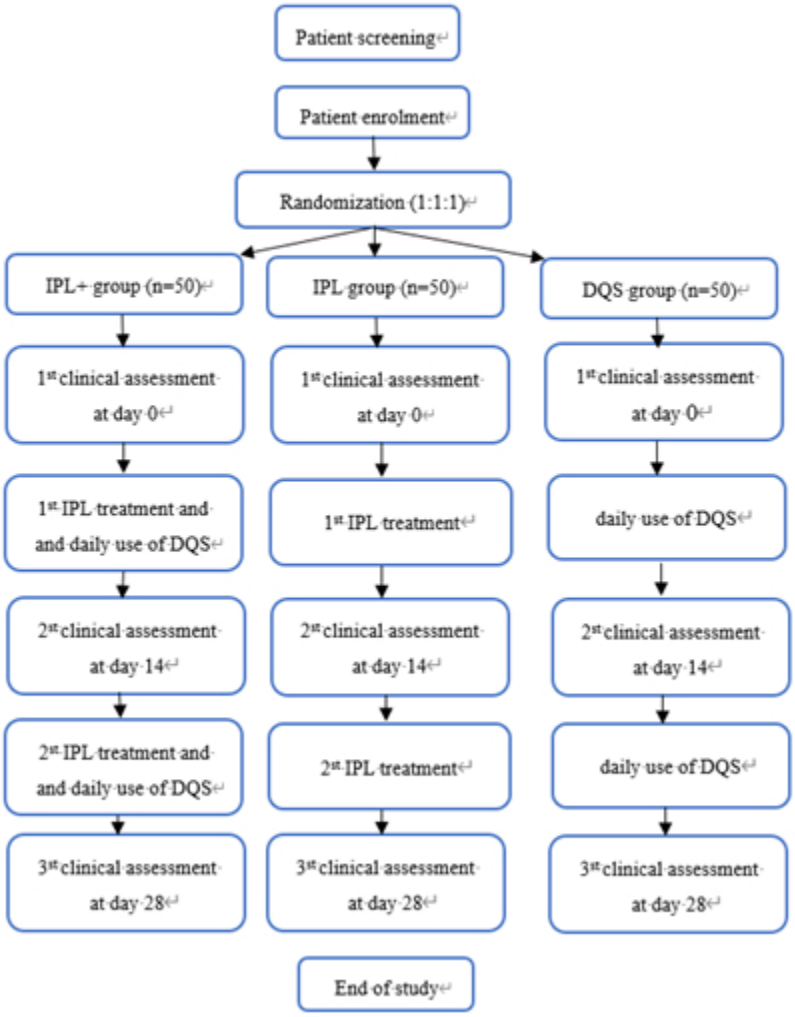
Figure 1. Study flow chart (The schedule for data collection and visits)



study flow chart

36x46mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	#3	Date and version identifier	3
Funding	#4	Sources and types of financial, material, and other support	3
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	3
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	3
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	4
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6

Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	7
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	12
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be	13

		provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	13
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	14
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	14
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	14
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	15
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15

Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	16
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	16
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	16
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	17
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	18
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	18
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	18

Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	18
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	18
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	19
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	19
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	19
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	19
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	19
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	19
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	19

BMJ Open

A protocol for a parallel assignment prospective, randomized, comparative trial to evaluate the safety and efficacy of intense pulsed light (IPL) combined with 3% diquafosol (DQS) ophthalmic solution in dry eye syndrome.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-073055.R1
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Complete List of Authors:	Chen, Jiayan; He Eye Specialist Hospital, Ophthalmology Qin, Guanghao; He Eye Specialist Hospital, Ophthalmology Li, Liangzhe; He Eye Specialist Hospital, Ophthalmology Qi, Yifan; He Eye Specialist Hospital, Ophthalmology Che, Huixin ; He Eye Specialist Hospital, Ophthalmology Huang, He; He Eye Specialist Hospital, Ophthalmology Xia, Yang; He Eye Specialist Hospital, Ophthalmology Zhang, Qing; Tianjin Medical University Eye Hospital, Ophthalmology Wu, Yi; China Medical University Second Hospital, Ophthalmology Yang, Lanting; Wenzhou Medical University Eye Hospital Moutari, Salissou ; Queen's University Belfast Moore, Jonathan ; Cathedral Eye Clinic Xu, Ling ; He Eye Specialist Hospital, Ophthalmology He, Wei; He Eye Specialist Hospital, Ophthalmology Yu, Sile; He Eye Specialist Hospital, Ophthalmology He, Xingru; He Eye Specialist Hospital, Ophthalmology Pazo, Emmanuel Eric; He Eye Specialist Hospital, Ophthalmology
Primary Subject Heading:	Ophthalmology
Secondary Subject Heading:	Research methods, Pharmacology and therapeutics
Keywords:	Orbital and lacrimal disorders < OPHTHALMOLOGY, Laser therapy < DERMATOLOGY, Corneal and external diseases < OPHTHALMOLOGY

Protocol

Title: A protocol for a parallel assignment prospective, randomized, comparative trial to evaluate the safety and efficacy of intense pulsed light (IPL) combined with 3% diquafosol (DQS) ophthalmic solution in dry eye syndrome.

Names protocol contributors： Jiayan Chen[1], Guanghao Qin[1], Liangzhe Li[1], Yifan Qi[1], Huixin Che[1], He Huang[1], Yang Xia[1], Qing Zhang[2], Yi Wu[3], Lanting Yang[4], Salissou Moutari[5], Jonathan E Moore[6], Ling Xu[1], Wei He[1], Sile Yu[1,7], Xingru He[1,7]*, Emmanuel Eric Pazo[1]*

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ABSTRACT

Introduction: Evaporative dry eye (EDE) is common and can lead to ocular pain, decreased visual quality, and reduced quality of life. Intense pulsed light (IPL) and 3% diquafosol ophthalmic solution have been found to be beneficial in reducing signs and symptoms of dry eye.

Methods and analysis: A randomized clinical trial will be performed at He Eye Specialist Hospital in Shenyang. 318 DED patients will be randomly equally divided into the IPL group, DQS group (diquafosol ophthalmic solution eye drops), and IPL+ group (IPL combined with 3% diquafosol eye drops). All groups will be followed up for four weeks. The primary outcome measures will be the non-invasive tear break-up time (NIBUT) and the Ocular Surface Disease Index (OSDI) change from the baseline. The secondary outcome measures included the conjunctival and cornea staining (CFS) with fluorescein and lissamine, meibomian gland function and secretion quality, tear film lipid layer score (TFLL), tear meniscus height (TMH), conjunctival hyperemia (RS score) change from the baseline for improving ocular symptoms. Adverse events also will be monitored and documented.

Discussion: This study aimed to assess whether the combination of IPL with 3% diquafosol ophthalmic solution (study group), IPL+ (study group), is more effective than IPL (active control group) or DQS (active control group) in participants with evaporative dry eye.

Ethics and dissemination: Registration number: Clniicaltrials.gov NCT05694026. Name of the trial registry: Management of dry eye with Intense Pulsed Light combined with 3% diquafosol ophthalmic solution, registered on Jan 10, 2023. Ethics approval number: IRB (2022) K029.01. The study's findings will be shared regardless of the effect's direction.

Keywords: Dry eye, intense pulsed light, diquafosol ophthalmic solution, RCT

Strengths and limitations of this study:

- The trial is designed to be embedded into routine clinical practice, providing more options for treatment.
- The protocol promotes standardization of therapy and outcome assessment, enabling credible inference about risks and benefits.
- A large RCT has not been conducted to understand the benefits of DQS and IPL on DED patients.
- Publications in high-impact, open-access medical journals and talks at national and international medical conferences will serve this purpose.
- In future studies, we will further conduct a deeper analysis on the mechanism of symptom improvement.

Administrative information

The numbers in curly brackets in this protocol refer to the SPIRIT checklist item numbers. The order of the items has been modified to similar group items (see http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/).

Title {1}	A protocol for a parallel assignment prospective, randomized, comparative trial to evaluate the safety and efficacy of intense pulsed light (IPL) combined with 3% diquafosol (DQS) ophthalmic solution in dry eye syndrome
Trial registration {2a and 2b}	Registration number: Clniicaltrials.gov NCT05694026. Ethics approval number: IRB (2022) K029.01
Protocol version {3}	2023, version 2
Funding {4}	This study was entirely funded by He Eye Specialist Hospital, Shenyang, China.
Author details {5a}	**Jiayan Chen**. He Eye Specialist Hospital, Shenyang, China. **Quanghao Qin**. He Eye Specialist Hospital, Shenyang, China.

	Liangzhe Li. He Eye Specialist Hospital, Shenyang, China. **Yifan Qi**. He Eye Specialist Hospital, Shenyang, China. **Huixin Che.** He Eye Specialist Hospital, Shenyang, China. **He Huang.** He Eye Specialist Hospital, Shenyang, China. **Yang Xia.** He Eye Specialist Hospital, Shenyang, China. **Qing Zhang**. Tianjin Medical University, Tianjin, China. **Yi Wu**. China Medical University, Shenyang, China. **Lanting Yang**. Wenzhou Medical University, Wenzhou, China. **Salissou Moutari**. Mathematical Sciences Research Centre, School of Mathematics and Physics, QQueen'sUniversity Belfast, Belfast, UK. **Jonathan E Moore**. Cathedral Eye Clinic, Belfast, United Kingdom. **Ling Xu**. He Eye Specialist Hospital, Shenyang, China. **Wei He**. He Eye Specialist Hospital, Shenyang, China. **Sile Yu**. School of Public Health, He University, Shenyang, China. Department of Ophthalmology, He Eye Specialist Hospital, Shenyang, China. **Xingru He**. School of Public Health, He University, Shenyang, China. Department of Ophthalmology, He Eye Specialist Hospital, Shenyang, China. **Emmanuel Eric Pazo**. Department of Ophthalmology, He Eye Specialist Hospital, Shenyang, China.
Name and contact information for the trial sponsor {5b}	This is an investigator-initiated research, so the principal investigator acts as the sponsor. Emmanuel Eric Pazo (Principal Investigator). ericpazo@outlook.com
Role of sponsor {5c}	Investigator-initiated research

INTRODUCTION

Background and rationale {6a}

Evaporative dry eye (EDE) has been reported to be the most prevalent form of dry eye disease (DED), [1–3] which is primarily caused by meibomian gland hypofunction or meibomian gland dysfunction (MGD).[4–6] MGD can be chronic or diffused anomaly of the meibomian glands, often characterized by terminal duct blockage and qualitative/quantitative alterations in glandular secretion" b" the International

Workshop on MGD.[1,7] These glands are modified sebaceous glands that release meibum directly onto the ocular surface. Signs and symptoms of EDE and MGD can be addressed by improving the quality and quantity of meibum secretion.[8]

Diquafosol ophthalmic sodium is a dinucleotide polyphosphate which is a purinoceptor agonist; when administered to the ocular surface, it binds to P2Y2 receptors and stimulates mucin and tear secretion.[9–11]. It also improves the tear film composition and stability[12–14]. It has a corneal epithelial-repairing effect and can be used to treat ocular surface damage caused by dry eye[5,15,16]. By targeting the inflammation involved in the pathogenesis of dry eye, it can inhibit the expression of inflammatory pathways and inflammatory factors that are involved in the pathogenesis of dry eye[17–19]. The safety and benefits of DQS in improving dry eye signs and symptoms have been demonstrated in randomized clinical trials[20]. At present, DQS is clinically available as a 3% ophthalmic solution (Diquas, Santen) which, due to rapid ocular clearance, requires frequent administration (6 times/day)[21].

Intense pulsed light (IPL) is widely used to treat dermatological conditions[22], and its noncoherent polychromatic light source with a wide wavelength range of 500–1200 nm has been reported to stimulate facial sebaceous glands[23,24]. The photothermal effect of IPL is postulated to relieve inflammation by removing aberrant surface microvasculature and enhancing meibomian gland function[25–27]. Furthermore, an increase in fibroblast proliferation, collagen formation, and local blood flow has been associated with the application of IPL on the skin[28,29]. Several studies including Toyos [30] et al. and Martínez-Hergueta [31] et al. have evaluated the safety

and benefits of IPL therapy for improving signs of DED. [32–34] and combined it with other therapies such as heated eye mask (HEM) [35,36], 0.1% sodium hyaluronate eye drops [27], and blood extract eye drops[37]. Therefore, an RCT is warranted to assess the safety and efficacy of combining IPL with DQS for patients suffering from DED.

Objectives {7}

The primary objective of this study is to assess whether the combination of intense pulsed light with 3% diquafosol ophthalmic solution is more effective than intense pulsed light and 3% diquafosol ophthalmic solution in alleviating signs and symptoms of DED.

Trial design {8}

This is a prospective, randomized controlled trial performed at He Eye Specialist Hospital (HESH) [ethics approval number: IRB (2022) K029.01]. The study adheres to the tenets of the Declaration of Helsinki and is registered at ClinicalTrails.gov (NCT05694026) using the SPIRIT reporting guidelines[38]. Randomization will be performed using a web-based, online, sealed envelope-based system (https://www.sealedenvelope.com). Specific study information sheets will be provided to patients prior to taking consent. Following a dedicated screening and randomization visit for eligible patients, participants will be randomized to one of three trial arms.

Methods: Participants, interventions, and outcomes

Study setting {9}

This study will be conducted between Mar 1, 2023, and Nov 30, 2023. Participants will be recruited at the Department of Ophthalmology, He Eye Specialist Hospital (HESH).

Eligibility criteria {10}

Inclusion criteria:

1. Age ≥18 years
2. Consenting participants.
3. Able and willing to comply with the treatment/follow-up schedule.
4. Bilateral signs and symptoms of dry eye disease: (i) Ocular Surface Disease Index (OSDI) questionnaire ≥13, (ii) Non-invasive tear break-up (NITBUT) ≤ 5 seconds, (iii) conjunctival staining score (CS) ≥3 points. The presence of two or more criteria was used to establish a positive DE diagnosis based on the 2016 Asia Dry Eye Society criteria.

Exclusion criteria:

1. A recent history (past 30 days) of topical ophthalmic medication use, including antibiotics, steroids, non-steroidal anti-inflammatory drugs, or required the chronic use of topical ophthalmic medications.
2. Eyelids or intraocular tumors.
3. Active allergy or infection, or inflammatory disease may prevent the subjects from completing the study at the ocular surface.

4. Any structural changes in the lacrimal passage.
5. Glaucoma.
6. Diabetes or other systemic, dermatologic, or neurologic diseases that affect the health of the ocular surface.
7. Use of any systemic anti-inflammatory drugs or medication that may interfere with tear production, such as antianxiety, anti-depressive, and antihistamine medications, within three months.
8. Pregnant or breastfeeding.
9. Contact lenses wearers.

Informed consent {26a}

Trained and experienced clinicians will seek informed permission from prospective participants.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

This trial does not involve collecting biological specimens.

Interventions

The explanation for the choice of comparators {6b}

After enrollment in the study, treatments will be initiated immediately after randomization. Participants in the DQS group and IPL+ group will use one drop of 3%

DQS (Diquas; Santen Pharmaceutical Co., Ltd., Osaka, Japan) 6 times per day for four weeks (28 days), whereas participants in the IPL+ group and IPL group will undergo two IPL treatment sessions of M22 (Lumenis Ltd., Yokneam, Israel) IPL system, two weeks apart. IPL treatment utilizes a noncoherent polychromatic light source with a wavelength spectrum of 500–1200 nm on the cutaneous facial sebaceous glands.

Intervention description {11a}

In this study, patients receive either DQS, IPL, or IPL combined with DQS for four weeks based on the group they are placed in. Two follow-up visits were performed at week two and week 4 in all groups; comprehensive eye exams will be conducted by an ophthalmologist, including primary outcomes, secondary outcomes, and safety evaluation.

Criteria for discontinuing or modifying allocated interventions {11b}

If dry eye signs and symptoms worsen, participants will be stopped and advised to use the designated device. Adverse events (AE) will be continuously monitored. In case of an AE, participants will be informed about the severity of the event, and PI will decide if participants can continue further. If participants consent and agree, they will be reminded daily regarding the administration of eye drops, recording their exposure to mobile telephones or computer time, and any queries regarding the study will be answered by trained clinical staff at HESH.

Strategies to improve adherence to interventions {11c}

Participants will be reminded by phone and email every week, and then appointments will be scheduled in advance according to their availability time. In order to improve adherence, patients will be given a medication record booklet, and their medication status will be checked at each follow-up visit. In the event of non-compliance, such as absence, participants will be contacted by phone or email to ask if they will continue or terminate the study early.

Relevant concomitant care permitted or prohibited during the trial {11d}

Any other dry eye systemic or topical medication, treatment, or therapy will be prohibited during the course of this study.

Provisions for post-trial care {30}

There is no anticipated harm and compensation for trial participation, but participants who show signs and symptoms of deterioration in their dry eye status will be directed to their local dry eye center for further treatment.

Outcomes {12}

All patients will be assessed at baseline, 14, and 28 days. We plan to use primary and secondary outcomes measures, symptoms, and corneal and meibomian gland improvement will be compared between the three groups.

Primary Outcome

Ocular Surface Disease Index (OSDI): OSDI is a questionnaire consisting of 12 questions for evaluating the effects of dry eye syndrome on vision, ocular symptoms, and any condition associated with DED[39]. The patient will answer each question on a scale ranging from 0 to 4, with '0' indicating 'none of the time' and '4' indicating 'all of the time.' If a particular question is deemed irrelevant, it will be marked as 'not applicable (N/A)' and excluded from the analysis. The OSDI total score is calculated according to the following formula. The total score ranges from 0 to 100, with higher scores representing more severe cases of dry eye disease symptoms [40,41].

Non-invasive tear break-up (NIBUT): The Keratograph 5M (Oculus, Germany) topographer will assess non-invasive initial tear film breaking time. Three sequential readings will be captured, the median value will be included in the final analysis, and the median value will be recorded [42,43].

Secondary outcomes

Fluorescein and lissamine conjunctival and cornea staining (CFS): Fluorescein and lissamine staining of the ocular surface will be divided into three zones comprising nasal conjunctival, corneal, and temporal conjunctival areas. The staining score ranged from 0 to 3 for each zone, yielding a total score of 0-9 for the ocular surface[44,45].

Tear meniscus height (TMH): Non-invasive first tear film break-up using the Keratograph 5M (Oculus, Germany) topographer will be measured three times consecutively, and the median value was recorded[42,46].

Conjunctival hyperemia (RS score): Conjunctival hyperemia (RS score) will be assessed by Keratograph image (Oculus, Germany) of 1156*873 pixels, redness score (RS) (accurate to 0.1 U) was displayed on the computer screen that ranged from 0.0 (normal) to 4.0 (severe)[43,47].

Meibomian gland function and secretion quality: Meibum quality will be assessed under a slit-lamp[48]: Five meibomian glands in the middle parts of the eyelid will be evaluated using a scale of 0 to 3 for each gland (0 represented clear meibum; 1 represented cloudy meibum; 2 represented cloudy and granular meibum; and three means thick, toothpaste-like consistency meibum)[49,50].

Tear Film Lipid Layer Score (TFLL): The interferometry patterns will be assessed using DR-1 (Kowa, Nagoya, Japan). The results will be graded as follows: grade 1, somewhat gray color, uniform distribution; grade 2, rather gray color, nonuniform distribution; grade 3, a few colors, nonuniform distribution; grade 4, many colors, nonuniform distribution; grade 5, corneal surface partially exposed [51–53].

Participant timeline {13}

The schedule for data collection and visits is shown in Table 1. After registration for this study, the assigned treatment intervention will be administered for four weeks. Furthermore, the effect will be examined during the 2-week follow-up period of 4 weeks (**Figure 1**).

Sample size {14}

The sample size calculation is based on the primary outcome measures, namely NITBUT and OSDI scores, to establish the non-inferiority of the IPL+ group compared to IPL group and DQS group in terms of the changes in the mean from the baseline in OSDI score at day 28. For the NITBUT scores, a sample size of 106 is sufficient to detect a clinically significant difference of 0.51 between the IPL+ group and either of the two other groups (IPL group and DQS group) while assuming a standard deviation of 1.15, using a two-tailed t-test of difference between means with 90% power and a 5% level of significance. For the OSDI scores, a sample size of 98 is sufficient to detect a clinically significant difference of 1.2 between the IPL+ group and either of the two other groups (IPL group and DQS group) while assuming a standard deviation of 2.6, using a two-tailed t-test of difference between means with 90% power and a 5% level of significance. Therefore, the required sample size is max (106, 98) = 106.

With the inclusion of the multidose treatment groups and a dropout rate of 8%, it is estimated that about 350 individuals will be enrolled. The intended-to-treat population comprised all randomized individuals and was utilized for all efficacy studies.

The primary and secondary efficacy analyses will utilize a two-way analysis of variance that will account for treatment and baseline OSDI score stratification in order to compare treatment differences. Using paired t-tests, within-treatment differences from baseline will be evaluated (alpha level 0.05). Using analysis of variance, additional analyses of OSDI subgroups and questionnaire data will be conducted. Using descriptive statistics, safety data will be summarized.

Recruitment {15}

This clinical study will be done in a single site, with participants blinded to the treatment assignment. This research is open to patients diagnosed with DED at He Eye Specialist Hospital's Department of Ophthalmology. Participants will be recruited using adverts in the distribution pamphlets, the website, and social media postings. Each participant's demographic information (including ocular diseases and current/previous usage of drugs and/or lubricating eye drops) will be collected during the first (screening) appointment. Participants will not be limited based on age, gender, or ethnicity (Table 2).

Items	Baseline	2w	4w
Informed consent	√		
Patient background	√		
Ocular Surface Disease Index (OSDI) scores	√	√	√
IOP	√	√	√
BCVA	√	√	√
Non-invasive tear break-up (NIBUT)	√	√	√
conjunctival and cornea staining (CFS)	√	√	√
Tear Film Lipid Layer Score (TFLL)	√	√	√
Corneal endothelial cells	√	√	√
Tear meniscus height (TMH)	√	√	√

Conjunctival hyperemia (RS score)	√	√	√
Meibomian gland function	√	√	√
Meibomian secretion quality	√	√	√
Adverse event (AE)		√	√

√: All groups

Patient background, including date of birth, gender, race, ethnicity, and allergy history.

Table 1. Schedule for data collection and visits

	STUDY PERIOD					
	Enrolment	**Allocation**	**Post-allocation**			**Close-out**
TIMEPOINT:	**Jan 2023**	**2023**	**DAY 0**	**DAY14**	**DAY28**	**End-2023**
ENROLMENT:						
Eligibility screen	×					
Informed consent	×					
Allocation		×				
INTERVENTIONS:						
[IPL+DQS]			←	—	→	
[IPL]			←	—	→	

[DQS]			←	—	→	
ASSESSMENTS:						
[The baseline variables]	×	×				
[The primary outcome]			×	×	×	×
[The second outcome]			×	×	×	×

Table 2. The schedule of enrolment, interventions, and assessments of this trial

Assignment of interventions: Allocation

Sequence generation {16a}

A web-based randomization application will be used (https://www.project-redcap.org/). Randomization will be by simple randomization. Allocation will be carried out using block randomization and stratified according to age (allocation factor: age <80 years or ≥80 years) (known only to the statistical team, not stated here to maintain masking). Participants will be in a 1:1:1 allocation ratio to IPL group, DQS group, or IPL+ group.

Concealment mechanism {16b}

The block size will be concealed from other researchers, and the randomization table will not be available for assessment by anyone else involved in the study [54].

Randomization is performed by an independent biostatistician. The biostatistician is the only one who has access to check the file. The allocation list is kept in a separate file on a different computer.

Implementation {16c}

Random allocation will be conducted after the enrolment. Random numbers with corresponding participants will be determined in the order of the time of the visit and divided into three groups (IPL+, IPL, or DQS group). The allocation result will not be announced to the participants until the end of the data collection phase of the trial. Researchers collecting and analyzing data related to this trial will be blinded to the participant allocation results.

Assignment of interventions:

Blinding {17a}

The treatment assignment for the study will be triple-masked. Participants in the research would be unable to recognize the contents. A masked examiner for all clinical assessments will not be involved in the data collection or group allocation procedure for this research. The investigator will not be aware of the three groups. Participants will be randomly assigned to one of the three treatment groups, and they will undergo IPL treatment with 12 homogeneously spaced pulsed light to both eyes and a sham treatment to both eyes. The box containing ampoules will be labeled with a batch number, including the study reference number, participant ID, contact number,

investigator name, site address, the expiration date of the eye drops, storage instructions, and a statement informing the participant that the eye drops are for use only in clinical trials and should not be ingested. The circumstances and procedures under which unblinding is permissible will be determined and performed by the PI.

Procedure for unblinding if needed {17b}

The PI will determine and perform the circumstances and procedures under which unblinding is permissible.

Participant withdrawal

Based on the following criteria, patients will be removed from the research.

1. When it is deemed challenging to continue the study owing to the emergence of new ailments.
2. When the research participant cannot be located.
3. In the case of pregnancy or pregnancy suspicion.
4. When participants or their legal guardians want to end their participation in a study.
5. When the participant's caretaker cannot guarantee their participation in the study.
6. When the research project is concluded.
7. When the lead investigator and sub-investigators believe that it is acceptable to cease the study for reasons other than those listed above.

Data collection and management

Plans for assessment and collection of outcomes {18a}

Data administration is the responsibility of Jiayan Chen, HESH, Department of Clinical Research, as chosen by the principal investigator (Emmanuel Eric Pazo). This research will collect data using a proprietary EMR case report form and management application. Following database lock, the individual responsible for the statistical analysis will get the locked data following the database. The data management handbook will provide the details on any specific information. At the end of the study, a report on the implementation and the status of data management will be compiled and sent to the PI with the locked research data.

Plans to promote participant retention and complete follow-up {18b}

Informed consent will include information regarding follow-up assessments for all participants. In the event of participants discontinuing or deviating from intervention protocols, the study team will initiate contact and prioritize addressing any concerns that may be impacting their adherence to the intervention protocols. If these concerns cannot be resolved, the participants will be requested to complete subsequent self-assessment questionnaires online.

Data will be gathered during pre-randomization, termination, and follow-up periods at four and eight weeks. The method of data collection for this study will involve the use of clinical tests and self-report questionnaires, which will be administered through an online platform. In order to guarantee the completeness and accuracy of the gathered data, the online questionnaires will be encoded in a manner

that necessitates respondents to provide comprehensive responses to all inquiries prior to submitting their answers.

Data management {19}

Data collection and data entry were performed by separate experienced staff members at HESH, Department of Clinical Research. Supervision and double confirmation were performed by Jiayan Chen, along with weekly backup, to ensure data quality.

Confidentiality {27}

Each participant's personal information will be kept confidential in the same way as their medical histories in the hospital before, during, and after the trial.

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

Not Applicable-There will be no biological specimens collected.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

The software Statistical Analysis in Social Sciences (SPSS, version 26, IBM Corp) for MacOS software will be used to analyze the data. Data from both eyes will be collected for all patients participating in the treatment at the following stages: baseline,

first follow-up at week 2, and second follow-up at week 4. Repeated measures analysis will be used to compare comparisons across time periods, while paired analyses will be used to compare pre-and post-treatment data at specific time periods. The Kolmogorov-Smirnoff test will be used to determine the normality of variables. The background of the subjects will be tabulated by calculating the mean and standard deviation for continuous variables and the frequency and percentage for categorical variables. Analysis of variance will be used to analyze ordinal variables and those having nonnormal distributions (ANOVA). The primary outcome measures for this study are NITBUT and OSDI scores before and after treatment. For the primary endpoint, between-group comparisons using baseline as a covariate and an analysis of covariance will be performed to estimate the adjusted mean, its 95% confidence interval, and the p-value.

Interim analyses {21b}

Not applicable- no anticipated problems are detrimental to the participant, so interim analysis is not warranted.

Methods for additional analyses (e.g., subgroup analyses) {20b}

Subgroup analyses are not planned for this study.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

After accounting for loss to follow-up and missing data in sample-size calculations. Using a two-tailed t-test of difference between means with a power of 80% and a significance level of 5%, we allowed for a dropout rate of 10%, using an additional 10% to compensate for potential deviations of dry eye measures from the normal distribution.

Plans to give access to the complete protocol, participant-level data, and statistical code {31c}

The datasets analyzed during the current study and statistical code are available from the corresponding author on reasonable request, as is the complete protocol.

Oversight and monitoring

Composition of the coordinating center and trial steering committee {5d}

The subject leader and the project manager will form the Steering Committee (SC). The SC is accountable for managing the whole project. The Monitor Group's (MG) inspectors are appointed by the SC. The MG will oversee the entire research procedure in compliance with the GCP requirements. The inspector will analyze the investigator's adherence to the protocol, the protection of participants' rights and interests, the quality of the CRF form, and the investigators' understanding of different standards before submitting inspection reports to the SC.

Composition of the data monitoring committee, its role and reporting structure {21a}

Due to the projected low frequency of adverse events and the modest numbers in each location, no data monitoring committee has been convened for this trial. The database will be constructed using Excel (Microsoft, USA 2022 version), and regular data monitoring will be undertaken in accordance with the sponsor's standard operating procedures. The steering committee (SC) will have oversight and access to the trial under the supervision of the trial manager (TM) at any time during the study.

Adverse event reporting and harms {22}

Adverse events are unanticipated indications, symptoms, or illnesses seen during a clinical study, regardless of their relationship to the treatment. There may be local, general, and psychological unwanted effects (Table 3). If any discomfort or new changes in condition during the study period, or any unexpected situation, whether related to the study or not, one should promptly notify the doctor, who will make a judgment and give appropriate medical treatment. At the end of each examination, the doctor will evaluate eye health status according to the examination results. If the condition deteriorates or is no longer suitable for the study, the study may be terminated early. At the same time, the doctor will provide other treatment options that are more suitable for the current situation to ensure health to the greatest extent. If major adverse events occur, HESH Certified Review Board will be notified; experimental treatments will be discontinued promptly, and appropriate therapies will be offered.

Adverse events	Solutions
Visual discomfort	Standard operation

Eye irritation, conjunctival hyperemia, eye pain	No special treatment was required, relieve and subside within 1-3 days
Periocular swelling	Resolve within a few hours
Bluish-purple bruise (purpura)	Rare cases may last from five to fifteen days; no special treatment is required
The skin around the eye becomes sensitive and fragile	Avoiding makeup and rubbing
Burn injury occurs	In rare cases, follow instructions
Allergy, abnormal sensation in the eye, etc.	Excluded and treatment

Table 3. Possible adverse events and solutions

Frequency and plans for auditing trial conduct {23}

The study will be reviewed and evaluated weekly by an independent supervisor not related to the PI and sponsors.

Plans for communicating significant protocol amendments to relevant parties (e.g., trial participants, ethical committees) {25}

If there are modifications to eligibility criteria, outcomes, or analyses, a revised protocol will be submitted for approval to the HESH Medical Ethics Committee.

Dissemination plans {31a}

The study's findings will be shared regardless of the effect's direction. All possible beneficiaries of the research, including patients, caretakers, family, doctors, advisory boards, and medical boards, will receive trial data. Publications in high-impact, open-access medical journals and talks at national and international medical conferences will serve this purpose.

Discussion

DQS stimulates P2Y2 receptors on the ocular surface, which enhances the secretion of water and secretory mucin from conjunctival tissue. At present, multi-center clinical trials have proved the advantages and efficacy of diquafosol sodium drops in the treatment of dry eyes, and the Asian Dry Eye Workshop identifies it as the current first-choice treatment for aqueous tear deficiency dry eyes and as one of the first choices for the treatment of mucin deficiency dry eyes. The primary untoward effects observed were ocular discharge, ocular irritation, and ocular pain; however, these manifestations resolved within a period of 28 days [55]. These events will be assessed and mentored continually during the study and follow-up phase of the study.

Literature review shows that intense pulsed light (IPL) is a relatively new method for the treatment of lipid-abnormal dry eye caused by MGD. IPL can relieve the symptoms and signs of MGD-related dry eye by reducing eyelid inflammation, thermal effect, sterilization, acariasis, and light regulation[56,57]. With respect to the adverse effects, the majority of studies have reported that participants didn't experience any significant negative effects, apart from temporary occurrences of erythema, edema, and pain. Nevertheless, the likelihood of hyperpigmentation, blisters, and a burning sensation cannot be ruled out in certain instances, particularly in patients with darker skin phototypes [58]. Potential corneal and/or retinal toxicity will be assessed and monitored continuously. Therefore, this study aims to assess the effectiveness of the combination of IPL with 3% DQS ophthalmic solution, providing more options for treatment. In future studies, we will further expand the sample size and conduct a deeper

analysis of the mechanism of symptom improvement in the hope of providing clinicians with more treatment options.

Trial status

Recruitment began in August 2023, and the approximate date when recruitment will be completed is December 2023. Protocol version 2.0 was approved on December 2022.

Abbreviations

BCVA: Best-corrected visual acuity; DED: Dry eye disease; DQS; Diquafosol; HRT II: Heidelberg Retina Tomography II; IOP: Intraocular pressure; GCP: Good Clinical Practice; RCT: Randomized control trial; SOPs: Standard operating procedures; AEs: Adverse events; CRF: Case report form

Declarations

Acknowledgments

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Authors' contributions {31b}

Conception and design of the research: JC, GQ, LL, YQ, HC, HH, YX, QZ, YW, LY, SM, JEM, LX, WH, SY, XH, and EEP; analysis and interpretation of the data: JC,

GQ, EEP; writing original draft preparation: JC; critical revision of the manuscript (reviewing and editing): JC and EEP; supervision: XH, SY, and EEP.

Funding statement {4}

This study was entirely funded and sponsored by He Eye Specialist Hospital, Shenyang, China, which included study design, data collection, analysis, interpretation, and manuscript writing. No support was received for the publication of this article.

Availability of data and materials {29}

Any data required to support the protocol can be supplied on request.

Ethics and dissemination {24}

The study was registered with the trial number NCT05694026 and was conducted in compliance with the tenets of the Declaration of Helsinki and the Institutional Review Board of the He Eye Specialist Hospital, Shenyang, China: IRB (2022) K029.01. Documented informed consent was obtained from all participants in this study. In the present study, all components with any individually identifiable information have been removed from the dataset.

Consent for publication {32}

Not applicable - no identifying images or other personal or clinical details of participants are presented here or will be presented in reports of the trial results. The participant information materials and informed consent form are available from the corresponding author on request.

Competing interests statement {28}

The authors declare that they have no competing interests.

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Figure legends

Figure 1. Study flow chart

Word count: 5374

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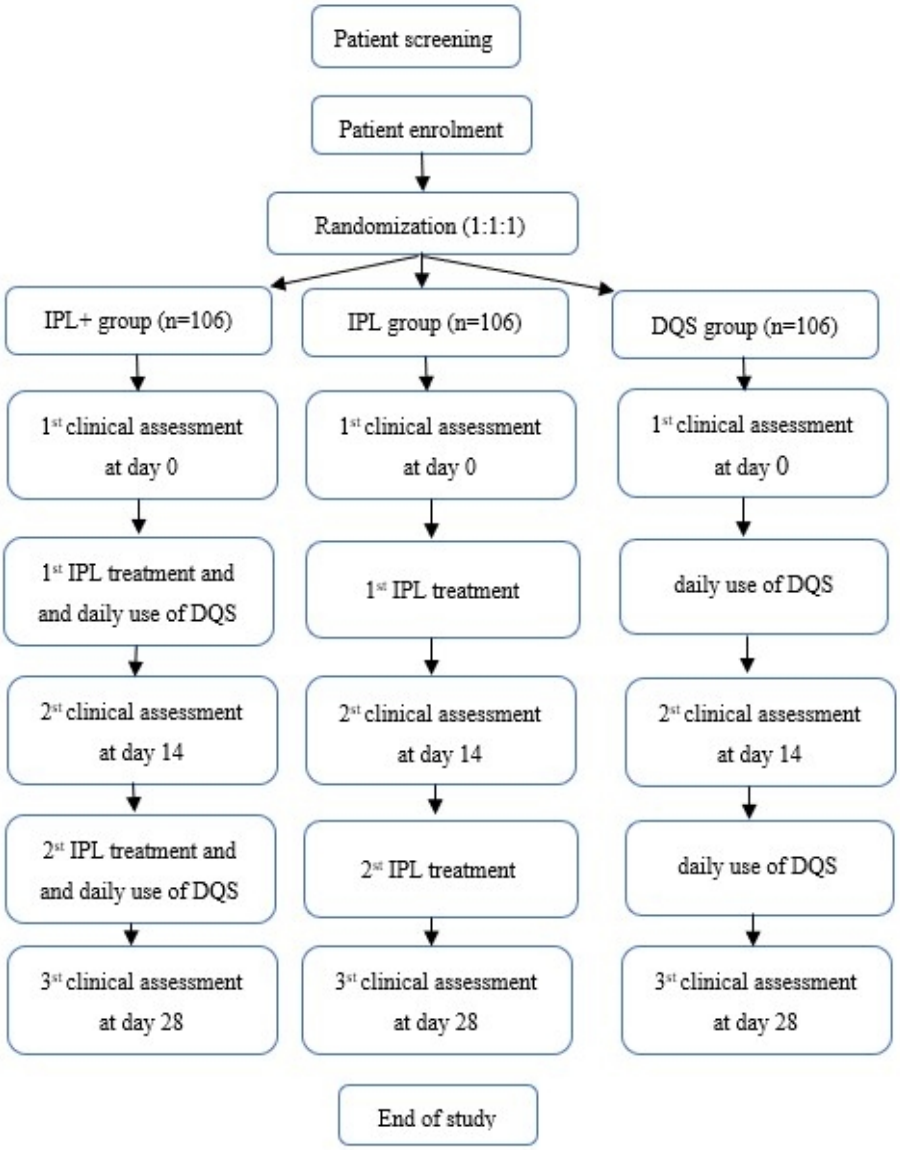

study flow chart

43x52mm (300 x 300 DPI)

Study Protocol template

Guidance: the numbers in curly brackets (e.g. {5a}) are SPIRIT item identifiers. **Please do not remove the numbers in curly brackets, or any heading that contains them**. The item identifiers are slightly out of sequence to make the document flow more easily, but it is important that they remain in the document to allow electronic searches by SPIRIT item number.

If you are certain that an item does not apply, please state "n/a" and provide a short explanation. Leaving an item blank or stating “n/a” without an explanation will lead to your manuscript being returned before review.

NB: All text in green can be removed once you have finished creating your Study Protocol. Text in black is mandatory. Please also read the submission guidelines for Study Protocols prior to submitting to *Trials*: https://trialsjournal.biomedcentral.com/submission-guidelines/preparing-your-manuscript/study-protocoll

CHECKLIST

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Names protocol contributors: *Line 6*

Abstract: *Line 18*

- **Introduction**: *Line 19*
- **Methods and analysis**: *Line 23*
- **Discussion**: *Line 34*

Ethics and dissemination: *Line 38*

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Note: the numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers. The

order of the items has been modified to group similar items (see http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/).

Title {1}: *line 60*	SPIRIT guidance: Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym.
Trial registration {2a and 2b}. *line 60*	SPIRIT guidance: Trial identifier and registry name. If not yet registered, name of intended registry. Item 2b is met if the register used for registration collects all items from the World Health Organization Trial Registration Data Set.
Protocol version {3} *line 60*	SPIRIT guidance: Date and version identifier.
Funding {4} *line 60*	SPIRIT guidance: Sources and types of financial, material, and other support.
Author details {5a} *line 60*	SPIRIT guidance: Affiliations of protocol contributors.
Name and contact information for the trial sponsor {5b} *line 60*	SPIRIT guidance: Name and contact information for the trial sponsor.
Role of sponsor {5c} *line 60*	SPIRIT guidance: Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities.

Introduction

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- Acknowledgements
- Authors' contributions
- Funding
- Availability of data and material
- Ethics approval and consent to participate
- Consent for publication
- Competing interests
- Authors' information (optional)

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Authors' contributions {31b}: *Line 508*

Funding {4}: *Line 514*

Availability of data and materials {29}: *Line 519*

Ethics approval and consent to participate {24}: *Line 522*

Consent for publication {32}: *Line 530*

Competing interests {28}: *Line 536*

Authors' information (optional): *Line 539*

References: *Line 551*

BMJ Open

A protocol for a parallel assignment prospective, randomized, comparative trial to evaluate the safety and efficacy of intense pulsed light (IPL) combined with 3% diquafosol (DQS) ophthalmic solution in dry eye syndrome.

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Primary Subject Heading:	Ophthalmology
Secondary Subject Heading:	Research methods, Pharmacology and therapeutics
Keywords:	Orbital and lacrimal disorders < OPHTHALMOLOGY, Laser therapy < DERMATOLOGY, Corneal and external diseases < OPHTHALMOLOGY

Protocol

Title: A protocol for a parallel assignment prospective, randomized, comparative trial to evaluate the safety and efficacy of intense pulsed light (IPL) combined with 3% diquafosol (DQS) ophthalmic solution in dry eye syndrome.

Names protocol contributors： Jiayan Chen[1], Guanghao Qin[1], Liangzhe Li[1], Yifan Qi[1], Huixin Che[1], He Huang[1], Yang Xia[1], Qing Zhang[2], Yi Wu[3], Lanting Yang[4], Salissou Moutari[5], Jonathan E Moore[6], Ling Xu[1], Wei He[1], Sile Yu[1,7], Xingru He[1,7]*, Emmanuel Eric Pazo[1]*

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ABSTRACT

Introduction: Evaporative dry eye (EDE) is common and can lead to ocular pain, decreased visual quality, and reduced quality of life. Intense pulsed light (IPL) and 3% diquafosol ophthalmic solution have been found to be beneficial in reducing signs and symptoms of dry eye.

Methods and analysis: A randomized clinical trial will be performed at He Eye Specialist Hospital in Shenyang. 360 DED patients will be randomly equally divided into the IPL group, DQS group (diquafosol ophthalmic solution eye drops), and IPL+ group (IPL combined with 3% diquafosol eye drops). All groups will be followed up for four weeks. The primary outcome measures will be the non-invasive tear break-up time (NIBUT) and the Ocular Surface Disease Index (OSDI) change from the baseline. The secondary outcome measures included the conjunctival and cornea staining (CFS) with fluorescein and lissamine, meibomian gland function and secretion quality, tear film lipid layer score (TFLL), tear meniscus height (TMH), conjunctival hyperemia (RS score) change from the baseline for improving ocular symptoms. Adverse events also will be monitored and documented.

Discussion: This study aimed to assess whether the combination of IPL with 3% diquafosol ophthalmic solution (study group), IPL+ (study group), is more effective than IPL (active control group) or DQS (active control group) in participants with evaporative dry eye.

Ethics and dissemination: Registration number: Clniicaltrials.gov NCT05694026. Name of the trial registry: Management of dry eye with Intense Pulsed Light combined with 3% diquafosol ophthalmic solution, registered on Jan 10, 2023. Ethics approval number: IRB (2022) K029.01. The study's findings will be shared regardless of the effect's direction.

Keywords: Dry eye, intense pulsed light, diquafosol ophthalmic solution, RCT

Strengths and limitations of this study:

- The trial is designed to be embedded into routine clinical practice, providing more options for treatment.
- The protocol promotes standardization of therapy, enabling credible inference aboutbenefits.
- A large RCT has not been conducted to understand the benefits of DQS and IPL on DED patients.
- The trial's data collection at a single site are limitation of the research
- The goal of this research is limited to assessing just tear film changes and DED symptoms

Administrative information

The numbers in curly brackets in this protocol refer to the SPIRIT checklist item numbers. The order of the items has been modified to similar group items (see http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/).

Title {1}	A protocol for a parallel assignment prospective, randomized, comparative trial to evaluate the safety and efficacy of intense pulsed light (IPL) combined with 3% diquafosol (DQS) ophthalmic solution in dry eye syndrome
Trial registration {2a and 2b}	Registration number: Clniicaltrials.gov NCT05694026. Ethics approval number: IRB (2022) K029.01
Protocol version {3}	2023, version 2
Funding {4}	This study was entirely funded by He Eye Specialist Hospital, Shenyang, China.
Author details {5a}	**Jiayan Chen**. He Eye Specialist Hospital, Shenyang, China. **Quanghao Qin**. He Eye Specialist Hospital, Shenyang, China. **Liangzhe Li**. He Eye Specialist Hospital, Shenyang, China. **Yifan Qi**. He Eye Specialist Hospital, Shenyang, China.

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Name and contact information for the trial sponsor {5b}	This is an investigator-initiated research, so the principal investigator acts as the sponsor. Emmanuel Eric Pazo (Principal Investigator). ericpazo@outlook.com
Role of sponsor {5c}	Investigator-initiated research

INTRODUCTION

Background and rationale {6a}

Evaporative dry eye (EDE) has been reported to be the most prevalent form of dry eye disease (DED), [1–3] which is primarily caused by meibomian gland hypofunction or meibomian gland dysfunction (MGD).[4–6] MGD can be chronic or diffused anomaly of the meibomian glands, often characterized by terminal duct blockage and qualitative/quantitative alterations in glandular secretion" b" the International Workshop on MGD.[1,7] These glands are modified sebaceous glands that release

meibum directly onto the ocular surface. Signs and symptoms of EDE and MGD can be addressed by improving the quality and quantity of meibum secretion.[8]

Diquafosol ophthalmic sodium is a dinucleotide polyphosphate which is a purinoceptor agonist; when administered to the ocular surface, it binds to P2Y2 receptors and stimulates mucin and tear secretion.[9–11]. It also improves the tear film composition and stability[12–14]. It has a corneal epithelial-repairing effect and can be used to treat ocular surface damage caused by dry eye[5,15,16]. By targeting the inflammation involved in the pathogenesis of dry eye, it can inhibit the expression of inflammatory pathways and inflammatory factors that are involved in the pathogenesis of dry eye[17–19]. The safety and benefits of DQS in improving dry eye signs and symptoms have been demonstrated in randomized clinical trials[20]. At present, DQS is clinically available as a 3% ophthalmic solution (Diquas, Santen) which, due to rapid ocular clearance, requires frequent administration (6 times/day)[21].

Intense pulsed light (IPL) is widely used to treat dermatological conditions[22], and its noncoherent polychromatic light source with a wide wavelength range of 500–1200 nm has been reported to stimulate facial sebaceous glands[23,24]. The photothermal effect of IPL is postulated to relieve inflammation by removing aberrant surface microvasculature and enhancing meibomian gland function[25–27]. Furthermore, an increase in fibroblast proliferation, collagen formation, and local blood flow has been associated with the application of IPL on the skin[28,29]. Several studies including Toyos [30] et al. and Martínez-Hergueta [31] et al. have evaluated the safety and benefits of IPL therapy for improving signs of DED. [32–34] and combined it with

other therapies such as heated eye mask (HEM) [35,36], 0.1% sodium hyaluronate eye drops [27], and blood extract eye drops[37]. Therefore, an RCT is warranted to assess the safety and efficacy of combining IPL with DQS for patients suffering from DED.

Objectives {7}

The primary objective of this study is to assess whether the combination of intense pulsed light with 3% diquafosol ophthalmic solution is more effective than intense pulsed light and 3% diquafosol ophthalmic solution in alleviating signs and symptoms of DED.

Trial design {8}

This is a prospective, randomized controlled trial performed at He Eye Specialist Hospital (HESH) [ethics approval number: IRB (2022) K029.01]. The study adheres to the tenets of the Declaration of Helsinki and is registered at ClinicalTrails.gov (NCT05694026) using the SPIRIT reporting guidelines[38]. Randomization will be performed using a web-based, online, sealed envelope-based system (https://www.sealedenvelope.com). Specific study information sheets will be provided to patients prior to taking consent. Following a dedicated screening and randomization visit for eligible patients, participants will be randomized to one of three trial arms.

Methods: Participants, interventions, and outcomes

Study setting {9}

This study will be conducted between Mar 1, 2023, and Nov 30, 2023. Participants will be recruited at the Department of Ophthalmology, He Eye Specialist Hospital (HESH).

Patient and Public Involvement

Patients and the public will not be involved in the design, implementation, reporting, or dissemination plans of this study.

Eligibility criteria {10}

Inclusion criteria:

1. Age ≥18 years
2. Consenting participants.
3. Able and willing to comply with the treatment/follow-up schedule.
4. Bilateral signs and symptoms of dry eye disease: (i) Ocular Surface Disease Index (OSDI) questionnaire ≥13, (ii) Non-invasive tear break-up (NITBUT) ≤ 5 seconds, (iii) conjunctival staining score (CS) ≥3 points. The presence of two or more criteria was used to establish a positive DE diagnosis based on the 2016 Asia Dry Eye Society criteria.

Exclusion criteria:

1. A recent history (past 30 days) of topical ophthalmic medication use, including antibiotics, steroids, non-steroidal anti-inflammatory drugs, or required the chronic use of topical ophthalmic medications.

2. Eyelids or intraocular tumors.
3. Active allergy or infection, or inflammatory disease may prevent the subjects from completing the study at the ocular surface.
4. Any structural changes in the lacrimal passage.
5. Glaucoma.
6. Diabetes or other systemic, dermatologic, or neurologic diseases that affect the health of the ocular surface.
7. Use of any systemic anti-inflammatory drugs or medication that may interfere with tear production, such as antianxiety, anti-depressive, and antihistamine medications, within three months.
8. Pregnant or breastfeeding.
9. Contact lenses wearers.

Informed consent {26a}

Trained and experienced clinicians will seek informed permission from prospective participants.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

This trial does not involve collecting biological specimens.

Interventions

The explanation for the choice of comparators {6b}

After enrollment in the study, treatments will be initiated immediately after randomization. Participants in the DQS group and IPL+ group will use one drop of 3% DQS (Diquas; Santen Pharmaceutical Co., Ltd., Osaka, Japan) 6 times per day for four weeks (28 days), whereas participants in the IPL+ group and IPL group will undergo two IPL treatment sessions of M22 (Lumenis Ltd., Yokneam, Israel) IPL system, two weeks apart. IPL treatment utilizes a noncoherent polychromatic light source with a wavelength spectrum of 500–1200 nm on the cutaneous facial sebaceous glands.

Intervention description {11a}

In this study, patients receive either DQS, IPL, or IPL combined with DQS for four weeks based on the group they are placed in. Two follow-up visits were performed at week two and week 4 in all groups; comprehensive eye exams will be conducted by an ophthalmologist, including primary outcomes, secondary outcomes, and safety evaluation.

Criteria for discontinuing or modifying allocated interventions {11b}

If dry eye signs and symptoms worsen, participants will be stopped and advised to use the designated device. Adverse events (AE) will be continuously monitored. In case of an AE, participants will be informed about the severity of the event, and PI will decide if participants can continue further. If participants consent and agree, they will be reminded daily regarding the administration of eye drops, recording their exposure

to mobile telephones or computer time, and any queries regarding the study will be answered by trained clinical staff at HESH.

Strategies to improve adherence to interventions {11c}

Participants will be reminded by phone and email every week, and then appointments will be scheduled in advance according to their availability time. In order to improve adherence, patients will be given a medication record booklet, and their medication status will be checked at each follow-up visit. In the event of non-compliance, such as absence, participants will be contacted by phone or email to ask if they will continue or terminate the study early.

Relevant concomitant care permitted or prohibited during the trial {11d}

Any other dry eye systemic or topical medication, treatment, or therapy will be prohibited during the course of this study.

Provisions for post-trial care {30}

There is no anticipated harm and compensation for trial participation, but participants who show signs and symptoms of deterioration in their dry eye status will be directed to their local dry eye center for further treatment.

Outcomes {12}

All patients will be assessed at baseline, 14, and 28 days. We plan to use primary

and secondary outcomes measures, symptoms, and corneal and meibomian gland improvement will be compared between the three groups.

Primary Outcome

Ocular Surface Disease Index (OSDI): OSDI is a questionnaire consisting of 12 questions for evaluating the effects of dry eye syndrome on vision, ocular symptoms, and any condition associated with DED[39]. The patient will answer each question on a scale ranging from 0 to 4, with '0' indicating 'none of the time' and '4' indicating 'all of the time.' If a particular question is deemed irrelevant, it will be marked as 'not applicable (N/A)' and excluded from the analysis. The OSDI total score is calculated according to the following formula. The total score ranges from 0 to 100, with higher scores representing more severe cases of dry eye disease symptoms [40,41].

Non-invasive tear break-up (NIBUT): The Keratograph 5M (Oculus, Germany) topographer will assess non-invasive initial tear film breaking time. Three sequential readings will be captured, the median value will be included in the final analysis, and the median value will be recorded [42,43].

Secondary outcomes

Fluorescein and lissamine conjunctival and cornea staining (CFS): Fluorescein and lissamine staining of the ocular surface will be divided into three zones comprising nasal conjunctival, corneal, and temporal conjunctival areas. The staining score ranged from 0 to 3 for each zone, yielding a total score of 0-9 for the ocular surface[44,45].

Tear meniscus height (TMH): Non-invasive first tear film break-up using the Keratograph 5M (Oculus, Germany) topographer will be measured three times consecutively, and the median value was recorded[42,46].

Conjunctival hyperemia (RS score): Conjunctival hyperemia (RS score) will be assessed by Keratograph image (Oculus, Germany) of 1156*873 pixels, redness score (RS) (accurate to 0.1 U) was displayed on the computer screen that ranged from 0.0 (normal) to 4.0 (severe)[43,47].

Meibomian gland function and secretion quality: Meibum quality will be assessed under a slit-lamp[48]: Five meibomian glands in the middle parts of the eyelid will be evaluated using a scale of 0 to 3 for each gland (0 represented clear meibum; 1 represented cloudy meibum; 2 represented cloudy and granular meibum; and three means thick, toothpaste-like consistency meibum)[49,50].

Tear Film Lipid Layer Score (TFLL): The interferometry patterns will be assessed using DR-1 (Kowa, Nagoya, Japan). The results will be graded as follows: grade 1, somewhat gray color, uniform distribution; grade 2, rather gray color, nonuniform distribution; grade 3, a few colors, nonuniform distribution; grade 4, many colors, nonuniform distribution; grade 5, corneal surface partially exposed [51–53].

Participant timeline {13}

The schedule for data collection and visits is shown in Table 1. After registration for this study, the assigned treatment intervention will be administered for four weeks. Furthermore, the effect will be examined during the 2-week follow-up period of 4

weeks (**Figure 1**).

Sample size {14}

The sample size calculation is based on the primary outcome measures, namely NITBUT and OSDI scores, to establish the non-inferiority of the IPL+ group compared to IPL group and DQS group in terms of the changes in the mean from the baseline in OSDI score at day 28. For the NITBUT scores, a sample size of 106 is sufficient to detect a clinically significant difference of 0.51 between the IPL+ group and either of the two other groups (IPL group and DQS group) while assuming a standard deviation of 1.15, using a two-tailed t-test of difference between means with 90% power and a 5% level of significance. For the OSDI scores, a sample size of 98 is sufficient to detect a clinically significant difference of 1.2 between the IPL+ group and either of the two other groups (IPL group and DQS group) while assuming a standard deviation of 2.6, using a two-tailed t-test of difference between means with 90% power and a 5% level of significance. Therefore, the required sample size is max (106, 98) = 106.

With the inclusion of the multidose treatment groups and a dropout rate of 8%, it is estimated that about 350 individuals. Therefore 360 individuals will be enrolled, 120 in each group. The intended-to-treat population will be randomly allocated to the three groups.

The primary and secondary efficacy analyses will utilize a two-way analysis of variance that will account for treatment and baseline OSDI score stratification to compare treatment differences. Using paired t-tests, within-treatment differences from

baseline will be evaluated (alpha level 0.05). Additional analyses of OSDI subgroups and questionnaire data will be conducted using an analysis of variance. Using descriptive statistics, safety data will be summarized.

Recruitment {15}

This clinical study will be done in a single site, with participants blinded to the treatment assignment. This research is open to patients diagnosed with DED at He Eye Specialist Hospital's Department of Ophthalmology. Participants will be recruited using adverts in the distribution pamphlets, the website, and social media postings. Each participant's demographic information (including ocular diseases and current/previous usage of drugs and/or lubricating eye drops) will be collected during the first (screening) appointment. Participants will not be limited based on age, gender, or ethnicity (Table 2).

Items	Baseline	2w	4w
Informed consent	√		
Patient background	√		
Ocular Surface Disease Index (OSDI) scores	√	√	√
IOP	√	√	√
BCVA	√	√	√
Non-invasive tear break-up (NIBUT)	√	√	√
conjunctival and cornea staining (CFS)	√	√	√

Tear Film Lipid Layer Score (TFLL)	√	√	√
Corneal endothelial cells	√	√	√
Tear meniscus height (TMH)	√	√	√
Conjunctival hyperemia (RS score)	√	√	√
Meibomian gland function	√	√	√
Meibomian secretion quality	√	√	√
Adverse event (AE)		√	√

√: All groups

Patient background, including date of birth, gender, race, ethnicity, and allergy history.

Table 1. Schedule for data collection and visits

	STUDY PERIOD					
	Enrolment	**Allocation**	**Post-allocation**			**Close-out**
TIMEPOINT:	**Jan 2023**	**2023**	**DAY 0**	**DAY14**	**DAY28**	**End-2023**
ENROLMENT:						
Eligibility screen	×					
Informed consent	×					
Allocation		×				
INTERVENTIONS						

:						
[IPL+DQS]			←	—	→	
[IPL]			←	—	→	
[DQS]			←	—	→	
ASSESSMENTS:						
[The baseline variables]	×	×				
[The primary outcome]			×	×	×	×
[The second outcome]			×	×	×	×

Table 2. The schedule of enrolment, interventions, and assessments of this trial

Assignment of interventions: Allocation

Sequence generation {16a}

A web-based randomization application will be used (https://www.project-redcap.org/). Randomization will be by simple randomization. Allocation will be carried out using block randomization and stratified according to age (allocation factor: age <80 years or ≥80 years) (known only to the statistical team, not stated here to maintain masking). Participants will be in a 1:1:1 allocation ratio to IPL group, DQS group, or IPL+ group.

Concealment mechanism {16b}

The block size will be concealed from other researchers, and the randomization table will not be available for assessment by anyone else involved in the study [54]. Randomization is performed by an independent biostatistician. The biostatistician is the only one who has access to check the file. The allocation list is kept in a separate file on a different computer.

Implementation {16c}

Random allocation will be conducted after the enrolment. Random numbers with corresponding participants will be determined in the order of the time of the visit and divided into three groups (IPL+, IPL, or DQS group). The allocation result will not be announced to the participants until the end of the data collection phase of the trial. Researchers collecting and analyzing data related to this trial will be blinded to the participant allocation results.

Assignment of interventions:

Blinding {17a}

The treatment assignment for the study will be triple-masked. Participants in the research would be unable to recognize the contents. A masked examiner for all clinical assessments will not be involved in the data collection or group allocation procedure for this research. The investigator will not be aware of the three groups. Participants will be randomly assigned to one of the three treatment groups, and they will undergo

IPL treatment with 12 homogeneously spaced pulsed light to both eyes and a sham treatment to both eyes. The box containing ampoules will be labeled with a batch number, including the study reference number, participant ID, contact number, investigator name, site address, the expiration date of the eye drops, storage instructions, and a statement informing the participant that the eye drops are for use only in clinical trials and should not be ingested. The circumstances and procedures under which unblinding is permissible will be determined and performed by the PI.

Procedure for unblinding if needed {17b}

The PI will determine and perform the circumstances and procedures under which unblinding is permissible.

Participant withdrawal

Based on the following criteria, patients will be removed from the research.

1. When it is deemed challenging to continue the study owing to the emergence of new ailments.
2. When the research participant cannot be located.
3. In the case of pregnancy or pregnancy suspicion.
4. When participants or their legal guardians want to end their participation in a study.
5. When the participant's caretaker cannot guarantee their participation in the study.
6. When the research project is concluded.
7. When the lead investigator and sub-investigators believe that it is acceptable to

cease the study for reasons other than those listed above.

Data collection and management

Plans for assessment and collection of outcomes {18a}

Data administration is the responsibility of Jiayan Chen, HESH, Department of Clinical Research, as chosen by the principal investigator (Emmanuel Eric Pazo). This research will collect data using a proprietary EMR case report form and management application. Following database lock, the individual responsible for the statistical analysis will get the locked data following the database. The data management handbook will provide the details on any specific information. At the end of the study, a report on the implementation and the status of data management will be compiled and sent to the PI with the locked research data.

Plans to promote participant retention and complete follow-up {18b}

Informed consent will include information regarding follow-up assessments for all participants. In the event of participants discontinuing or deviating from intervention protocols, the study team will initiate contact and prioritize addressing any concerns that may be impacting their adherence to the intervention protocols. If these concerns cannot be resolved, the participants will be requested to complete subsequent self-assessment questionnaires online.

Data will be gathered during pre-randomization, termination, and follow-up periods at four and eight weeks. The method of data collection for this study will

involve the use of clinical tests and self-report questionnaires, which will be administered through an online platform. In order to guarantee the completeness and accuracy of the gathered data, the online questionnaires will be encoded in a manner that necessitates respondents to provide comprehensive responses to all inquiries prior to submitting their answers.

Data management {19}

Data collection and data entry were performed by separate experienced staff members at HESH, Department of Clinical Research. Supervision and double confirmation were performed by Jiayan Chen, along with weekly backup, to ensure data quality.

Confidentiality {27}

Each participant's personal information will be kept confidential in the same way as their medical histories in the hospital before, during, and after the trial.

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

Not Applicable-There will be no biological specimens collected.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

The software Statistical Analysis in Social Sciences (SPSS, version 26, IBM Corp) for MacOS software will be used to analyze the data. Data from both eyes will be collected for all patients participating in the treatment at the following stages: baseline, first follow-up at week 2, and second follow-up at week 4. Repeated measures analysis will be used to compare comparisons across time periods, while paired analyses will be used to compare pre-and post-treatment data at specific time periods. The Kolmogorov-Smirnoff test will be used to determine the normality of variables. The background of the subjects will be tabulated by calculating the mean and standard deviation for continuous variables and the frequency and percentage for categorical variables. Analysis of variance will be used to analyze ordinal variables and those having nonnormal distributions (ANOVA). The primary outcome measures for this study are NITBUT and OSDI scores before and after treatment. For the primary endpoint, between-group comparisons using baseline as a covariate and an analysis of covariance will be performed to estimate the adjusted mean, its 95% confidence interval, and the p-value.

Interim analyses {21b}

Not applicable- no anticipated problems are detrimental to the participant, so interim analysis is not warranted.

Methods for additional analyses (e.g., subgroup analyses) {20b}

Subgroup analyses are not planned for this study.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

After accounting for loss to follow-up and missing data in sample-size calculations. Using a two-tailed t-test of difference between means with a power of 80% and a significance level of 5%, we allowed for a dropout rate of 10%, using an additional 10% to compensate for potential deviations of dry eye measures from the normal distribution.

Plans to give access to the complete protocol, participant-level data, and statistical code {31c}

The datasets analyzed during the current study and statistical code are available from the corresponding author on reasonable request, as is the complete protocol.

Oversight and monitoring

Composition of the coordinating center and trial steering committee {5d}

The subject leader and the project manager will form the Steering Committee (SC). The SC is accountable for managing the whole project. The Monitor Group's (MG) inspectors are appointed by the SC. The MG will oversee the entire research procedure in compliance with the GCP requirements. The inspector will analyze the investigator's adherence to the protocol, the protection of participants' rights and interests, the quality of the CRF form, and the investigators' understanding of different standards before submitting inspection reports to the SC.

Composition of the data monitoring committee, its role and reporting structure {21a}

Due to the projected low frequency of adverse events and the modest numbers in each location, no data monitoring committee has been convened for this trial. The database will be constructed using Excel (Microsoft, USA 2022 version), and regular data monitoring will be undertaken in accordance with the sponsor's standard operating procedures. The steering committee (SC) will have oversight and access to the trial under the supervision of the trial manager (TM) at any time during the study.

Adverse event reporting and harms {22}

Adverse events are unanticipated indications, symptoms, or illnesses seen during a clinical study, regardless of their relationship to the treatment. There may be local, general, and psychological unwanted effects (Table 3). If any discomfort or new changes in condition during the study period, or any unexpected situation, whether related to the study or not, one should promptly notify the doctor, who will make a judgment and give appropriate medical treatment. At the end of each examination, the doctor will evaluate eye health status according to the examination results. If the condition deteriorates or is no longer suitable for the study, the study may be terminated early. At the same time, the doctor will provide other treatment options that are more suitable for the current situation to ensure health to the greatest extent. If major adverse events occur, HESH Certified Review Board will be notified; experimental treatments

will be discontinued promptly, and appropriate therapies will be offered.

Adverse events	Solutions
Visual discomfort	Standard operation
Eye irritation, conjunctival hyperemia, eye pain	No special treatment was required, relieve and subside within 1-3 days
Periocular swelling	Resolve within a few hours
Bluish-purple bruise (purpura)	Rare cases may last from five to fifteen days; no special treatment is required
The skin around the eye becomes sensitive and fragile	Avoiding makeup and rubbing
Burn injury occurs	In rare cases, follow instructions
Allergy, abnormal sensation in the eye, etc.	Excluded and treatment

Table 3. Possible adverse events and solutions

Frequency and plans for auditing trial conduct {23}

The study will be reviewed and evaluated weekly by an independent supervisor not related to the PI and sponsors.

Plans for communicating significant protocol amendments to relevant parties (e.g., trial participants, ethical committees) {25}

If there are modifications to eligibility criteria, outcomes, or analyses, a revised protocol will be submitted for approval to the HESH Medical Ethics Committee.

Dissemination plans {31a}

The study's findings will be shared regardless of the effect's direction. All possible beneficiaries of the research, including patients, caretakers, family, doctors, advisory boards, and medical boards, will receive trial data. Publications in high-impact, open-

access medical journals and talks at national and international medical conferences will serve this purpose.

Discussion

DQS stimulates P2Y2 receptors on the ocular surface, which enhances the secretion of water and secretory mucin from conjunctival tissue. At present, multi-center clinical trials have proved the advantages and efficacy of diquafosol sodium drops in the treatment of dry eyes, and the Asian Dry Eye Workshop identifies it as the current first-choice treatment for aqueous tear deficiency dry eyes and as one of the first choices for the treatment of mucin deficiency dry eyes. The primary untoward effects observed were ocular discharge, ocular irritation, and ocular pain; however, these manifestations resolved within a period of 28 days [55]. These events will be assessed and mentored continually during the study and follow-up phase of the study.

Literature review shows that intense pulsed light (IPL) is a relatively new method for the treatment of lipid-abnormal dry eye caused by MGD. IPL can relieve the symptoms and signs of MGD-related dry eye by reducing eyelid inflammation, thermal effect, sterilization, acariasis, and light regulation[56,57]. With respect to the adverse effects, the majority of studies have reported that participants didn't experience any significant negative effects, apart from temporary occurrences of erythema, edema, and pain. Nevertheless, the likelihood of hyperpigmentation, blisters, and a burning sensation cannot be ruled out in certain instances, particularly in patients with darker skin phototypes [58]. Potential corneal and/or retinal toxicity will be assessed and

monitored continuously. Therefore, this study aims to assess the effectiveness of the combination of IPL with 3% DQS ophthalmic solution, providing more options for treatment. In future studies, we will further expand the sample size and conduct a deeper analysis of the mechanism of symptom improvement in the hope of providing clinicians with more treatment options.

Trial status

Recruitment began in August 2023, and the approximate date when recruitment will be completed is December 2023. Protocol version 2.0 was approved on December 2022.

Abbreviations

BCVA: Best-corrected visual acuity; DED: Dry eye disease; DQS; Diquafosol; HRT II: Heidelberg Retina Tomography II; IOP: Intraocular pressure; GCP: Good Clinical Practice; RCT: Randomized control trial; SOPs: Standard operating procedures; AEs: Adverse events; CRF: Case report form

Declarations

Acknowledgments

The authors would like to express their appreciation for the effort of all personnel involved in this trial.

Authors' contributions {31b}

Conception and design of the research: JC, GQ, LL, YQ, HC, HH, YX, QZ, YW, LY, SM, JEM, LX, WH, SY, XH, and EEP; analysis and interpretation of the data: JC, GQ, EEP; writing original draft preparation: JC; critical revision of the manuscript (reviewing and editing): JC and EEP; supervision: XH, SY, and EEP.

Funding statement {4}

This study was entirely funded and sponsored by He Eye Specialist Hospital, Shenyang, China, which included study design, data collection, analysis, interpretation, and manuscript writing. No support was received for the publication of this article.

Availability of data and materials {29}

Any data required to support the protocol can be supplied on request.

Ethics and dissemination {24}

The study was registered with the trial number NCT05694026 and was conducted in compliance with the tenets of the Declaration of Helsinki and the Institutional Review Board of the He Eye Specialist Hospital, Shenyang, China: IRB (2022) K029.01. Documented informed consent was obtained from all participants in this study. In the present study, all components with any individually identifiable information have been removed from the dataset.

Consent for publication {32}

Not applicable - no identifying images or other personal or clinical details of

participants are presented here or will be presented in reports of the trial results. The participant information materials and informed consent form are available from the corresponding author on request.

Competing interests statement {28}

The authors declare that they have no competing interests.

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Figure legends

Figure 1. Study flow chart

Word count: 5413

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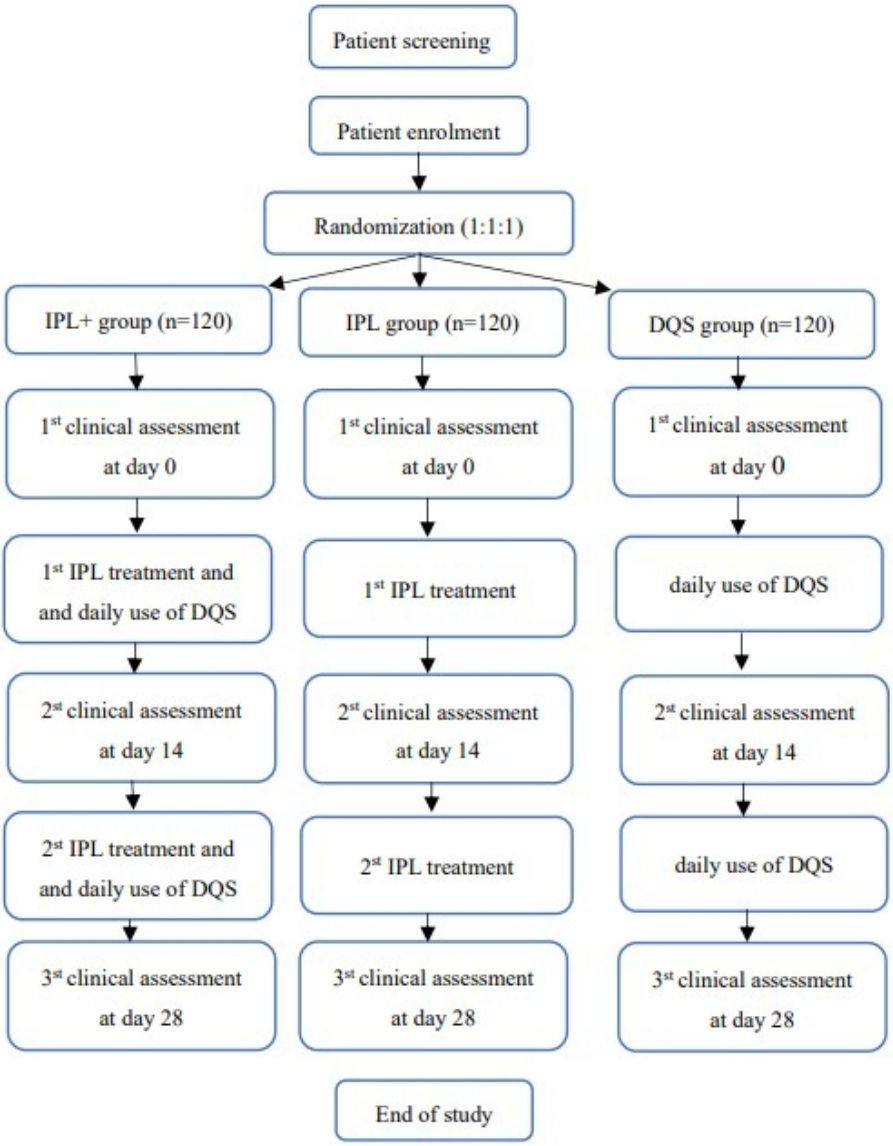

Figure 1. Study flow chart

143x174mm (96 x 96 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1 Page 1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a Page 2	Trial identifier and registry name. If not yet registered, name of intended registry
	2b Page 2	All items from the World Health Organization Trial Registration Data Set
Protocol version	3 Page 3	Date and version identifier
Funding	4 Page 3	Sources and types of financial, material, and other support
Roles and responsibilities	5a Page 4	Names, affiliations, and roles of protocol contributors
	5b Page 4	Name and contact information for the trial sponsor
	5c Page 4	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d Page 22	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a Page 4	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b Page 8	Explanation for choice of comparators

Objectives	7 Page 6	Specific objectives or hypotheses
Trial design	8 Page 6	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
Methods: Participants, interventions, and outcomes		
Study setting	9 Page 7	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	10 Page 7	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	11a Page 9	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b Page 9	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c Page 10	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d Page 10	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12 Page 10	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	13 Page 12	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	14 Page 13	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	15 Page 14	Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a Page 16	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
Allocation concealment mechanism	16b Page 16	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c Page 17	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a Page 17	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b Page 18	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial

Methods: Data collection, management, and analysis

Data collection methods	18a Page 19	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	18b Page 19	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19 Page 20	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	20a Page 20	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol

	20b Page 21	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c Page 22	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring		
Data monitoring	21a Page 22	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
	21b Page 21	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22 Page 23	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23 Page 24	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
Ethics and dissemination		
Research ethics approval	24 Page 27	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	25 Page 24	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	26a Page 8	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b Page 8	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27 Page 20	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	28 Page 28	Financial and other competing interests for principal investigators for the overall trial and each study site

Access to data	29 Page 27	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30 Page 10	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a Page 24	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b Page 26	Authorship eligibility guidelines and any intended use of professional writers
	31c Page 22	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
Informed consent materials	32 Page 27	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33 Page 20	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.