DRCR Retina Network

Use of Diagnostic Dataset to Enrich Recruiting for Clinical Trials for Diabetic Retinal Disease: A Feasibility Study

(Protocol AQ)

Sponsor: Jaeb Center for Health Research (JCHR)

Version Number: 1.0

June 16, 2023

Signature Page

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Coordinating Center Director	
Name, degree	Adam Glassman, MS
Signature/Date	Digitally signed by Adam Glassman Reason: I am approving this document Date: 2023-06-22 09:32-04:00
JCHR Protocol Director	
Name, degree	Cynthia Stockdale, MSPH
Signature/Date	Cynthia Stockdale I agree to the terms defined by the placement of my signature in this document 2023-06-22 08:33-04:00
Protocol Co-Chair	
Name, degree	Maureen G. Maguire, PhD
Signature/Date	Maureen G. Maguire Digitally signed by Maureen G. Maguire Date: 2023.06.22 22:59:46 -04'00'
Protocol Co-Chair	
Name, degree	Hani Salehi-Had, MD
Signature/Date	DocuSigned by: 3E327835EEC047F... June 26, 2023

KEY ROLES

Protocol Co-Chair	
Name	Maureen G. Maguire, PhD
Title	Biostatistician
Institution Name	Jaeb Center for Health Research, Tampa, FL
Protocol Co-Chair	
Name	Hani Salehi-Had, MD
Title	Principal Investigator
Institution Name	Retina Associates of Southern California
Coordinating Center Director	
Name	Adam Glassman, MS
Title	Director, DRCR Retina Network Coordinating Center
Institution Name	Jaeb Center for Health Research, Tampa, FL
JCHR Protocol Director	
Name	Cynthia Stockdale, MSPH
Title	Associate Director, DRCR Retina Network Coordinating Center
Institution Name	Jaeb Center for Health Research, Tampa, FL
JCHR Protocol Manager	
Name	Gabriela Vieyra, PhD, MPH
Title	Epidemiologist
Institution Name	Jaeb Center for Health Research, Tampa, FL
Network Chair	
Name	Jennifer K. Sun, MD, PhD
Title	Chair, Diabetes Initiatives
Institution Name	Joslin Diabetes Center, Boston, MA

VERSION HISTORY

The following table lists versions of the protocol.

VERSION NUMBER	AUTHOR	APPROVER	EFFECTIVE DATE	REVISION DESCRIPTION
1.0	Gabriela Vieyra	Cynthia Stockdale	16JUN2023	Initial Version

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AST	Adaptive Sensory Technology
CC	Coordinating Center
CFR	Code of Federal Regulations
CRF	Case Report Form
DM	Diabetes Mellitus
DME	Diabetic Macular Edema
DR	Diabetic Retinopathy
DRSS	Diabetic Retinopathy Severity Score
eConsent	electronic Informed Consent
eCRF	electronic Case Report Form
E-ETDRS	Electronic-Early Treatment Diabetic Retinopathy Study
eGFR	Estimated Glomerular Filtration Rate
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICD	International Classification of Diseases
IRB	Institutional Review Board
JCHR	Jaeb Center for Health Research
NIH	National Institutes of Health
NPDR	Non-Proliferative Diabetic Retinopathy
OCT	Optical Coherence Tomography
OR	Odds Ratio
PDR	Proliferative Diabetic Retinopathy
PHI	Protected Health Information
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SD	Standard Deviation

ABBREVIATION	DEFINITION
UWF	Ultra-Wide Field
VA	Visual Acuity
WHO	World Health Organization

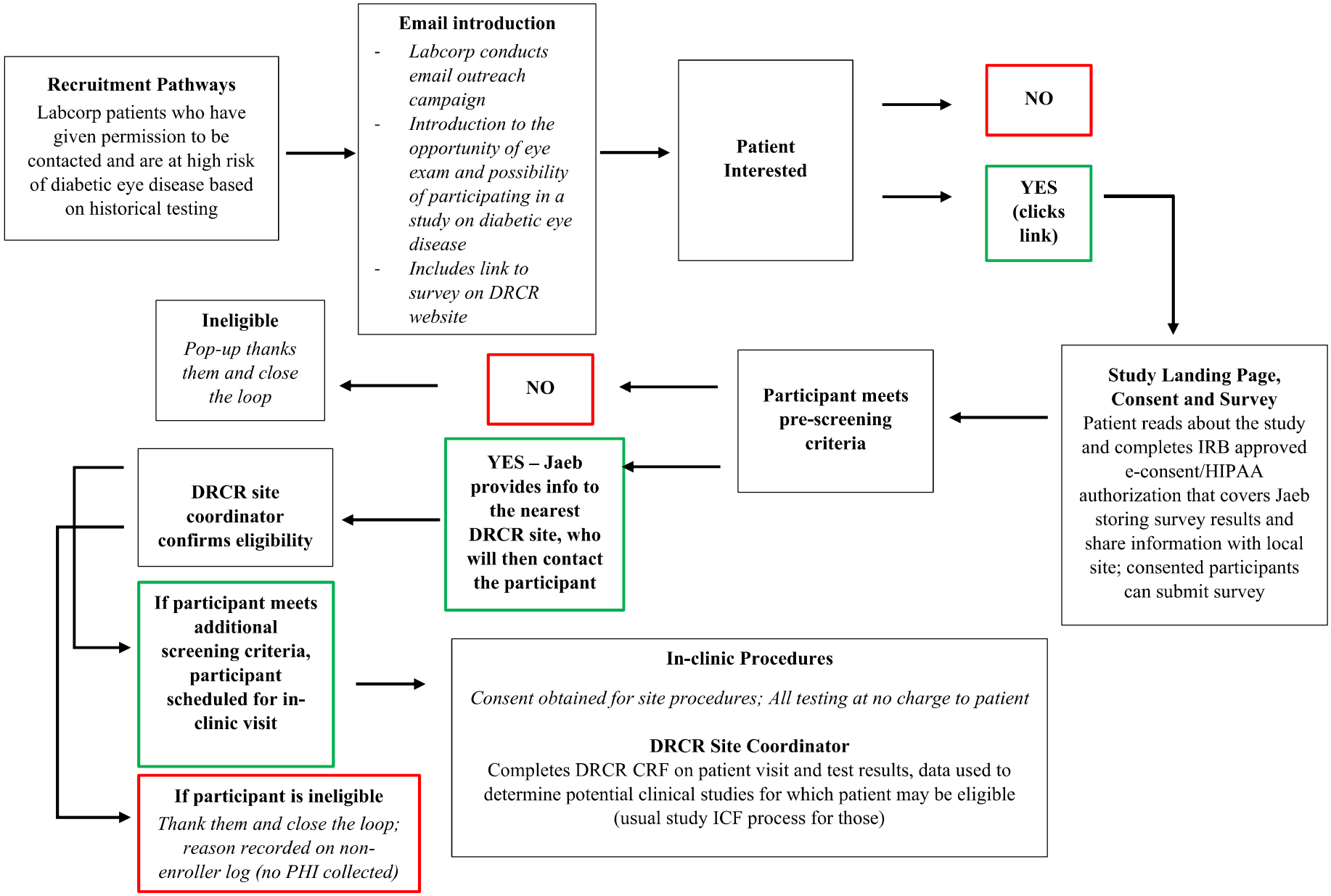
PROTOCOL AQ SUMMARY

PARTICIPANT AREA	DESCRIPTION
Title	Use of Diagnostic Dataset to Enrich Recruiting for Clinical Trials for Diabetic Retinal Disease: A Feasibility Study
Précis	There is an inherent challenge in the recruitment for clinical trials of participants who are at risk for diabetic eye diseases but do not visit a retina specialist regularly. This study will explore and evaluate the identification of candidates for DRCR Retina Network clinical trials for patients with diabetic retinopathy or diabetic macular edema by using historical results from Laboratory Corporation of America Holdings, commonly known as Labcorp, and Adaptive Sensory Technology contrast sensitivity testing.
Objectives	The objective of this study is to evaluate the identification of clinical study candidates through a collaboration with Labcorp and Adaptive Sensory Technology to select and contact high-risk patients for diabetic retinopathy based on results from laboratory tests with the ultimate goal to facilitate and increase the recruitment of patients for clinical research studies on diabetes-related eye diseases. A secondary objective is to evaluate the role of contrast sensitivity testing in selecting high-risk patients for diabetic retinopathy.
Study Design	Prospective screening protocol
Number of Sites	5
Population	Patients will be recruited from five DRCR sites with historical test results available from Labcorp. ***To be eligible, the following criteria and none of the exclusion criteria must be met:*** 1. Have received an email outreach from Labcorp 2. Age ≥18 years and < 80 years o *Individuals ≥ 80 years old are excluded to limit co-morbidities and to be consistent with other DRCR studies.* 3. Able to read and understand English 4. Able to provide own consent 5. Diagnosed with diabetes 6. At least one of the following based on historical test results: • HbA1c 8.0 to 15.0% and diabetes duration 10 or more years OR • eGFR 15 mL/min to 59 mL/min, inclusive OR • HbA1c 7.0 to 7.9% and diabetes duration 15 or more years 7. None of the following current exclusions: • Pregnant, nursing, or planning pregnancy within the next 2 years • Kidney failure requiring dialysis

PARTICIPANT AREA	DESCRIPTION
	• Any health condition or other situation that may limit the participant's ability to attend medical appointments
Sample Size	Goal is to have 125 participants complete an in-person clinic visit (25 patients at each of the 5 sites) *It is anticipated that it may require contacting >100 eligible participants per site by phone to reach this goal*
Outcomes	Number and percentages of patients who are identified as possible candidates for DRCR clinical trials at each step in the identification process: 1. Receive email outreach campaign from Labcorp based on historical testing 2. Respond to the online pre-screening survey (i.e., Labcorp email outreach campaign) by accessing the online survey/eConsent landing page. 3. Give eConsent and complete the online survey 4. Eligible after taking the online survey 5. Eligible and agree to be contacted by DRCR site 6. Successfully contacted for telephone screening 7. Eligible after completing the telephone screening 8. Make an appointment for in-clinic evaluation at a DRCR site 9. Complete an in-clinic evaluation 10. Have specific features of diabetic eye disease. • Non-proliferative diabetic retinopathy (DRSS 35 to <60) • Proliferative diabetic retinopathy (DRSS > 60) • Any diabetic macular edema • Center-involved diabetic macular edema ▪ Without visual impairment (VA 20/25 or better) ▪ With visual impairment (VA 20/32 or worse) 11. Have received prior treatment for DME or DR 12. Do not meet exclusion criteria for systemic or ocular health for ongoing DRCR studies 13. Percentage of evaluated patients who are enrolled in each DRCR Protocol The above outcomes will be stratified by 1) clinical site, 2) risk factor groups A-C (defined in Chapter 4, and 3) contrast sensitivity testing
Participant Duration	Pre-screening online survey followed by a telephone interview with a DRCR site coordinator followed by a single in-person visit (see flow chart below)
Protocol Overview/Synopsis	1. Labcorp will initiate an email outreach campaign in collaboration with DRCR.

PARTICIPANT AREA	DESCRIPTION
	2. If the patient is interested, they follow a link to a DRCR managed website that includes a brief description of the project and optional eConsent which includes authorization to share their PHI with Jaeb and a local DRCR site. 3. If consented, participant fills out a short pre-screening survey online for Jaeb (duration of diabetes, other questions that will further narrow to those at highest risk of diabetic eye disease, contact information). 4. If still eligible, Jaeb staff will notify a nearby DRCR site and provide them with the participant's contact information. The site coordinator will then contact the participant to confirm eligibility and the participant will be scheduled for a one-day screening visit. 5. Screening visit consists of: • Medical history and HbA1c • Protocol refraction and visual acuity testing • AST contrast sensitivity testing • Color fundus photographs • OCT • Dilated eye examination by an ophthalmologist and discussion of clinical findings 6. If participant remains eligible for a DRCR clinical study that is in the recruitment phase, participant will be presented with the enrolling DRCR study consent form(s). Depending on the study, the in-clinic visit may be extended on the same day to complete the enrollment procedures for the subsequent study, if the participant is agreeable.

SCHEMATIC OF STUDY DESIGN



Chapter 1: Background Information

1.1 Background

Diabetes mellitus (DM) is considered the fastest growing chronic disease in the world, and it is a leading cause of vision loss.[1] It is estimated that the total number of people with diabetes will double from 171 million in 2000 to 366 million by the year 2030.[1] Diabetic Retinopathy (DR), a microvascular complication of DM, is considered the leading cause of acquired blindness in the Western world.[2] According to the World Health Organization (WHO), DR accounts for 4.8% (37 million) of the number of cases of blindness worldwide. [1] In 2018, 10.5% of the U.S. population had diabetes and 13% of all U.S. adults 18 years and older.[3] This number increased with age reaching about 26.8% among those 65 years or older.[3] Notably, 7.3 million adults aged 18 or older who met laboratory criteria for diabetes were not aware or did not report having diabetes, representing 2.8% of all U.S. adults and 21.4% of all U.S. adults with diabetes.[3]

The Centers for Disease Control and Prevention estimates that 4.1 million Americans are affected with Diabetic Retinopathy (DR) and 899,000 are threatened with vision-threatening retinopathy.[4] It is estimated that DR and Diabetic Macular Edema (DME) affect 28.5% and 3.8%, respectively, of U.S. adults 40 years and older with diabetes.[5] Varma et al. (2014) found that Non-Hispanic Blacks had statistically significant higher odds of prevalent DME (OR=2.64) compared to Non-Hispanic Whites.[6] Similarly, higher HbA1C levels and diabetes duration longer than 10 years were associated with increased odds of prevalent DME, OR= 1.47 and 8.51, respectively.[6]

1.2 DRCR Retina Network and Labcorp Collaboration

The DRCR Retina Network conducts multiple concurrent and consecutive protocols. At any one time, the Network usually has several protocols that are recruiting patients with diabetes.

Laboratory Corporation of America Holdings, commonly known as Labcorp, is a global life sciences and healthcare company. The company processes more than 3 million patient specimens per week.[7] Labcorp is also committed to promoting clinical trial participation through email outreach campaigns.

The objective of this feasibility study is to explore and evaluate the identification of candidates for the DRCR Retina Network clinical studies of patients with DR or DME by using the results from Labcorp laboratory tests.

1.3 Adaptive Sensory Technology (AST) Contrast Sensitivity

Contrast sensitivity is reduced among patients with diabetes, often before signs of DR develop. It is known that mean levels of contrast sensitivity decrease with more severe levels of DR and with macular edema.[8-12] A method of measuring contrast sensitivity developed by Adaptive Sensory Technology (AST) will obtain the full contrast sensitivity curve across a spectrum of spatial frequencies. If AST contrast sensitivity is strongly associated with DR severity level or presence/absence of DME, it may serve as an additional screening tool outside of a retina specialist's office beyond laboratory test results.

1.4 Rationale

There is an inherent challenge in the recruitment for clinical trials of participants that are at risk for diabetic eye diseases who do not visit a retina specialist regularly. This study aims to identify candidates for DRCR Retina Network clinical trials through an email outreach and pre-screening program. If successful, the proposed study will aid in increasing the recruitment of these patients for clinical research and broaden the diversity and generalizability of the Jaeb Center's clinical trial population. This same data science approach may be applied to population health screenings if successful.

1.5 Study Objectives

1. Evaluate the effectiveness of an email outreach campaign to facilitate and increase the recruitment of patients for clinical research studies on diabetes-related eye diseases.
2. Evaluate the role of contrast sensitivity testing in selecting high-risk patients.

1.6 Potential Risks and Benefits of the Study

1.6.1 Known Potential Risks Related to Common Procedures

Many of the procedures in this study are part of daily ophthalmologic practice in the United States and pose few if any known risks. The blood draw could cause bruising, discomfort, bleeding, infection, or fainting. These risks are possible but unlikely, and usually mild.

1.6.2 Risks Related to Confidentiality

The risk of disclosure of protected health information is very small. Efforts are taken to ensure that this does not occur, in compliance with HIPAA.

1.6.3 Known Potential Benefits

Patients may learn more information about their current level of diabetic disease and will have access to opportunities for clinical trials if certain eligibility criteria for those studies are met. Patients that do not meet criteria for ongoing clinical trials will be given options for continued ophthalmology care to include returning to their current eye care provider, if applicable.

1.6.4 Risk Assessment

The protocol risk assessment for this non-interventional study has been categorized as no greater than minimal risk.

1.7 General Considerations

The study is being conducted in compliance with the policies described in the DRCR Retina Network policies document, with the ethical principles that have their origin in the Declaration of Helsinki, with the protocol described herein, and with the standards of Good Clinical Practice (GCP).

Chapter 2: Enrollment and Screening

2.1 Participant Recruitment and Enrollment

Labcorp will initiate an email outreach campaign in collaboration with DRCR to contactable patients at high risk of diabetic eye disease. If interested, the participant will follow a link within the email to a DRCR-managed website, which will include a study information landing page, eConsent which includes HIPAA authorization for Jaeb to store survey results and share contact information with a local DRCR site, and a short survey that includes additional medical history factors that may impact potential eligibility for DRCR Retina Network clinical trials. Before completing any procedures or collecting any data at the site, in-person informed consent will be obtained.

After completion of the short survey on the DRCR website and selection of the nearest clinical site by the participant, those meeting specified selection criteria will be contacted by telephone by a DRCR site coordinator to confirm eligibility. Each participant will be called, asked screening questions, and scheduled for an in-clinic visit if they remain eligible and agree to the in-clinic visit. The DRCR coordinator will complete a general non-enroller log for those who are deemed ineligible, but no PHI information will be collected, and no case report form (CRF) will be completed during the phone call.

Eligible participants will be reminded of the upcoming in-clinic visit and will be rescheduled as needed. Participants arriving for their visit will sign an informed consent form with the site and have the screening procedures completed as described in Chapter 3. As part of the consent process, participants will be asked whether they want results sent to their current eyecare provider. Results will also be sent to the participant upon receipt of reading center grading.

The goal is for 125 participants to complete an in-person clinic visit (approximately 25 per participating site). There is no maximum number of participants to be emailed and who will complete the online survey in order to reach this goal. Additional participants may be screened beyond this goal if already scheduled at the time recruitment is closed. All eligible participants will be included without regard to gender, race, or ethnicity. The study will be conducted at approximately 5 clinical centers in the United States. Each participating clinical site will first receive training for project procedures. Potential eligibility for an in-clinic visit will be assessed by 1) Labcorp email outreach campaign parameters, 2) pre-screening survey questions, and 3) follow-up phone call by site staff.

Participants who eConsent and complete the survey will contribute data to the protocol. Aggregate data such as counts and percentages of those contacted that do or do not click the link will also be generated based on aggregate data provided by Labcorp for each DRCR clinical site.

In addition, there may be participants identified who may be eligible for other DRCR protocols, for which separate consent will be obtained.

2.2 Informed Consent

Informed consent will occur in two stages, according to JCHR IRB requirements:

1) HIPAA Authorization and consent for Jaeb to store survey results and share patient contact information with local sites will be obtained electronically after the participant navigates to the DRCR website.
2) Informed consent for study procedures and data collection at the site will be obtained in person with a paper form according to IRB requirements of the JCHR.

Upon navigation to the DRCR website, a summary of the study will be displayed. If interested, the patient will complete a verification step required for HIPAA compliant electronic signature. Here the participant will create a unique username and password, where the password is unknown to others. This username and password will be used to provide e-signature for the first stage of consent described above. As part of the informed consent process, each participant will be asked to provide authorization for Jaeb to store their survey results and release of personal information. The participant will also provide authorization for the DRCR site coordinator at a local DRCR site to contact them to schedule the in-clinic screening visit. After contacting the participant, any questions will be answered about the visit by the DRCR site coordinator.

2.3 Population

Individuals invited to participate will be recruited from geographical areas near DRCR sites that are certified to recruit for Protocol AQ. Participants recruited should have received an email invitation directly from Labcorp based on the criteria below.

2.4 Participant Inclusion Criteria

To be eligible, the following inclusion criteria and none of the exclusion criteria must be met:

1. Have received an email outreach from Labcorp
2. Age ≥18 years and < 80 years
   - *Individuals < 18 years old are not being included because DR is so rare in this age group that the diagnosis may be questionable.*
   - *Individuals ≥ 80 years old are excluded to limit co-morbidities and to be consistent with other DRCR studies.*
3. Able to read and understand English
4. Able to provide own consent
5. At least one of the following based on historical test results:
   - HbA1c 8.0 to 15.0% and diabetes duration 10 or more years

   OR
   - eGFR 15 mL/min to 59 mL/min, inclusive

   OR
   - HbA1c 7.0 to 7.9% and diabetes duration 15 or more years
6. None of the following current exclusions:
   - Pregnant, nursing, or planning pregnancy within the next 2 years
   - Kidney failure requiring dialysis

- Any health condition or other situation that may limit the participant's ability to attend medical appointments

2.5 Screening Survey

After the e-consent and HIPPA authorization have been obtained, a potential participant will be evaluated for study eligibility through the elicitation of a brief medical history via online survey.

As will be described in the e-consent form, participants will be asked to provide contact information, including an email address and a phone number. The participant will select the nearest DRCR site for potential follow-up.

2.6 Site Follow-up via Phone Contact

Contact information from eligible participants will be provided to DRCR sites via a secure method. Sites will contact participants to confirm eligibility. If ineligible, the reason will be documented on a general non-enroller log (no PHI will be collected at this step). If eligible, the screening visit will be scheduled.

Once the goal has been met for in-clinic visits, eligible participants who have not been contacted for scheduling will be notified via email that the screening event has been closed.

Chapter 3: In-Clinic Visit

3.1 Visit Procedures

During the in-clinic visit the DRCR site Coordinator will first obtain consent and HIPAA Authorization via the paper informed consent and HIPAA form(s) (ICF). DRCR CRFs will be completed during the in-clinic visit. The procedures listed below will be conducted to determine diabetic retinopathy status and potential eligibility for other DRCR studies. The testing procedures are detailed in the DRCR Retina Network procedures manuals. Visual acuity testing, ocular exam, fundus photography, and OCT will be performed by certified personnel. The fundus photographs will be sent to a Reading Center for grading. OCT images meeting DRCR.net criteria for manual grading will be sent to a Reading Center.

1. Self-reported demographics (date of birth, sex, race, and ethnicity)
2. Medical history (including ocular diseases, surgeries, and treatment)
    - Medical history will be obtained by medical charts if available at the enrolling site; otherwise, it will be self-reported *(Note: Additional documentation may be required for enrollment into clinical trials, e.g., obtain records from other care provider(s)*
3. Physical examination to include:
    - Weight and height, if is equipment available
    - Blood pressure
4. Hemoglobin A1c (fingerstick or capillary tube via central lab testing or DCAVantage)
5. Electronic-ETDRS visual acuity testing at 3 meters using the Electronic Visual Acuity Tester (including protocol refraction) in each eye
6. AST contrast sensitivity testing – *performed pre-dilation, prior to imaging*
7. Color fundus photographs on both eyes using the widest approach available (e.g., ultra-widefield imaging device (UWF), if available)
8. Spectral-domain OCT using Zeiss Cirrus or Heidelberg Spectralis in both eyes
9. Ocular examination on each eye including slit lamp, measurement of intraocular pressure, lens assessment, and dilated ophthalmoscopy

All the testing procedures do not need to be performed on the same day. If the participant declines to complete all procedures, the testing that was performed will be collected.

3.2 Visit Conclusion and Follow-up Next Steps

At the conclusion of the visit, the investigator will review the results of the visit examination including DR and DME status and recommended next steps to include returning for a DRCR clinical trial screening, referral back to current eye care provider, continuing care at the site, or no additional follow-up.

Following receipt of central reading center grading, a written summary of the visit will be sent to the participant and to the participant's current eye care provider, if applicable and the participant agrees.

3.3 Adverse Event Reporting

Only adverse events related to study participation and requiring medical intervention will be reported.

3.4 Unanticipated Problems

Site investigators will promptly report to the Coordinating Center all unanticipated problems meeting the criteria below. For this protocol, an unanticipated problem is an incident, experience, or outcome that meets all the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied
2. Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research)
3. Suggests that the research places participants or others at a greater risk of harm than was previously known or recognized **(**including physical, psychological, economic, or social harm)

The Coordinating Center also will report to the IRB all unanticipated problems not directly involving a specific site such as unanticipated problems that occur at the Coordinating Center or at another participating entity such as a pharmacy or laboratory.

3.5 Miscellaneous Considerations

3.5.1 Participant Compensation

Participant compensation will be specified in the informed consent form.

3.5.2 Participant Withdrawal

Participation in the study is voluntary, and a participant may withdraw without completing the study. For participants who withdraw, their data will be used up until the time of withdrawal.

3.5.3 Confidentiality

Protected health information gathered for this study will be shared with the Coordinating Center, the Jaeb Center for Health Research in Tampa, FL. De-identified participant information may also be provided to research sites involved in the study.

For security and confidentiality purposes, participants who complete the online survey will be assigned an identifier that will be stored with study data instead of their name. The Coordinating Center will be provided with contact information for each study participant and will share the

information only with the clinical site selected by the participant for follow-up and with Labcorp for the purposes of linking back to the Labcorp data that prompted contact. Permission to obtain and share such information will be included in the eConsent and HIPAA Authorization. The contact information will be maintained in a secure database and will be maintained separately from the study data. It will be shared in a secure manner.

DRCR sites involved in the study will be given access to the information to contact the participants who selected their site as part of the online consent and survey. Additional phone contacts from the Coordinating Center will be made if necessary to facilitate the scheduling of the study participant.

3.5.4 Criteria for Suspending or Stopping Overall Study

The DRCR Retina Network Executive Committee may request suspension of study activities or termination of the study if deemed necessary at any time.

Chapter 4: Statistical Methods

4.1 Primary Objectives and Key Outcomes

This study has two objectives. Firstly, to evaluate the identification of clinical trial candidates through a collaboration with Labcorp with the goal of facilitating and increasing recruitment of patients for clinical trials on diabetes-related eye diseases. Secondly, to evaluate the role of contrast sensitivity testing in identifying high-risk patients who may be clinical trial candidates.

Key Outcomes:

Number and percentages of patients who are identified as possible candidates for DRCR clinical trials at each step in the identification process:

1. Receive email outreach campaign from Labcorp based on historical testing
2. Respond to the online pre-screening survey (i.e., Labcorp email outreach campaign) by accessing the online survey/consent landing page.
3. Give consent and complete the online survey
4. Eligible after taking the online survey
5. Eligible and agree to be contacted by DRCR site
6. Successfully contacted for telephone screening
7. Eligible after completing the telephone screening
8. Make an appointment for in-clinic evaluation at a DRCR site
9. Complete an in-clinic evaluation
10. Have specific features of diabetic eye disease.
    - Non-proliferative diabetic retinopathy (DRSS 35 to <60)
    - Proliferative diabetic retinopathy (DRSS > 60)
    - Any diabetic macular edema
    - Center-involved diabetic macular edema
        - Without visual impairment (VA 20/25 or better)
        - With visual impairment (VA 20/32 or worse)
11. Have received prior treatment for DME or DR
12. Do not meet exclusion criteria for systemic or ocular health for ongoing DRCR studies
13. Percentage of evaluated patients who are enrolled in each DRCR Protocol

The above outcomes will be stratified by 1) clinical site, 2) risk factor groups A-C below, and 3) contrast sensitivity testing.

Participants will be categorized into the following key risk factor groups based on historical test results:

- Group A: HbA1c test value between 7.0% and 7.9%
- Group B: HbA1c test value between 8.0% and 15.0%
- Group C: eGFR 15 mL/min to 59 mL/min

Preliminary estimates are that for every 100 patients contacted by a coordinator, 25 will arrive for an in-clinic examination. 2 will have DME, 1 will have PDR, and 4 will have mild or moderate NPDR (including DRSS 20).

4.1.1 Sample Size

The goal is for 125 participants to complete an in-person clinic visit (25 patients at each of the 5 clinical sites). It is anticipated that it may require contacting > 100 eligible participants per site by phone or email to reach this goal (>100,000 will be initially contacted by Labcorp and invited to complete an online pre-screening survey). The email invitation from Labcorp will be sent out in waves, starting with the highest risk patients, because the percentage of patients who complete the online prescreening survey is not known.

The goal of enrolling 125 participants for an in-clinic examination was chosen based on the following assumptions:

1. The percent of patients who attend a screening visit who have the following diabetic eye conditions is estimated based on 1) prevalence rates among people with diabetes from Medicare in 2018 (Chew, 2022) and 2) from the Eye Disease Prevalence Study Group (published 2004), and 3) the prevalence of HbA1c of ≥8% in previous DRCR trials (S, T, W).
    - Non-proliferative diabetic retinopathy (NPDR) [Any stage] – 14%
    - Proliferative diabetic retinopathy (PDR) – 3.6%
    - Any diabetic macular edema (DME) - 7.2%

However, the percentages of patients, recruited through the practices of retina specialists, in DRCR Protocol M with disease among those with (HbA1c of ≥8% and duration of 10 or more years) were considerably higher, approximately 4 times higher.

- Non-proliferative diabetic retinopathy (NPDR) [Any stage] – 51%
- Proliferative diabetic retinopathy (PDR) – 20%
- Any diabetic macular edema (DME) - 27%

Based on these assumptions, the increase in precision gained by increasing the sample size beyond 125, was considered small compared with the cost and effort to recruit additional patients, as demonstrated in the table below.

Table 1. Sample calculations of gained precision with increased sample size beyond 125*

	N=125		N=200		N=250	
Observed Proportion	**Lower Bound**	**Upper Bound**	**Lower Bound**	**Upper Bound**	**Lower Bound**	**Upper Bound**
2%	1%	6%	1%	5%	1%	5%
4%	2%	9%	2%	8%	2%	7%
6%	3%	12%	3%	10%	4%	10%
8%	4%	14%	5%	13%	5%	12%
10%	6%	17%	7%	15%	7%	14%
12%	7%	19%	8%	17%	9%	17%
14%	9%	21%	10%	19%	10%	19%

16%	11%	23%	12%	22%	12%	21%
18%	12%	26%	13%	24%	14%	23%
20%	14%	28%	15%	26%	16%	25%
22%	16%	30%	17%	28%	17%	28%
24%	17%	32%	19%	30%	19%	30%
26%	19%	34%	20%	32%	21%	32%
28%	21%	36%	22%	35%	23%	34%
30%	23%	39%	24%	37%	25%	36%

* 95% confidence intervals calculated based on the assumption of normal distribution for a known proportion: 95% $CI = p \pm z(\sqrt{\frac{p*q}{n}})$, where p is the observed proportion, z is the z-score for two-sided test, q is 1-p, and n is the sample size.

4.1.2 Descriptive Statistics

Data description will be presented as summarized descriptive statistics of the outlined outcomes (n, mean, standard deviation [SD], median, minimum, maximum, and percentages).

4.1.3 Additional Analyses

The cost of the study with respect to funding the clinical sites and the reading center, as well as an estimate of the personnel costs at the coordinating center, will be compared to the number of patients meeting eligibility criteria for DRCR studies. An estimated cost per patient recruited will be calculated.

Chapter 5: Data Collection and Monitoring

5.1 Case Report Forms and Other Data Collection

The main study data from the in-person visit are collected on electronic case report forms (eCRFs). When data are directly collected in eCRFs, this will be considered the source data. For any data points for which the eCRF is not considered the source, the original source documentation must be maintained in the participant's study chart or medical record. This source must be readily verifiable against the values entered into eCRF. Even where all study data are directly entered into the eCRFs at office visits, evidence of interaction with a live subject must be recorded (e.g., office note, visit record, etc.).

5.2 Study Records Retention

Each participating site will maintain appropriate medical and research records for this study, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of participants.

Study documents should be retained for a minimum of 3 years following the NIH grant cycle for which the last visit was completed. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the JCHR, if applicable. It is the responsibility of JCHR to inform the investigator when study documents no longer need to be retained.

5.3 Quality Assurance and Monitoring

Designated personnel from the Coordinating Center will be responsible for maintaining quality assurance (QA) and quality control (QC) systems to ensure that the clinical portion of the study is conducted and data are generated, documented and reported in compliance with the protocol, Good Clinical Practice (GCP) and the applicable regulatory requirements, as well as to ensure that the rights and wellbeing of study participants are protected and that reported study data are accurate, complete, and verifiable.

CC representatives or their designees may visit the study facilities at any time in order to maintain current and personal knowledge of the study through review of the records, comparison with source documents, observation and discussion of the conduct and progress of the study. The DRCR site will provide direct access to all study related sites, source data/documents, and reports for the purpose of monitoring and auditing by the CC, and inspection by local and regulatory authorities.

5.4 Protocol Deviations

A protocol deviation is any noncompliance with the study protocol, GCP, or procedure requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. The site principal investigator (PI) and study staff delegated to study responsibilities are responsible for knowing and adhering to their IRB requirements.

Chapter 6: Ethics/Protection of Human Participants

6.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Participants of Research codified in 45 Code of Federal Regulations (CFR) Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

6.2 Institutional Review Boards

The protocol, ICF(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

6.3 Informed Consent Process

6.3.1 Consent Procedures and Documentation

Informed consent is a process that will be initiated upon the individual's positive response (clicking the link to the study's landing page) to learning more about the current study. Once at the landing page, the participant will read about the study and will complete the IRB approved electronic consent and HIPAA authorization, covering the survey and in-person testing that will be conducted.

The participant will sign the electronic consent document prior to any procedures being done specifically for the study. A copy of the informed consent document can be printed directly from the website for the participants records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

6.3.2 Participant and Data Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff, the sponsor(s), and their agents. This confidentiality is extended to cover testing of biologic samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of JCHR.

The study monitor, other authorized vendors, or representatives of JCHR, representatives of the IRB, or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to medical records (office, clinic, or hospital) for the participants in this study. The clinical study site will permit access to such records.

Separately from any research data, JCHR will be provided with participant contact information. Study participant's contact information will be securely stored separately from research data and

will be destroyed at the end of the study. Contact information will be made available to each clinical site via a secure method for internal use during the study. For participants who agree, JCHR will share names, phone number, and address with Labcorp for the purposes of linking back to the Labcorp data that prompted contact to confirm prior test results. Permission to obtain and share such information will be included in the Informed Consent Form. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the DRCR Retina Network coordinating center, located at the Jaeb Center for Health Research in Tampa, Florida. This will not include the participant's contact or identifying information, unless otherwise specified in the informed consent form. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the DRCR Retina Network coordinating center research staff will be secured, and password protected. At the end of the study, all study databases will be de-identified and archived at the DRCR Retina Network coordinating center.

To further protect the privacy of study participants, a Certificate of Confidentiality will be obtained from the NIH. This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

6.3.3 Future Use of Data

After the study is completed, the de-identified, archived data will made publicly available for use by other researchers including those outside of the study. In addition, OCT scans and fundus photographs may be made publicly available. These images of the retina are considered identifiable information but are only identifiable if they can be matched to a database that already includes retinal images for identification purposes (directly identifiable information will be removed). Permission to make data and retinal images publicly available will be included in the informed consent form.

Chapter 7: References

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