Johnson & Johnson Vision Care, Inc.

Clinical Study Protocol

ACUVUE® OASYS with Transitions™ Light Intelligent Technology™ Clinical Performance Registry

Protocol CR-6334

Version: 4.0

Date: 24 November 2020

Test Articles: ACUVUE® OASYS with Transitions™ Light Intelligent Technology™

Key Words: senofilcon A, Photosol® 7-1911, ACUVUE® OASYS with Transitions™ Light Intelligent Technology™, daily wear reusable, dispensing, physiological responses, subjective responses

Statement of Compliance to protocol, GCP and applicable regulatory guidelines:
This trial will be conducted in compliance with the protocol, ISO 14155[1], the International Conference on Harmonization Good Clinical Practice E6 (ICH-GCP),[2] the Declaration of Helsinki,[3] and all applicable regulatory requirements.

Confidentiality Statement:

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PROTOCOL TITLE, NUMBER, VERSION

Title: ACUVUE® OASYS with Transitions™ Light Intelligent Technology™ Clinical Performance Registry
Protocol Number: CR-6334
Version: 4.0
Date: 24 November 2020

SPONSOR NAME AND ADDRESS

Johnson & Johnson Vision Care (JJVC)
7500 Centurion Parkway
Jacksonville, FL 32256

MEDICAL MONITOR

Medical Monitoring Committee: Comprising JJVC medical monitor [redacted] Visioncare Research representative [redacted] and one appointed eye care practitioner from each country where this study is conducted.

Main point of contact:

The Medical Monitor must be notified by the clinical institution/site by e-mail, fax, or telephone within 24 hours of learning of a Serious Adverse Event. The Medical Monitor may be contacted during business hours for adverse event questions. General study related questions should be directed towards your assigned clinical research associate.

The Medical Monitoring Plan is maintained as a separate document and included in the Trial Master File.

AUTHORIZED SIGNATURES

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations[4], ICH guidelines,[2] ISO 14155,[1] and the Declaration of Helsinki.[3]

Author	[redacted]	DATE
Co-author / Study Responsible Clinician	[redacted] 25 Nov. 2020	DATE
Clinical Operations Manager	See Electronic Signature Report [redacted]	DATE
Biostatistician	See Electronic Signature Report [redacted]	DATE
Data Management	See Electronic Signature Report [redacted]	DATE
Reviewer	See Electronic Signature Report [redacted]	DATE
Approver	See Electronic Signature Report [redacted]	DATE

CHANGE HISTORY

Version	Originator	Description of Change(s) and Section Number(s) Affected	Date
1.0	[redacted]	Original Protocol	24 July 2019
2.0	[redacted]	Modified to exclude minors (i.e. under 18-year-old) from the study. Clarification of entry criteria – Section 3.2. Patient Release of Medical Records Form appendix removed.	23 Sep. 2019
3.0	[redacted]	Clarification of inclusion criteria 1, section 3.2: '… the use of a new ***reusable silicone hydrogel*** lens type and have purchased a supply of lenses.' Add exclusion criteria section 3.3. non spherical lens wearers Add Netherlands (country) to section 3.4 and enrollment estimation in figure 1	03 December 2019
4.0	[redacted]	Language added to section 3.1 clarifying the intended study population.	24 November 2020

SYNOPSIS

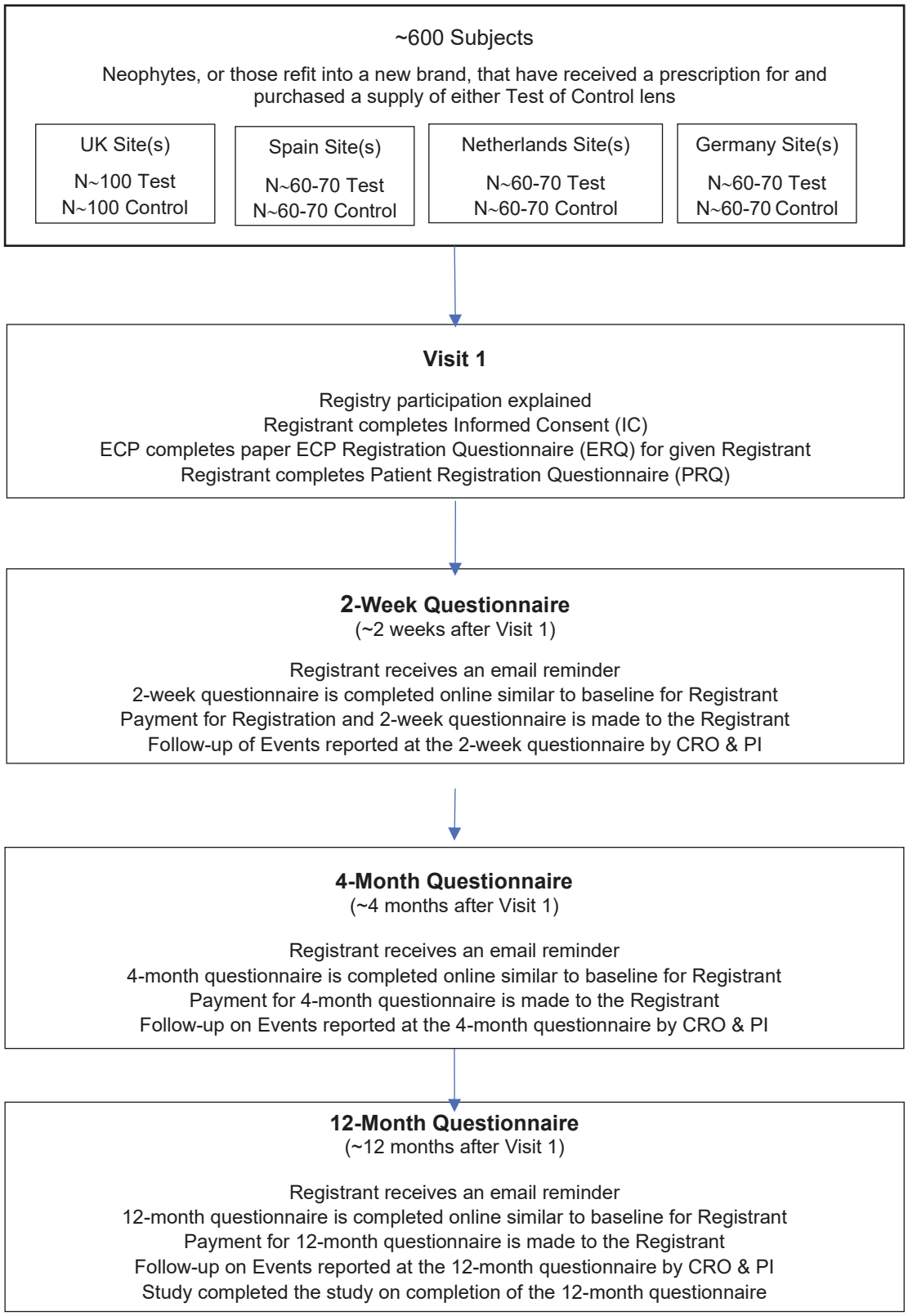
Protocol Title	ACUVUE® OASYS with Transitions™ Light Intelligent Technology™ Clinical Performance Registry
Sponsor	Johnson and Johnson Vision Care, Inc. (JJVC), 7500 Centurion Parkway, Jacksonville, FL 32256
Clinical Phase	Post Marketing (Registry) phase 4
Trial Registration	This study will be registered on ClinicalTrials.gov by the Sponsor
Test Article(s)	Investigational Products: JJVC spherical senofilcon A with photochromic additive (ACUVUE® OASYS with Transitions™ contact lenses) Control Products: spherical non-photochromic reusable marketed silicone hydrogel contact lenses.
Wear and Replacement Schedules	Wear schedule: Daily wear Recommended replacement schedule: 2-weekly or as determined by the prescribing eyecare practitioner.
Objectives	Evaluate the performance of JJVC senofilcon A with photochromic additive (ACUVUE® OASYS with Transitions™ contact lenses) compared to non-photochromic reusable contact lenses over a period of one year in the following areas: • Vision satisfaction in bright lighting • Overall quality of vision • Subjective assessment of Pulfrich Effect • Overall comfort • Reported serious or significant adverse events

Study Endpoints	Primary endpoint: 1. Vision satisfaction in bright lighting Secondary endpoints: 1. Overall quality of vision 2. Subjective assessment of Pulfrich Effect 3. Overall comfort 4. Reported serious or significant adverse events Other endpoints: 1. Overall satisfaction 2. Cosmetic appearance assessment 3. Lens storage compliance 4. Reasons for discontinuation 5. Other subjective assessments (indoor performance, overall opinion, average wear time, etc.)
Study Design	This registry study is a one-year, one-visit, observational, prospective, open-label, two-arm, multi-center, multi-national, post-market study of approximately 300 patients who have recently been fitted with the ACUVUE® OASYS with Transitions™ and approximately 300 patients who have recently been fitted with spherical non- photochromic reusable marketed silicone hydrogel contact lenses (of any brand). Visit 1 is conducted in-person at the eyecare practitioner (ECP) office. Assessments 2-4 are online surveys, conducted remotely. • Visit 1: Registration visit • Assessment 2: 2-week questionnaire • Assessment 3: 4-month questionnaire • Assessment 4: 12-month questionnaire The documentation of adverse events in the registered wearer's clinical record will reflect routine clinical practices that are outside the scope of this protocol. Medical records from any subject who reports having experienced "a problem with their eyes while wearing lenses that required you to visit an eyecare practitioner or hospital" will be obtained from the treating facility after they are reported via the 2-week, 4-month or 12-month questionnaires. See the flowchart at the end of the synopsis table for the schematic of the study visits and procedures of main observations (Figure 1).

Sample Size	Approximately 600 eligible subjects will be enrolled (~300 subjects per arm) with a target of 480 to complete the study (~240 subjects per arm).
Study Duration	The study will start within 6 months of launch in a given country and will observe the clinical performance of the Test and Control lenses for approximately one year in that country.
Anticipated Study Population	• Patient age: minimum 18 years old, no maximum age • Patients with no known history that would contradict contact lens wear. • Neophyte patients or those refit from habitual contact lenses
Eligibility Criteria	Potential subjects must satisfy all of the following criteria to be enrolled in the study: 1. Contact lens neophytes or those who have recently (i.e. within last 2 months) begun the use of a new reusable silicone hydrogel lens type and have purchased a supply of lenses. 2. A minimum age of 18 years, with no maximum age. 3. The registrant must read and sign the Informed Consent form. 4. The registrant must appear able and willing to adhere to the instructions set forth in this clinical protocol. Potential subjects who meet any of the following criteria will be excluded from participating in the study: 1. Current participant in another research study. 2. Employee or relative of site, or family member of Recruiting Practitioner or Johnson & Johnson. 3. Non-spherical contact lens wearers, i.e. toric or multifocal lenses.
Disallowed Medications/Interventions	Pre-study and concomitant medications are not being tracked in this Registry. Concomitant and incident therapy noted in the medical source record will be considered as part of the adjudicated diagnosis in subjects who experience events in the study.
Measurements and Procedures	• Physiological responses • Subjective questionnaires
Study Termination	Since all of the products associated with the study are marketed products, there are no anticipated circumstances in which the study would be prematurely terminated.

Ancillary Supplies/ Study-Specific Materials	None
Principal Investigator(s) and Study Institution(s)/Site(s)	A full list of Principal Investigators, clinical sites, and institutions is kept separately from the Study Protocol and is included in the study Trial Master File.

Figure 1: Study Flowchart



ABBREVIATIONS AND DEFINITIONS OF TERMS

ADE	Adverse Device Effect
AE	Adverse Event/Adverse Experience
CL	Contact Lens
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
ECP	Eye Care Practitioner
EDC	Electronic Data Capture
ERQ	ECP Registration Questionnaire
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HEV	High Energy Visible
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISO	International Organization for Standardization
JJVC	Johnson & Johnson Vision Care, Inc.
PI	Principal Investigator
PQC	Product Quality Complaint
PRO	Patient Reported Outcome
PRQ	Patient Registration Questionnaire
SAE	Serious Adverse Event/Serious Adverse Experience
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SOP	Standard Operating Procedure
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect
UK	United Kingdom
UV	Ultraviolet
VCR	Visioncare Research Ltd

1. INTRODUCTION AND BACKGROUND

In April 2018, the U.S. Food and Drug Administration (FDA) cleared the first contact lens to incorporate a photochromic additive that automatically darkens the lens in the presence of ultraviolet (UV) and high energy visible (HEV) light and lightens in its absence. The ACUVUE® OASYS with Transitions™ Light Intelligent Technology™ are soft contact lenses indicated for daily use to correct the vision and to reduce the effect of bright light. The intended users are people with non-diseased eyes who are nearsighted (myopia) or farsighted (hyperopia). They can also be used by people with certain degrees of astigmatism. The global roll-out of the lens began in the spring of 2019, with countries being added over forthcoming years.

The goal of this registry study is to provide real world data on the effectiveness of ACUVUE® OASYS with Transitions™ in the general population of spherical contact lens wearers and under general clinical practice. Vision satisfaction in bright lighting and overall quality of vision will be assessed using a longitudinal survey questionnaire over a period of one year. Pulfrich effect and reported serious and significant ocular adverse events will also be evaluated. This a non-randomized study and the sponsor, Johnson and Johnson Vision Care, Inc. (JJVC), has no control of the treatment assignment and minimal input on the study targeted population.

The sponsor has contracted with Visioncare Research (VCR) to monitor the study.

This Clinical Investigation Plan is to be used in conjunction with JJVC standard operating procedures (SOPs) (except for as outlined in this plan) as a project-specific working plan by VCR and designees during the conduct of the study. The following plan provides the minimum acceptable criteria for this study. This plan does not replace an understanding or adherence to the requirements contained in the study protocol, applicable regulations and ICH/GCP guidelines.

1.1. Name and Descriptions of Investigational Products

All products are approved and marketed within the countries participating in this Registry study. ACUVUE® OASYS with Transitions™ will serve as the Test lens. Other reusable spherical silicone hydrogel lenses will serve as the Control lenses. Further details about the Test lenses are found in Section 6 of this protocol.

1.2. Intended Use of Investigational Products

The intended use of the Test product is for correcting ametropia and the attenuation of bright light. During the study, the Test article will be worn bilaterally in a daily wear, reusable, 2-weekly modality, or as determined by the prescribing eyecare practitioner (ECP).

1.3. Summary of Findings from Nonclinical Studies

Not Applicable – Marketed product only.

1.4. Summary of Known Risks and Benefits to Human Subjects

The risks of wearing soft contact lenses are well known and are described in the relevant Package Insert.

1.5. Relevant Literature References and Prior Clinical Data Relevant to Proposed Clinical Study

Refer to relevant Package Insert.

2. STUDY OBJECTIVES, ENDPOINTS AND HYPOTHESES

2.1. Objectives

The objective of this study is to evaluate the performance of JJVC senofilcon A with photochromic additive (ACUVUE® OASYS with Transitions™ contact lenses) compared to non-photochromic reusable contact lenses over a period of one year in the following areas:

- Vision satisfaction in bright lighting
- Overall quality of vision
- Subjective assessment of Pulfrich Effect
- Overall comfort
- Reported serious or significant adverse events

2.2. Endpoints

All of the primary and secondary endpoints will be assessed using the follow-up questionnaire administered at 2-weeks, 4-months and 12-months after the enrollment visit (Visit 1).

Primary endpoints

Vision Satisfaction in Bright Lighting

Subjects will be asked to evaluate their vision satisfaction in bright lighting by rating their level of agreement with the statement "I was satisfied with the quality of my vision in bright lighting with these contact lenses" using a 5-point agreement Likert scale (1: Strongly Disagree, 2: Disagree, 3: Neither Agree nor Disagree, 4: Agree and 5: Strongly Agree).

Secondary endpoints

Overall quality of vision

This will be assessed subjectively using the item "I am satisfied with the overall quality of my vision with these contact lenses". The item uses a 5-point agreement scale (1: Strongly Disagree to 5: Strongly Agree)

Pulfrich Effect

This will be assessed subjectively using the item "While wearing these lenses, my depth perception of moving objects has NOT been impacted". Subjects who disagree or strongly disagree with the statement will be considered to have experienced the Pulfrich effect.

Overall comfort
This will be assessed using the item "How would you rate the overall comfort of these contact lenses?". The item uses the 5-point satisfaction scale, 1: Excellent, 2: Very Good, 3: Good, 4: Fair and 5: Poor.

Reported serious and significant ocular adverse events:
Incidence rate serious and significant ocular adverse events during the study period will be calculated (in 100 patient-year) using all available data from the entire study.

Other endpoint(s):

1. Overall satisfaction
2. Cosmetic appearance assessment
3. Lens storage compliance
4. Reasons for discontinuations
5. All reported ocular and non-ocular adverse events
6. Other subjective assessments (indoor performance, overall opinion, average wear time, etc.)

2.3. Hypotheses

Primary Hypotheses

Subjects wearing JJVC senofilcon A contact lenses with photochromic additive (ACUVUE® OASYS with Transitions™ contact lenses) will have superior vision satisfaction in bright lighting compared to subjects wearing non-photochromic reusable silicone hydrogel contact lenses over a period of one year.

Secondary Hypotheses

1. Subjects wearing JJVC senofilcon A contact lenses with photochromic additive (ACUVUE® OASYS with Transitions™ contact lenses) will have superior vision satisfaction compared to subjects wearing non-photochromic reusable silicone hydrogel contact lenses at 12-month evaluation. This hypothesis will also be tested at 2-week and 4-month evaluation periods.
2. Subjects wearing JJVC senofilcon A contact lenses with photochromic additive (ACUVUE® OASYS with Transitions™ contact lenses) will have superior overall quality of vision compared to subjects wearing non-photochromic reusable silicone hydrogel contact lenses over a period of one year. This hypothesis will also be tested at each evaluation period.
3. Subjects wearing JJVC senofilcon A contact lenses with photochromic additive (ACUVUE® OASYS with Transitions™ contact lenses) will have superior overall comfort compared to subjects wearing non-photochromic reusable silicone hydrogel contact lenses over a period of one year. This hypothesis will also be tested at each evaluation period.

No hypotheses are formulated about Pulfrich effect or, serious and significant ocular adverse events (AEs). The following will be calculated by arm:

1. Proportion of subjects who experienced the Pulfrich effect at each evaluation period.
2. Incidence rate of serious and significant ocular AEs (in patient-year)

3. Proportion of subjects with at least one reported serious or significant ocular AE at each evaluation period.
4. Proportion of eyes with a least one reported serious or significant ocular AE at each evaluation period.
5. Proportion of all reported serious and significant ocular AEs at each evaluation period.

3. TARGETED STUDY POPULATION

3.1. General Characteristics

Subjects may be of any race, nationality, and ethnicity that meet the following inclusion and exclusion criteria. Subjects will not be fitted with contact lenses specifically for the purposes of this study. Instead, patients recently fitted or refitted with contact lenses will be invited to take part in this observational study.

3.2. Inclusion Criteria

Potential subjects must satisfy all of the following criteria to be enrolled in the study:

Inclusion Criteria after Screening:

1. Contact lens neophytes or those who have recently (i.e. within last 2 months) begun the use of a new reusable silicone hydrogel lens type and have purchased a supply of lenses.
2. A minimum age of 18 years, with no maximum age.
3. The registrant must read and sign the Informed Consent form.
4. The registrant must appear able and willing to adhere to the instructions set forth in this clinical protocol.

For clarification, non-neophyte subjects may include previous wearers of any type of soft contact lens (e.g. daily disposable), however, the new lens type must be a reusable silicone hydrogel. Also, non-neophyte subjects may have previously worn soft contact lenses at any point in time; in other words, it is not necessary for recently refitted subjects to have transitioned from their old to new lenses without a break in wear.

3.3. Exclusion Criteria

Potential subjects who meet any of the following criteria will be excluded from participating in the study:

Exclusion Criteria after Screening:

1. Current participant in another research study.
2. Employee or relative of site, or family member of Recruiting Practitioner or Johnson & Johnson.
3. Non-spherical contact lens wearers, i.e. toric or multifocal lenses.

3.4. Enrollment Strategy

Study subjects will be recruited from the clinical site's subject database and/or utilizing Independent Ethics Committee (IEC) or Institutional Review Board (IRB) approved materials.

Site recruitment based on actively prescribing a new device is a method that has been used in two prior post-market surveillance studies for FDA.[5,6] Proposed regions include but are not limited to areas within the United Kingdom (UK), Spain, Netherlands and Germany. Regions will be replaced or supplemented if there is inadequate response to invitations to participate.

The Principal Investigator and CRO will recruit sub-investigators, referred to as 'Recruiting Practitioners' throughout this document at clinical sites. Clinical sites in the selected regions that are actively prescribing the ACUVUE® OASYS with Transitions™ lenses will be invited to participate as Recruiting Practitioners. Recruiting Practitioners will be allowed a maximum of 50 registered wearers per site, so that no one site will contribute more than 25% of the sample population in a given country. The study anticipates unequal enrollment across the sites, as their rate of prescribing ACUVUE® OASYS with Transitions™ will vary considerably. Unequal enrollment should reflect the population exposures to the Test lens and follows the tenets of surveillance. A convenience, rather than random, sample is necessary for the study because ACUVUE® OASYS with Transitions™ contact lenses have not yet been widely launched and are only available to some eye care practitioners. Thus, active prescribers of ACUVUE® OASYS with Transitions™ lenses will be invited to participate within each region in order to provide a large enough sample size for the study.

Within sites, wearers of ACUVUE® OASYS with Transitions™ lenses will be invited to participate without regard to any demographic or other ocular features. Wearers will be registered after they have recently (i.e. within last 2 months) received a prescription for and a supply of ACUVUE® OASYS with Transitions™ lenses.

The study design also allows an unconstrained relative proportion of ACUVUE® OASYS with Transitions™ lenses within a site in order to reflect the exposure profile present in that site. When the study has enrolled 300 Test lens subjects, enrollment will be actively curtailed but leaving the enrollment open to the other lens type until complete (or vice versa).

4. STUDY DESIGN AND RATIONALE

4.1. Description of Study Design

This registry study is a one-year, one-visit, observational, prospective, open-label, two-arm, multi-center, multi-national, post-market study. Approximately 300 patients who have recently been fitted with the ACUVUE® OASYS with Transitions™ (Test) and approximately 300 patients who have recently been fitted with spherical non-photochromic reusable marketed silicone hydrogel contact lenses (of any brand) (Control) will be enrolled in the study, a total of 600 subjects. The goal is for a sample size of 480 subjects (~240/arm) after subjects who withdraw or are lost-to-follow-up.

At Visit 1, each subject will be first consented to participate in the study. The ECP will then complete the paper ECP Registration Questionnaire (ERQ) for the given consented subject and collect his/her demographics and baseline information. Participants who meet eligibility criteria, will be asked to complete the Patient Registration Questionnaire (PRQ). At the end of the visit, registrants will be instructed to complete the survey follow-up questionnaire online at 2-weeks (day 10-30), 4-months (day 110-150) and 12-months (day 345-395) from Visit 1

(day 0). The registrants will receive an email reminder and link to the online questionnaire (Kiosk) prior to each evaluation period. Follow-up on events reported at each evaluation period will be completed by the Recruiting Practitioner/PI.

Country specific Good Clinical Practice (GCP) standards, laws, and applicable regulations were reviewed in designing the clinical study protocol to ensure compliance in the management of the clinical trial and to protect the rights and interest of subjects.

4.2. Study Design Rationale

The study is designed as an observational, prospective, non-interventional, multi-center, multi-national post-market study to evaluate the effectiveness of ACUVUE® OASYS with Transitions™ over a period of one year in the general population of spherical contact lens wearers and under general clinical practice. By allowing wide subject eligibility criteria, wide age range and different clinical practices from different countries, the study is ideal for obtaining real world data to assesses the effectiveness of this new technology.

This a non-randomized study and the sponsor has no control of the treatment assignment. The Test and Control groups may have large differences on their baseline characteristics, and these differences can lead to biased estimates of treatment effects. Appropriate statistical methods will be used to reduce the bias (see Section 14 for more details).

4.3. Subject Numbers

The study will enroll approximately 300 (maximum: 330) subjects in each arm with the intent of completing at least 240 in each arm. Thus, the study will enroll approximately 600 subjects with a maximum of 660 (Figure 1).

Multiple sites in the UK, Netherlands, Spain, and Germany will participate with other countries a possibility. Each site will enroll approximately similar numbers of test and control subjects.

4.4. Study Duration

Study enrollment occurs with execution of the study-related forms and informed consent. Study completion occurs with completion of the 12-month survey.

Once the Test lens is launched in the study-participating country, the first subject registration will occur within six (6) months.

The enrolment period should not exceed twelve (12) months in any country without prior authorization from the Sponsor.

Subjects will present to the investigational site for Visit 1. Follow-up assessments are performed online at approximately 2-weeks, 4-months, and 12-months following Visit 1. Therefore, each subject is enrolled in the study for approximately 12 months. With the 12-month enrollment period, the study will last approximately two (2) years per country.

5. TEST ARTICLE ALLOCATION AND MASKING

5.1. Test Article Allocation

This is a non-randomized observational study. Subjects receiving a new lens brand as part of the routine practice at the investigational site will be asked to participate:

- Subjects receiving an ACUVUE® OASYS with Transitions™ contact lens on both eyes will comprise the Test group.
- Subjects receiving any other spherical silicone hydrogel lens to be worn as daily wear and frequent replacement (2-weekly or monthly) will comprise the Control group.
- The Test/Control allocation per site is approximately 1:1. Sites should not recruit a larger number of control subjects than test subjects.

5.2. Masking

This is an open label registry study. The identity of the lenses is known to all. Given this, there are no procedures for maintaining and breaking the masking.

6. STUDY INTERVENTION

6.1. Identity of Test Articles

The following contact lenses will be used in this study:

Table 1: Study Lenses

	Test	Control
Name	ACUVUE® OASYS with Transitions™	Any reusable spherical silicone hydrogel brand that is approved and marketed in the country conducting the study.
Manufacturer	Johnson & Johnson	
[redacted]	Commercial	
Lens Material	senofilcon A	
Nominal Base Curve @ 22°C (mm)	8.4, 8.8	
Nominal Diameter @ 22°C (mm)	14.0	
Nominal Distance Powers (D)	+8.00 through -12.00	
Water Content (%)	38	
Center Thickness (mm)	0.085	
Oxygen Permeability (Dk)	103	
Packaging Form (vial, blister, etc.)	Sterile blister pack	
Wear Schedule in Current Study	DW	DW
Replacement Frequency	2 weeks or as recommended by ECP	2 weeks/monthly
Photochromic Additive	Yes	No

6.2. Ancillary Supplies/Products

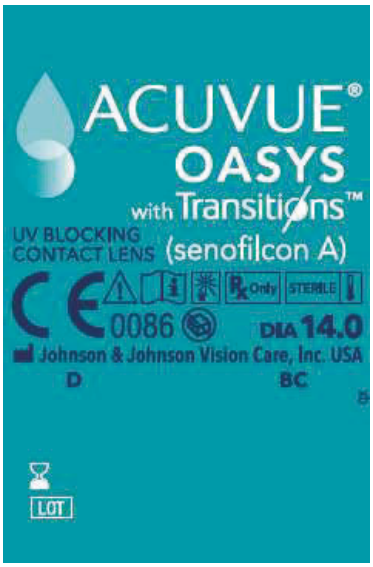
None specified. Subjects may use any approved and marketed contact lens care products or wetting drops that would normally be prescribed by the investigator in their country of practice. Care products initially recommended by the ECP will be tracked.

6.3. Administration of Test Articles

The study lenses will be those prescribed by the investigator and purchased by the subject.

6.4. Packaging and Labeling

The test products will be packaged in sterile blister packs as the primary packaging. A sample Test lens label and packaging are shown below:



6.5. Storage Conditions

Any test lenses stored at the clinical site should be maintained at ambient temperatures and out of direct sunlight.

6.6. Collection and Storage of Samples

No samples will be collected as part of the study procedures.

6.7. Accountability of Test Articles

Not applicable.

7. STUDY EVALUATIONS

7.1. Time and Event Schedule

Table 2: Time and Events

Visit Information	Visit 1 Registration	2-Week Questionnaire	4-Month Questionnaire	12-Month Questionnaire
Time Point	Day 0	Day 10-30	Day 110-150	Day 345-395
Statement of Informed Consent	X			
Inclusion / Exclusion Criteria	X			
Contact Information	X			
ECP Registration Questionnaire	X			
Patient Registration Questionnaire	X			
Reminder		X	X	X
2-Week Questionnaire		X		
4-Month Questionnaire			X	
12-Month Questionnaire				X
ECP Adverse Event Form (paper CRF)		As Needed	As Needed	As Needed

7.2. Detailed Study Procedures

Prior to Visit 1, the registrant is fitted with the Test or Control lens, and purchases a supply of lenses.

VISIT 1

Visit 1: Registration		
Step	Procedure	Details
1.1	Study Explained	Recruiting Practitioner or Staff explains participation in Registry
1.2	Statement of Informed Consent	Registrant completes Informed Consent (IC) **Note**: The subject must be provided with a signed copy of this document.
1.3	Demographics	Record the subject's year of birth, age and gender
1.4	ECP Registration Questionnaire (ERQ)	The Eye Care Practitioner (ECP) completes a paper ECP Registration Questionnaire (ERQ) for each Registrant recording the following information (steps below) as source documentation.
1.5	Iris Color	The investigator will record the subject's iris color based on the 15-color scale provided (Appendix C).
1.6	Contact Lens History	Experienced CL wearer (Yes/No) If Yes, number of years total, last CL brand, replacement frequency, and when last used.
1.7	Contact Lens Details (New lenses)	Brand (full name), base curve, powers, recommended replacement period, recommended care system, and planned usage (Full/Part-Time). If part-time, number of days/week.
1.8	Reason for Lens Selection	Up to three reasons for selection of lens type to be indicated by the ECP investigator.
1.9	Eligibility after Screening	All responses to Screening Inclusion Criteria questions must be answered "Yes" and all responses to Exclusion Criteria must be answered "No" for the subject to be considered eligible.
1.10	Patient Registration Questionnaire (PRQ)	Registrants complete the Patient Registration Questionnaire. When possible, the PRQ should be completed on the same day as the ERQ. Please refer to [redacted] attached to this protocol (Appendix D)
1.11	Contact Details	Subject provides contact details to CRO by texting study ID number and email address to the dedicated Kiosk Set-Up texting line that will be provided to them by the site.

Visit 1: Registration		
Step	Procedure	Details
1.12	Kiosk Set-up	On receiving, the subjects contact details, subjects Kiosk will be set up and reminders will send to subjects.

2-Week Questionnaire		
Step	Procedure	Details
2.1.	Reminder	Registrant receives an email reminder and link to online follow-up questionnaire (Kiosk). In cases where a subject fails to respond to the email prompts, at least two additional emails will be sent, approximately 1 week apart. As a final resort a text message may be sent with a similar prompt.
2.2.	2-Week Questionnaire	2-Week Questionnaire is completed online by Registrant.
2.3.	Remuneration	Payment for Registration and 2-Week Questionnaire is arranged (electronic voucher).
2.4.	Adverse Events	Follow-up on Events reported at 2-Week Questionnaire are completed by the Recruiting Practitioner/PI.

4-Month Questionnaire		
Step	Procedure	Details
3.1.	Reminder	Registrant receives an email reminder and link to online follow-up questionnaire (Kiosk). In cases where a subject fails to respond to the email prompts, at least two additional emails will be sent. As a final resort a text message may be sent with a similar prompt.
3.2.	4-Month Questionnaire	4-Month Questionnaire is completed online similar to 2-week Questionnaire for Registrant.
3.3.	Remuneration	Payment for 4-Month Questionnaire is arranged (electronic voucher).
3.4.	Adverse Events	Follow-up on Events reported at 4-Month Questionnaire are completed by the Recruiting Practitioner/PI.

12-Month Questionnaire		
Step	Procedure	Details
4.1.	Reminder	Registrant receives an email reminder and link to online follow-up questionnaire (Kiosk) In cases where a subject fails to respond to the email prompts, at least two additional emails will be sent. As a final resort a text message may be sent with a similar prompt.
4.2.	12-Month Questionnaire	12-Month Questionnaire is completed online similar to the previous follow-up questionnaires for Registrant.
4.3.	Remuneration	Payment for completing the 12-Month Questionnaire is arranged (electronic voucher).
4.4.	Adverse Events	Follow-up on Events reported at 12-Month Questionnaire are completed by the Recruiting Practitioner/PI.
4.5.	Final Form	Indicate if the subject completed the study successfully. If subject discontinued from the study, indicate the reason.

7.3. Unscheduled Visits

Since there are no scheduled follow-up visits, unscheduled visits are not applicable. Registrant will attend aftercare visits in the normal course of routine care.

7.4. Laboratory Procedures

Not applicable

8. SUBJECTS COMPLETION/WITHDRAWAL

8.1. Completion Criteria

Subjects are considered to have completed the study if they:

- Provided informed consent
- Are eligible
- Completed at least two follow-up questionnaires including the 12-month Questionnaire.

8.2. Withdrawal/Discontinuation from the Study

A subject will be withdrawn from the study for any of the following reasons:

- Subject withdrawal of consent

- Subject not compliant to protocol
- Subject lost to follow-up, i.e. misses two consecutive follow-up questionnaires.
- Subject death during the study period
- Subject develops significant or serious adverse events causing discontinuation of study lens wear
- Investigator's clinical judgment regarding for subject safety reasons (that it is in the subject's best interest to stop contact lens use)

9. PRE-STUDY AND CONCOMITANT INTERVENTION/MEDICATION

Concomitant medications will not be documented during the study.

10. DEVIATIONS FROM THE PROTOCOL

Investigator will notify study sponsor upon identification of a protocol deviation. Major protocol deviations must be reported to the sponsor within 24 hours after discovery of the protocol deviation. The Investigator will report deviations per IRB/IEC requirements. All deviations will be tracked and corrective actions implemented as appropriate.

11. STUDY TERMINATION

Since all of the products associated with the study are marketed products, there are no anticipated circumstances in which the study would be prematurely terminated.

The Sponsor will determine if and when the study will be stopped. JJVC reserves the right to terminate the study at any time for any reason. Additionally, the IEC/IRB may reserve the right to terminate the study if an unreasonable risk is determined.

JJVC (and the IEC/IRB and DMC, if applicable) will evaluate all adverse events.

12. PROCEDURE FOR HANDLING PRODUCT QUALITY COMPLAINTS

Given the nature of the study, and since the subjects will be using normally marketed product, the monitoring of Product Quality Complaints (PQCs) is out of the scope of this study.

If the subject reports 'poor' overall comfort during a follow-up questionnaire, the subject will automatically be advised as part of the online questionnaire to consult their ECP.

13. ADVERSE EVENTS

This study is only concerned with ocular adverse events or adverse events related to the study lenses (test & control).

Investigators will not automatically report any adverse event. Instead, these will be captured by a question in the follow-up questionnaire regarding 'a problem with their eyes while wearing lenses that required them to visit an eyecare practitioner or hospital'. If subjects answer 'Yes' to this question the ECP investigator will be asked to complete a paper adverse

event form, detailing the problem. In the event of the subject having been seen by another clinic (e.g. emergency room) copies of the medical records will be requested.

The records of any adverse event will be reviewed by a Data Monitoring Committee (DMC) who will adjudicate the diagnosis, severity and causality of any adverse events.

13.1. Definitions and Classifications

Adverse Event (AE) – An AE is "any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.
NOTES:
Note 1 to entry: This definition includes events related to the investigational medical device or the comparator.
Note 2 to entry: This definition includes events related to the procedures involved.
Note 3 to entry: For users or other persons, this definition is restricted to events related to investigational medical devices."[1]

In this study, monitored AEs will be confined to ocular AEs or non-ocular AEs related to the study lenses (e.g. injury sustained through poor vision).

Serious Adverse Event (SAE) – An SAE is any untoward medical occurrence that:

- Is potentially sight-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity (e.g., a sight threatening event, a significant persistent or permanent change, impairment, damage, or disruption to the subject's body)
- Requires intervention to prevent permanent damage (the use of the test article resulting in a condition which requires medical or surgical intervention to preclude permanent impairment of the body structure or a body function). Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition

Diagnoses and conditions that are considered Ocular Serious Adverse Events include, but not limited to:

- Microbial Keratitis (MK)
- Iritis (including cells in the anterior chamber)
- Permanent decrease in best spectacle corrected visual acuity equivalent to 2 acuity lines or greater
- Central Corneal Opacity
- Central Corneal Neovascularization
- Uveitis
- Endophthalmitis
- Hypopyon

- Hyphema
- Penetration of Bowman's Membrane
- Persistent Epithelial Defect
- Limbal cell Damage

Significant Adverse Events – Those events that are usually symptomatic and warrant discontinuation (temporary or permanent) of the test article (excluding Serious Adverse Events).
Diagnoses and conditions that are considered Ocular Significant Adverse Events include, but not limited to the following:

- Contact Lens Induced Peripheral Ulcer (CLPU)
- Significant Infiltrative Events (SIE)
- Superior Epithelial Arcuate Lesions (SEALs)
- Any Temporary Loss of >2 Lines of BSCVA
- Other grade 3 or higher corneal findings, such as abrasions or edema
- Non-contact lens related corneal events - e.g. Epidemic Keratoconjunctivitis (EKC)
- Asymptomatic Corneal Scar
- Any corneal event which necessitates temporary lens discontinuation > 2 weeks

Non-Significant Adverse Events – Those conditions that are usually asymptomatic and usually do not warrant discontinuation (temporary or permanent) of the test article. However, the Investigator may choose to treat as a precautionary measure.
Diagnoses and conditions that are considered Ocular Non-Significant Adverse Events include, but not limited to the following:

- Non-significant Infiltrative Event (NSIE)
- Contact Lens Papillary Conjunctivitis (CLPC)
- Superficial Punctate Keratitis (SPK)
- Conjunctivitis: Bacterial, Viral, Allergic
- Blepharitis
- Meibomianitis
- Contact Dermatitis
- Localized Allergic Reactions
- Any corneal event not explicitly defined as serious or significant adverse event, which necessitates temporary lens discontinuation < 2 weeks

Adverse Device Effect (ADE) – An ADE is an "adverse event related to the use of an investigational medical device.
NOTES:
Note 1 to entry: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.
Note 2 to entry: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device."[1]

Unanticipated Serious Adverse Device Effect (USADE) – Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, the test

article, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan, Investigator's Brochure or protocol, or any other unanticipated serious problem associated with the test article that relates to the rights, safety and welfare of subjects.

13.2. Assessing Adverse Events

In conjunction with the medical monitor, the Investigator will evaluate adverse events to ensure the events are categorized correctly. Elements of categorization will include:

- Seriousness/Classifications (see definition in Section 13.1)
- Causality or Relatedness – i.e. the relationship between the test article, study treatment or study procedures and the adverse event (not related; unlikely related; possibly related; related - see definition in Section 13.2.1)
- Adverse Event Severity – Adverse event severity is used to assess the degree of intensity of the adverse event (mild; moderate; severe for all events - see definition in Section 13.2.2)
- Outcome – not recovered or not resolved; recovering or resolving; recovered or resolved with sequelae; recovered or resolved; death related to adverse event; unknown
- Actions Taken – none; temporarily discontinued; permanently discontinued; other.

13.2.1. Causality Assessment

Causality Assessment – A determination of the relationship between an adverse event and the test article. The test article relationship for each adverse event should be determined by the investigator using these explanations:

- Not Related- An adverse event that is not related to the use of the test article, study treatment or study procedures
- Unlikely Related – An adverse event for which an alternative explanation is more likely, e.g. concomitant treatment, concomitant disease(s), or the relationship of time suggests that a causal relationship is not likely
- Possibly Related – An adverse event that might be due to the use of the test article, or to the study treatment or study procedures. An alternative explanation, e.g. concomitant treatment, concomitant disease(s), is inconclusive. The relationship in time is reasonable. Therefore, the causal relationship cannot be excluded
- Related – An adverse event that is listed as a possible adverse effect (device) or adverse reaction (drug) and cannot be reasonably explained by an alternative explanation, e.g. concomitant treatment of concomitant disease(s). The relationship in time is very suggestive, e.g. it is confirmed by de-challenge and re-challenge.

13.2.2. Severity Assessment

Severity Assessment – A qualitative assessment of the degree of intensity of an adverse event as determined by the Investigator or reported to him/her by the subject. The assessment of severity is made irrespective of test article, study treatment or study procedure relationship or seriousness of the event and should be evaluated according to the following scale:

- Mild – Event is noticeable to the subject, but is easily tolerated and does not interfere with the subject's daily activities

- Moderate – Event is bothersome, possible requiring additional therapy, and may interfere with the subject's daily activities
- Severe – Event is intolerable, necessitates additional therapy or alteration of therapy and interferes with the subject's daily activities.

13.3. Documentation and Follow-Up of Adverse Events

If a subject reports through the follow-up questionnaire 'a problem with their eyes while wearing lenses that required them to visit an eyecare practitioner or hospital', this will be followed-up with the treating facility. If this is the ECP investigator, they will be asked to complete a paper adverse event form and to supply copies of any other relevant records. In the event of the subject having been seen by another clinic (e.g. emergency room) copies of the medical records will be requested.

Investigators are recommended to include the following in the patients records:

- Adverse event (diagnosis not symptom)
- Drawings or photographs (where appropriate) that detail the finding (e.g., size, location, and depth, etc.)
- Date the clinical site was notified
- Date and time of onset
- Date and time of resolution
- Adverse event classification, severity, and relationship to test articles, as applicable
- Treatment regimen instituted, including concomitant medications prescribed, in accordance with applicable licensing requirements
- Any referral to another health care provider if needed
- Outcome, ocular damage (if any)
- Likely etiology
- Best corrected visual acuity at the discovery of the event and upon conclusion of the event.

13.4. Reporting Adverse Events

In addition, a written report will be submitted by the Principal Investigator to the IEC/IRB according to their requirements. The report will comment whether the adverse event was considered to be related to the test article, study treatment or study procedures.

13.5. Event of Special Interest

None

13.6. Reporting of Pregnancy

Not applicable for this study.

14. STATISTICAL METHODS

14.1. General Considerations

Statistical Analysis will be undertaken by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be implemented in this clinical trial is outlined below. More details will be included in the stand-alone Statistical Analysis Plan (SAP). The SAP will be finalized prior to database lock.

All data summaries and statistical analyses will be performed using the SAS software 9.4 or higher (SAS Institute, Cary, NC).[7] Throughout the analysis of data, the results for each subject/eye will be used when available for summarization and statistical analysis.

Summary tables (descriptive statistics and/or frequency tables) will be provided by arm for all baseline variables, ECP registration questionnaire (ERQ), Patient registration questionnaire (PRQ), and 2-week, 4-month and 12-month survey questionnaires. Continuous variables will be summarized with descriptive statistics (n, mean, standard deviation (SD), median, minimum and maximum). Frequency count and percentage of subjects or eyes within each category will be provided for categorical data.

14.2. Sample Size Justification

This study was designed and powered to show superiority of JJVC senofilcon A contact lenses with photochromic additive (Test) compared to non-photochromic reusable silicone hydrogel contact lenses (Control) with respect to vision satisfaction in bright lighting over a period of one year.
The sample size calculation was based on historical data from six Johnson & Johnson Vision Care sponsored randomized clinical trials [redacted] In all of the studies, the Test lens and ACUVUE OASYS were worn as a daily wear for approximately 2 weeks each. Table 3 summarizes the percentage of patients with vision satisfaction in bright lighting (agree/strongly agree) pooled from all studies. When the trial is a crossover design, only data from the first period were considered.

Table 3: Summary of vision satisfaction in bright lighting at 2-week follow-up

Study Lens	Number of Patients	Vision satisfaction in bright lighting (%)
ACUVUE OASYS®	397	77.1%
ACUVUE® OASYS with Transitions™	395	86.6%

The sample size was estimated from the formula given by Diggle et al.[14] for clustered binary data:

$$N = \frac{[Z_\alpha\sqrt{2\bar{p}\bar{q}} + Z_\beta\sqrt{p_C\,q_C + p_T\,q_T}\,]^2\,(1+(n-1)\rho}{n(p_T - p_C)^2}$$

Where p_C: Response proportion in the Control group, $q_C = 1 - p_C$, p_T: Response proportion in the Test group, $q_T = 1 - p_T$, $\bar{p} = (p_C + p_T)/2$, $\bar{q} = 1 - \bar{p}$, n: number of observations per subject (i.e. n = 3) and ρ is the common correlation across n observations. The terms Z_α and Z_β are the Z scores that correspond to the pre-specified type I error α and power $1-\beta$ repectively.

Based on the historical data reported in Table 3, we calculated the sample size for different possible scenarios of correlation ρ, p_C and p_T. Here we assume the response proportions will be the same over time. The results are summarized in Table 4 below

Table 4: Required sample size per arm for different scenarios of $\boldsymbol{\rho}$, $\boldsymbol{p_C}$ and $\boldsymbol{p_T}$

$\boldsymbol{p_C}$	$\boldsymbol{p_T}$	**Difference** $(\boldsymbol{p_T - p_C})$	$\boldsymbol{\rho}$		
			0.3	**0.5**	**0.7**
0.50	**0.62**	**0.12**	143	178	213
0.65	**0.77**	**0.12**	119	149	178
0.70	**0.80**	**0.10**	156	195	234
0.75	**0.85**	**0.10**	133	167	200
0.77	**0.86**	**0.09**	145	194	242

As shown in Table 4, a sample size of 240 subjects per arm is considered sufficiently large to test for superiority under different scenarios of p_C and p_T and with a minimum power of 80% and a two-sided type I error of 0.05.

The plan is to enroll 300 subjects per arm with a target completion of 240 subjects per arm. During the enrollment period, the subject's dropouts will be monitored. If the dropout rate is over 20% in certain arms, the targeted total enrollment number will be increased accordingly to ensure a minimum of 240 subjects per group to complete the study.

14.3. Analysis Populations

Per-Protocol Population:
All eligible subjects who have completed at least two follow-up questionnaires including the 12-month questionnaire and did not substantially deviate from the protocol as determined by the trial cohort review committee prior to database hard lock (Per-Protocol Population). Justification of excluding subjects with protocol deviations in the per-protocol population set will be documented in a memo to file.

Full Analysis Population:
All enrolled subjects (signed consent form) regardless of subsequent withdrawal from study or deviation from protocol. At least one observation should be recorded.

Both primary and secondary analysis will be conducted on full analysis set. A sensitivity analysis will be conducted on the per-protocol population. To evaluate the impact of missing data, sensitivity analysis will be conducted using multiple imputation.

14.4. Level of Statistical Significance

All planned analysis for this study will be conducted with an overall type I error rate of 5%. The secondary analysis will be adjusted for multiple comparisons between the Test and the Control groups across the evaluation periods using a simulated-based approach (Edward and Berry).[15]

14.5. Primary Analysis

Vision Satisfaction in Bright Lighting
Subjects' responses will first be categorized into a binary outcome of 1 if the response is positive (Agree or Strongly Agree) or 0 otherwise (Neither Agree Nor Disagree, Disagree or Strongly Disagree). The outcome will then be analyzed using a generalized linear mixed model for correlated binary data. The model will include treatment group (Test, Control), evaluation period (2-week, 4-month and 12-month) and group by evaluation period as fixed factors, and site as random effect (G-side). The model will be adjusted for baseline values, country, age, gender and race as fixed covariates when appropriate. The correlation between responses from the same subjects across evaluation periods will be modeled using an unstructured (UN) covariance matrix (R-side). If problem of convergence encountered, a Compound Symmetry (CS) covariance structure will be considered.

The null and alternative hypotheses for the primary hypothesis are as follows:

$$H_0: OR \leq 1$$
$$H_A\ OR > 1;$$

where OR is the overall odds ratio of having a positive rating of vision satisfaction in bright lighting (Test over Control). The superiority test will be based on the OR and corresponding 95% confidence interval calculated using the final selected model. The lower bound of the 95% confidence interval will be compared to 1. If the lower bound is above 1, the Test lens will be considered superior to the Control lenses with respect to vision satisfaction in bright lighting. The odds ratio at 2-week, 4-month and 12-month evaluation periods will be calculated with their corresponding adjusted 95% confidence intervals to test the secondary hypothesis #1.

This is an observational study and the treatment assignment is not randomized. The Test and Control groups may have large differences on their baseline characteristics, and these differences can lead to biased estimates of treatment effects. Instead of adjusting the model to all covariates including interactions with treatment group and higher order terms, the propensity score will be used. The propensity score, defined as the conditional probability of

being in Test or Control group given the covariates, will be used to balance the covariates in the two groups, and therefore reduce this bias. The propensity will be calculated using a logistic regression model.

A generalized linear mixed model for correlated ordinal data may be considered if the proportion of subjects with positive response is low. Cumulative odds ratio will be used for hypothesis tests.

14.6. Secondary Analysis

Overall Quality of Vision and Overall Comfort

Overall quality of vision and overall comfort ratings will be analyzed separately using the same statistical method described in the primary analysis. The hypothesis tests will be conducted using adjusted 95% confidence intervals of odds ratios.

Pulfrich Effect

The proportion of subjects who experienced the Pulfrich effect will be calculated as the proportion of subjects who disagree or strongly disagree with the statement "While wearing these lenses, my depth perception of moving objects has NOT been impacted". The Pulfrich effect will be evaluated over time at 2-week, 4-month and 12-month evaluation periods. The proportion of subjects who experienced the Pulfrich effect at least once will also be calculated.

Serious and Significant Ocular AEs

No statistical hypothesis will be tested. The following will be calculated:

1. Incidence rate of serious and significant ocular AEs (in patient-year) will be calculated as follow:

$$IR = \frac{Number\ of\ subjects\ with\ an\ event}{(Sum\ of\ subjects'\ exposure\ times)/365.25}$$

   Where each subject's exposure time is defined as number of days in the study after the enrollment, censored only by events such as first serious or significant ocular AE, dropouts, death or the end of the study.

2. Proportion of subjects with at least one reported serious or significant ocular AE at each evaluation period.
3. Proportion of eyes with a least one reported serious or significant ocular AE at each evaluation period.
4. Proportion of all reported serious and significant ocular AEs at each evaluation period.

14.7. Other Exploratory Analyses

Subgroup analysis of the primary and secondary endpoints will be conducted by country, age group and lens material. Other subgroup analysis may be considered by factors showing interaction effects with the treatment. The control group will be categorized by lens materials and/or wear modality for further comparisons with the Test lens.

Further analysis using a generalized linear mixed model using Poison or negative binomial distribution will be considered to test for statistical difference in incidence rates between Test and Control groups. Non-ocular lens related AEs will be evaluated.

14.8. Interim Analysis

There will be three interim analyses once 50% of enrolled subjects have completed the 2-week, 4-month and 12-month questionnaires. The interim data will be summarized using descriptive statistics. Reasons for dropouts and ocular adverse events will be monitored. An interim statistical analysis plan (ISAP) may be considered, if necessary, for further analysis prior to the database lock.

14.9. Procedure for Handling Missing Data and Drop-Outs

Missing or spurious values will not be imputed. The count of missing values will be included in the summary tables and listings.
Subject dropout is expected to be one of the main reasons of missing data in this registry study. Past clinical trials do not provide the evidence that subject dropout is systematic or not-at-random. To evaluate the impact of missing data, sensitivity analysis will be conducted using multiple imputation. The SAS/STAT procedures PROC MI and PROC MIANALYZE will be utilized with a parametric regression method used to make at least 50 imputations.

14.10. Procedure for Reporting Deviations from Statistical Plan

The analysis will be conducted according to that specified in above sections. There are no known reasons for which it is planned to deviate from these analysis methods. If for any reason a change is made, the change will be documented in the study report along with a justification for the change.

15. DATA HANDLING AND RECORD KEEPING/ARCHIVING

15.1. Case Report Form/Data Collection

The data collected by the investigators for this study will be captured on paper case report forms (CRFs). These will be returned to the CRO and then entered into an electronic data collection (EDC) system.

Once completed, the eCRFs will be reviewed for accuracy and completeness. The sponsor or sponsor's representatives will be authorized to gain access to the subject recordation for the purposes of monitoring and auditing the study.

The questionnaire data will be entered by the subjects into an EDC system. Edit checks, electronic queries, and audit trails are built into the system to ensure accurate and complete data collection. Electronic data will be transmitted to a secure central database as forms are completed or updated, ensuring information accuracy, security, and confidentiality.

The content and structure of the eCRFs are compliant with ISO14155:2011.[1]

15.2. Subject Record

At a minimum, the subject record should be available for the following:

- subject identification
- eligibility
- study identification
- provision of and date of informed consent
- a record of all adverse events
- follow-up of adverse events

The subject record is the eCRF or an external record. The author of an entry in the subject record must be identifiable. The first point of entry is considered to be the source record.

16. DATA MANAGEMENT

16.1. Access to Source Data/Document

The Investigator/Institution will permit trial-related monitoring, audits, IEC/IRB review and regulatory inspection(s) by providing direct access to source data/documents. Should the clinical site be contacted for an audit by an IEC/IRB or regulatory authority, JJVC must be contacted and notified in writing within 24 hours.

16.2. Confidentiality of Information

Information concerning the investigational product and patent application processes, scientific data or other pertinent information is confidential and remains the property of JJVC. The Investigator may use this information for the purposes of the study only. It is understood by the Investigator that JJVC will use information developed in this clinical study in connection with the development of the investigational product and therefore may disclose it as required to other clinical investigators and to regulatory agencies. In order to allow the use of the information derived from this clinical study, the Investigator understands that he/she has an obligation to provide complete test results and all data developed during this study to the Sponsor.

16.3. Data Quality Assurance

Steps will be taken to ensure the accuracy and reliability of data, include the selection of qualified investigators and appropriate clinical sites and review of protocol procedures with the Principal Investigator. The Principal Investigator, in turn, must ensure that all Sub-Investigators and clinical site personnel are familiar with the protocol and all study-specific procedures and have appropriate knowledge of the study article.

Training on case report form completion will be provided to clinical site personnel before the start of the study. The Sponsor will review case report forms for accuracy and completeness remotely during the conduct of the study, during monitoring visits, and after transmission to data management. Any data discrepancies will be resolved with the Investigator or designee, as appropriate.

Quality Assurance representatives from JJVC may visit clinical sites to review data produced during the study and to access compliance with applicable regulations pertaining to the conduct of clinical trials. The clinical sites will provide direct access to study-related source data/documents and reports for the purpose of monitoring and auditing by JJVC and for inspection by local and regulatory authorities.

17. MONITORING

The study monitors will maintain close contact with the Principal Investigator and the Investigator's designated clinical site personnel. The monitor's responsibilities will include:

- Ensuring that the investigation is being conducted according to the protocol, any subsequent amendments, and regulatory requirements are maintained
- Ensuring the rights and wellbeing of subjects are protected
- Ensuring that protocol deviations are documented with corrective action plans, as applicable
- Clarifying questions regarding the study
- Resolving study issues or problems that may arise
- Reviewing of informed consent forms and source documentation verification in accordance with the monitoring plan.

18. ETHICAL AND REGULATORY ASPECTS

18.1. Study-Specific Design Considerations

Potential subjects will be fully informed of the requirements of the study. Subjects will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who have provided their consent voluntarily will be enrolled.

18.2. Investigator Responsibility

The Principal Investigator is responsible for ensuring that the clinical study is performed in accordance with the signed agreement, the investigational plan, Section 4 of the ICH E6 guidelines on Good Clinical Practice (GCP),[2] and applicable regulatory requirements. GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles of the Declaration of Helsinki 2013[3] and that the clinical study data are credible. The Investigator must maintain clinical study files in accordance with Section 8 of the ICH E6 guidelines on Good Clinical Practice (GCP),[2] and applicable regulatory requirements.

18.3. Independent Ethics Committee or Institutional Review Board (IEC/IRB)

Before the start of the study, the Investigator (or Sponsor when applicable) will provide the IEC/IRB with current and complete copies of the following documents (where applicable):

- Final protocol and, if applicable, amendments

- Sponsor-approved informed consent form (and any other written materials to be provided to the subjects)
- Sponsor-approved subject recruitment materials
- Information on compensation to subjects for participation in the study
- Investigator's curriculum vitae, clinical licenses, or equivalent information (unless not required, as documented by IEC/IRB)
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after IEC/IRB has given full approval of the final protocol, amendments (if any), the informed consent form, applicable recruiting materials, and subject compensation programs, and the Sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the documents being approved.

During the study, the Investigator (or Sponsor when applicable) will send the following documents to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments
- Revision(s) to informed consent form and any other written materials to be provided to subjects
- If applicable, new or revised subject recruitment materials approved by the Sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study
- Summaries of the status of the study (at intervals stipulated in guidelines of the IEC/IRB)
- Reports of adverse events that are serious, unanticipated, and associated with the test articles, according to the IRB's requirements
- Major protocol deviations as required by the IEC/IRB
- Any other requirements of the IEC/IRB

At least once a year, the IEC/IRB will review and reapprove this clinical study. This request should be documented in writing.

At the end of the study, the Investigator (or Sponsor where required) will notify the IEC/IRB about the study completion. Documentation of this notification must be retained at the clinical site and a copy provided to the CRO or Sponsor as applicable.

18.4. Informed Consent

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The consent form must be signed before performance of any study-related activity. The consent form that is used must be approved by both the Sponsor and by the reviewing IEC/IRB. The informed consent is in accordance with principles that originated in the Declaration of Helsinki,[3] current ICH[2] and ISO 14155[1] guidelines, applicable regulatory requirements, and Sponsor Policy.

Before entry into the study, the Investigator or an authorized member of the clinical site personnel must explain to potential subject the aims, methods, reasonably anticipated benefits,

and potential hazards of the study, and any discomfort it may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time.

The subject will be given sufficient time to read the informed consent form and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the subject's dated signature. After having obtained the consent, a copy of the informed consent form must be given to the subject.

The subjects will be informed that choosing not to participate will not affect the care they will receive. Finally, they will be told that the Investigator will maintain a subject identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized Sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the Informed Consent Form the subject is authorizing such access and agrees to be contacted after study completion by health authorities and authorized Sponsor personnel for the purpose of obtaining consent for additional safety evaluations if needed.

18.5. Privacy of Personal Data

The collection, processing and disclosure of personal data and medical information related to the Study Subject, and personal data related to Principal Investigator and any clinical site personnel (e.g., name, clinic address and phone number, curriculum vitae) is subject to compliance with the Data Protection Act in the United Kingdom[16] and other applicable personal data protection and security laws and regulations. Appropriate measures will be employed to safeguard these data, to maintain the confidentiality of the person's related health and medical information, to properly inform the concerned persons about the collection and processing of their personal data, to grant them reasonable access to their personal data and to prevent access by unauthorized persons.

All information obtained during the course of the investigation will be regarded as confidential. All personal data gathered in this trial will be treated in strictest confidence by Investigators, monitors, Sponsor's personnel and IEC/IRB. No data will be disclosed to any third party without the express permission of the subject concerned, with the exception of Sponsor personnel (monitor, auditor), IEC/IRB and regulatory organizations in the context of their investigation related activities that, as part of the investigation will have access to the CRFs and subject records.

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to investigate the efficacy, safety, quality, and utility of the investigational product(s) used in this study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations.

The Sponsor ensures that the personal data will be:

- processed fairly and lawfully

- collected for specified, explicit, and legitimate purposes and not further processed in a way incompatible with these purposes
- adequate, relevant, and not excessive in relation to said purposes
- accurate and, where necessary, kept current

Explicit consent for the processing of personal data will be obtained from the participating subject before collection of data. Such consent should also address the transfer of the data to other entities and to other countries.

The subject has the right to request through the Investigator access to his personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps should be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of study subjects confidential.

19. STUDY RECORD RETENTION

In compliance with the ICH/GCP guidelines,[2] the Investigator/Institution will maintain all CRFs and all subject records that support the data collected from each subject, as well as all study documents as specified in ICH/GCP[2] and all study documents as specified by the applicable regulatory requirement(s). The Investigator/Institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained for at least two (2) years after study completion. These documents will be retained for a longer period if required by the applicable regulatory requirements or instructed by the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/Institution as to when these documents no longer need to be retained.

If the responsible Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the Investigator relocate or dispose of any study documents before having obtained written approval from the Sponsor.

If it becomes necessary for the Sponsor or the appropriate regulatory authority to review any documentation relating to this study, the Investigator must permit access to such reports.

If the Investigator has a question regarding retention of study records, he/she should contact JJVC.

20. FINANCIAL CONSIDERATIONS

Remuneration for study services and expenses will be set forth in detail in the Clinical Research Agreement. The Research Agreement will be signed by the Principal Investigator and a JJVC management representative prior to study initiation.
JJVC reserves the right to withhold remuneration for costs associated with protocol violations, such as, registering an ineligible subject.

JJVC reserves the right to withhold final remuneration until all study related activities have been completed, such as: i) query resolution, ii) completion of any follow-up action items.

21. PUBLICATION

This study will be registered on ClinicalTrials.gov by the Sponsor.

22. REFERENCES

1. ISO14155:2011: Clinical investigation of Medical Devices for Human Subjects-Good Clinical Practice. Available at: https://www.iso.org/standard/45557.html
2. International Conference on Harmonization Good Clinical Practice E6 (ICH-GCP) Available at: http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html
3. Declaration of Helsinki - Ethical principles for Medical Research Involving Human Subjects. Available at: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/
4. United States (US) Code of Federal Regulations (CFR) Available at : https://www.gpo.gov/fdsys/browse/collectionCfr.action?collectionCode=CFR
5. Gleason. W, Albright RC. Menicon Z 30-day continuous wear lenses: a clinical comparison to ACUVUE 7-day extended wear lenses. . *Eye & contact lens.* 2003;S1:S149-152.
6. Schein OD, McNally JJ, Katz J, et al. The Incidence of Microbial Keratitis Among Wearers of 30-day Silicone Hydrogel Extended-Wear Contact Lenses. *Ophthalmology.* 2005;112(12):2172-2179.
7. SAS Institute Inc: SAS® 9.4 Statements: Reference, Third Edition. Cary, NC: SAS Institute Inc; 2014.
8. Buch J. *Clinical Study Report* [redacted] *Long-term Evaluation of Investigational lenses containing new UV- Blocker* 2017.
9. Buch J. *Clinical Study Report* [redacted] *Confirmation of ECL100 pilot line clinical performance.* 2018.
10. Buch J. *Clinical Study Report* [redacted] *Long-term Evaluation of Investigational Lenses containing new UV-Blocker* 2017.
11. Buch J. *Clinical Study Protocol* [redacted] *Evaluation of Approved and Investigational Contact Lenses* 2018.
12. Buch J. *Clinical Study Report* [redacted] *Initial Evaluation of Investigational Lenses Manufactured on a New Production Line.*2018.

13. Buch J. *Clinical Study Report* [redacted] *Design Validation of senofilcon A with New UV Blocking Additive.*2018.
14. Diggle PJ, Heagerty P, Liang K-Y, Zeger SL. *Analysis of Longitudinal Data, Second Edition.* Oxford2002.
15. Edwards D, Berry JJ. The efficiency of simulation-based multiple comparisons. *Biometrics.* 1987;43(4):913-928.
16. Data Protection Act. Available at: http://www.legislation.gov.uk/ukpga/1998/29/contents

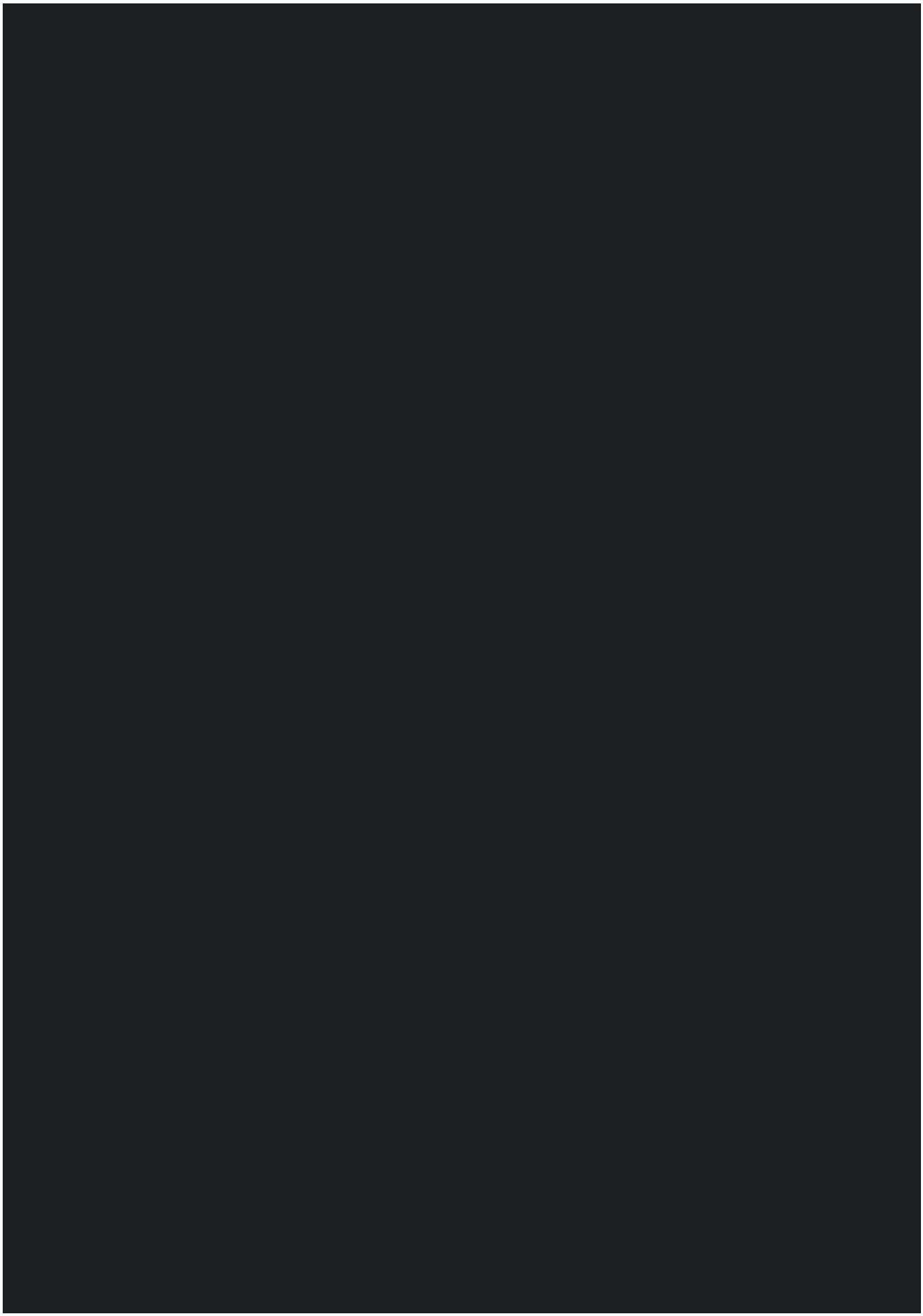
APPENDIX A: PATIENT REPORTED OUTCOMES FORM SPECIFICATIONS

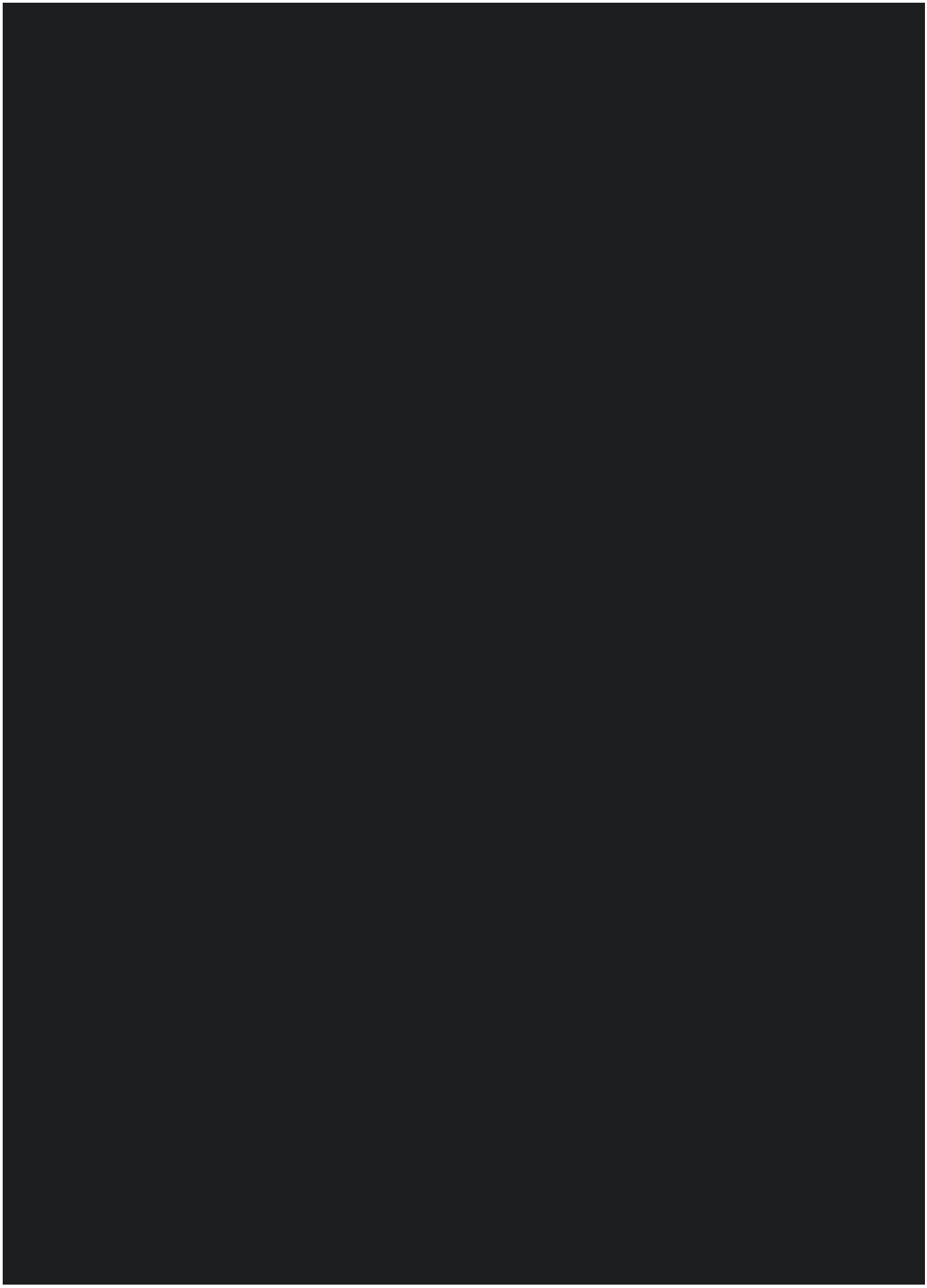
[redacted]

[redacted]

[redacted]

[redacted]





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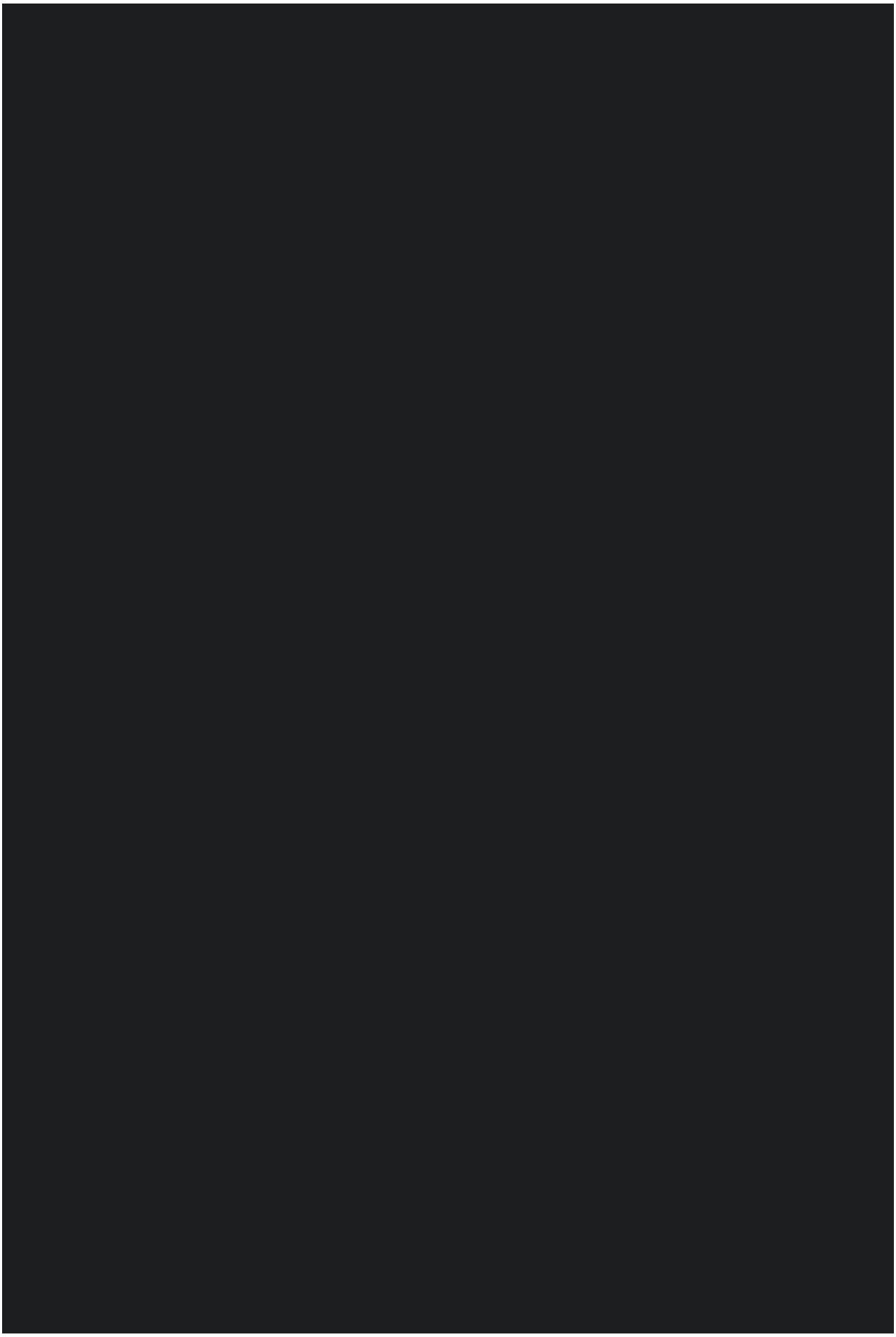

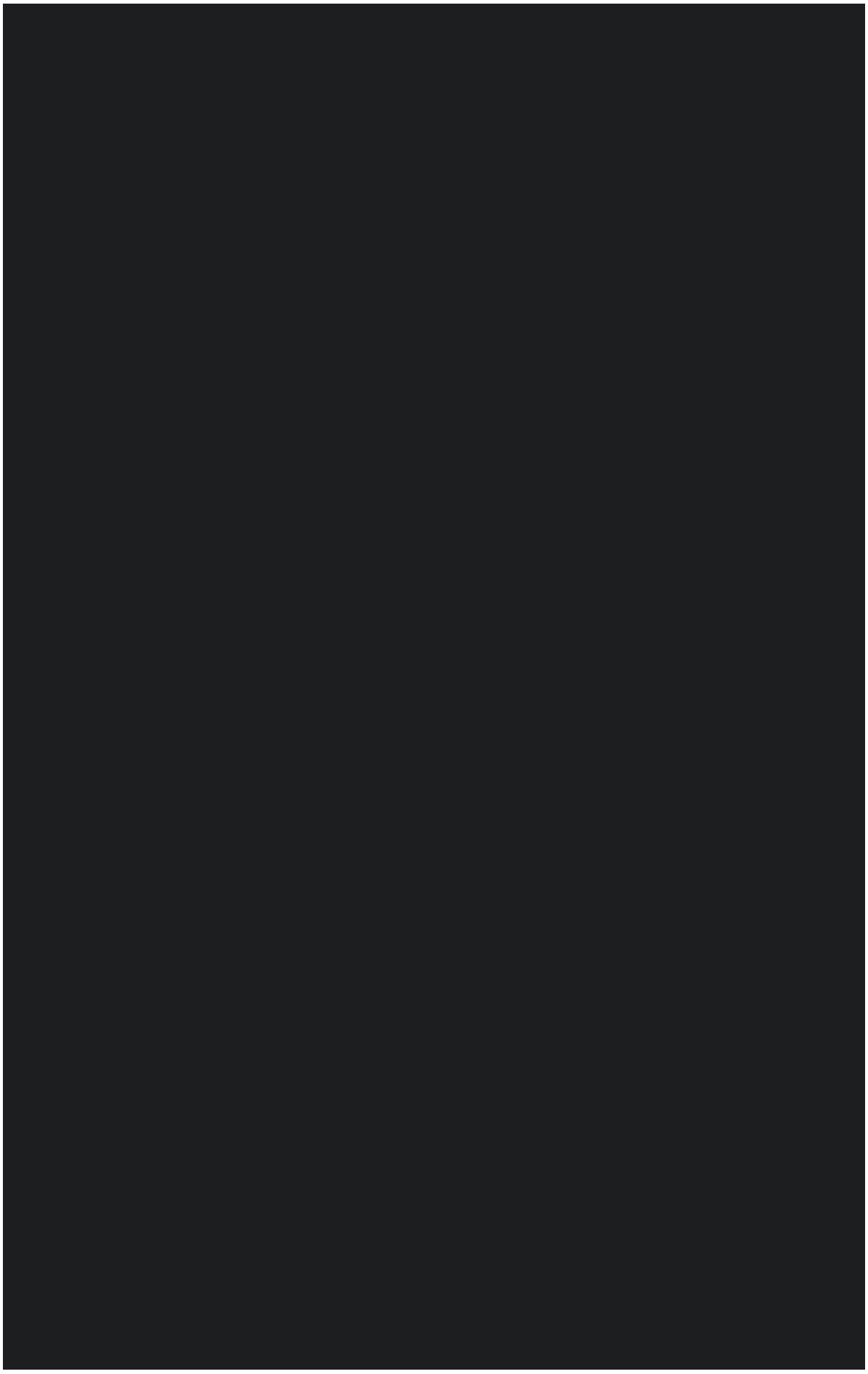

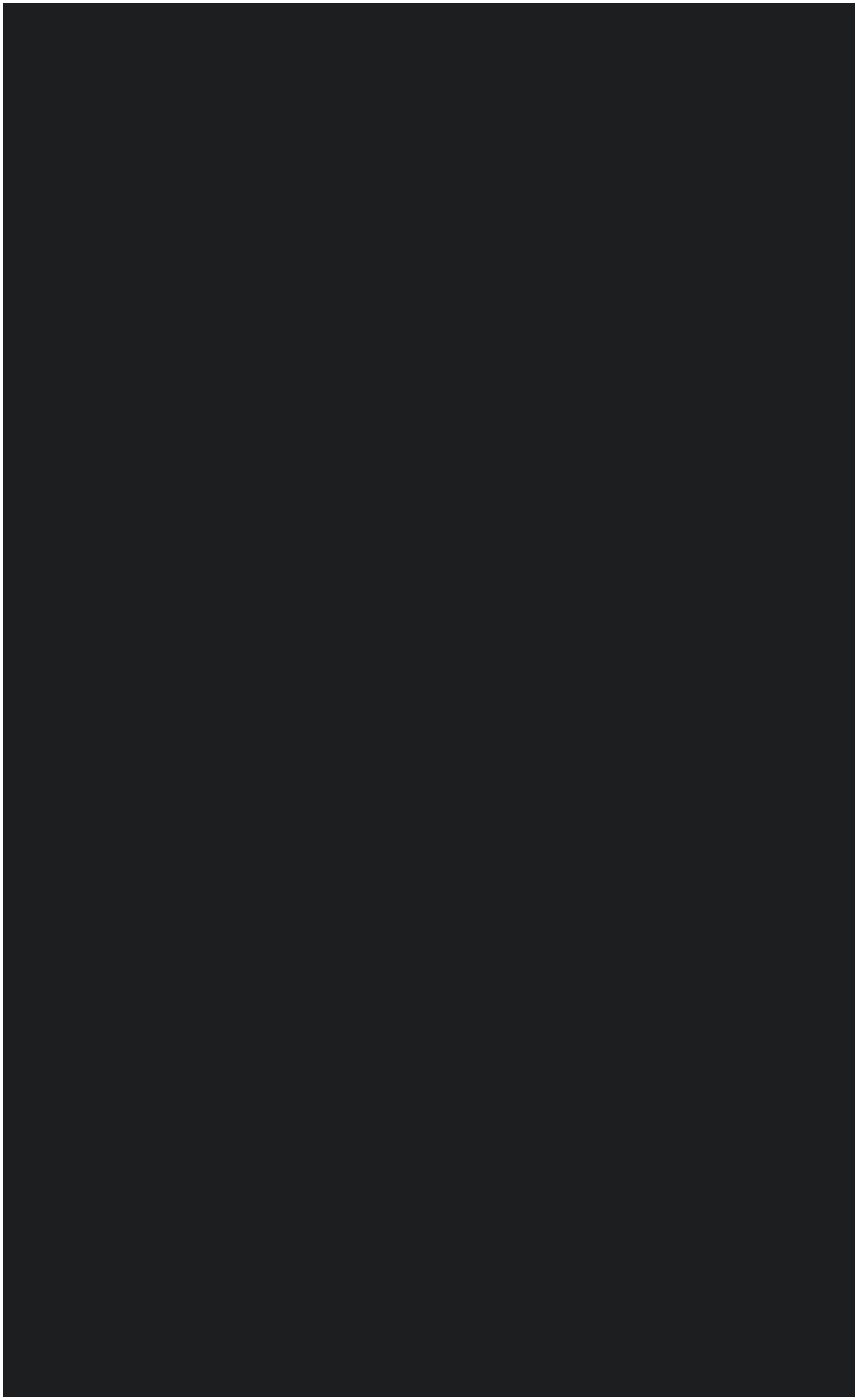

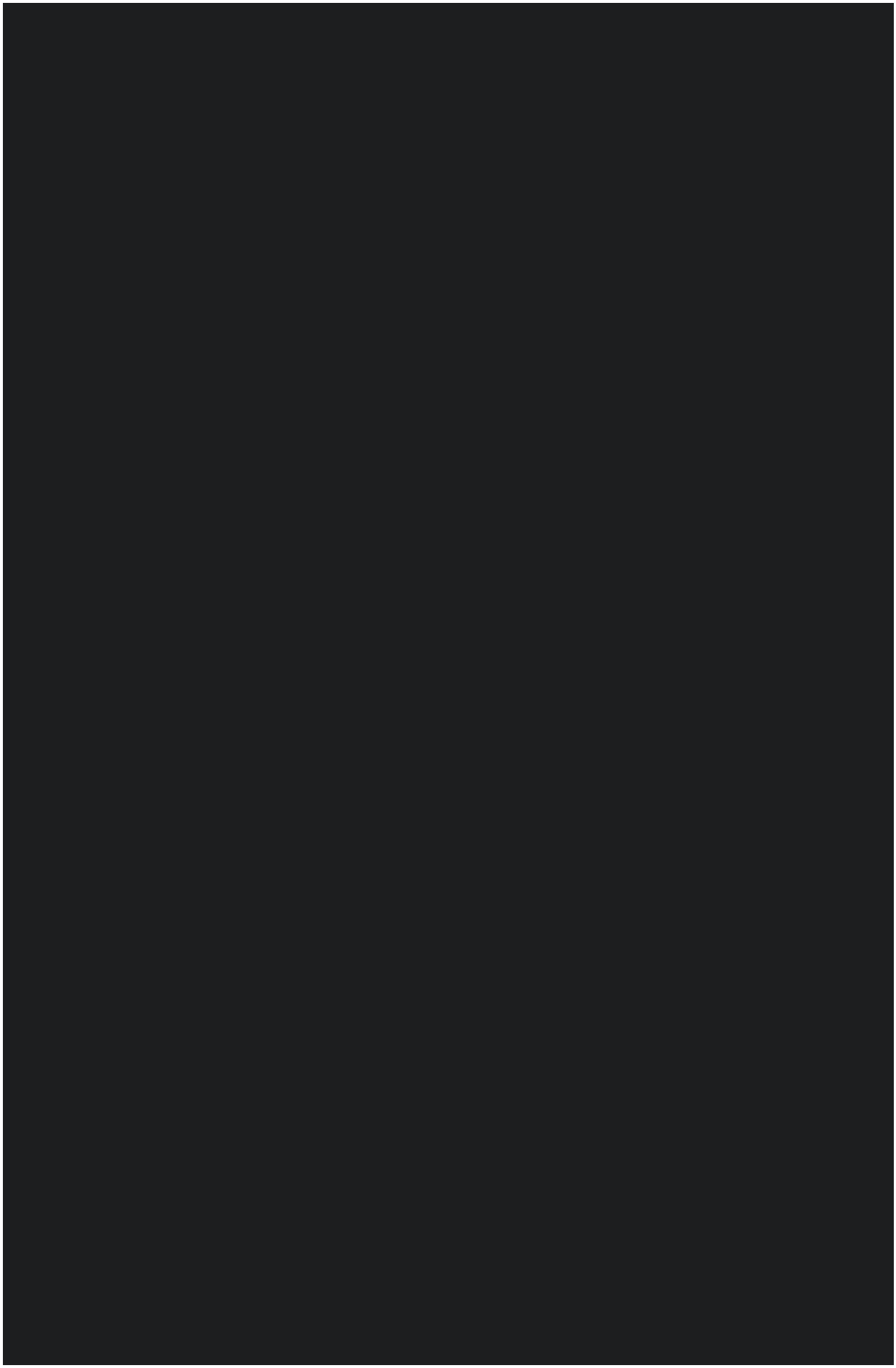

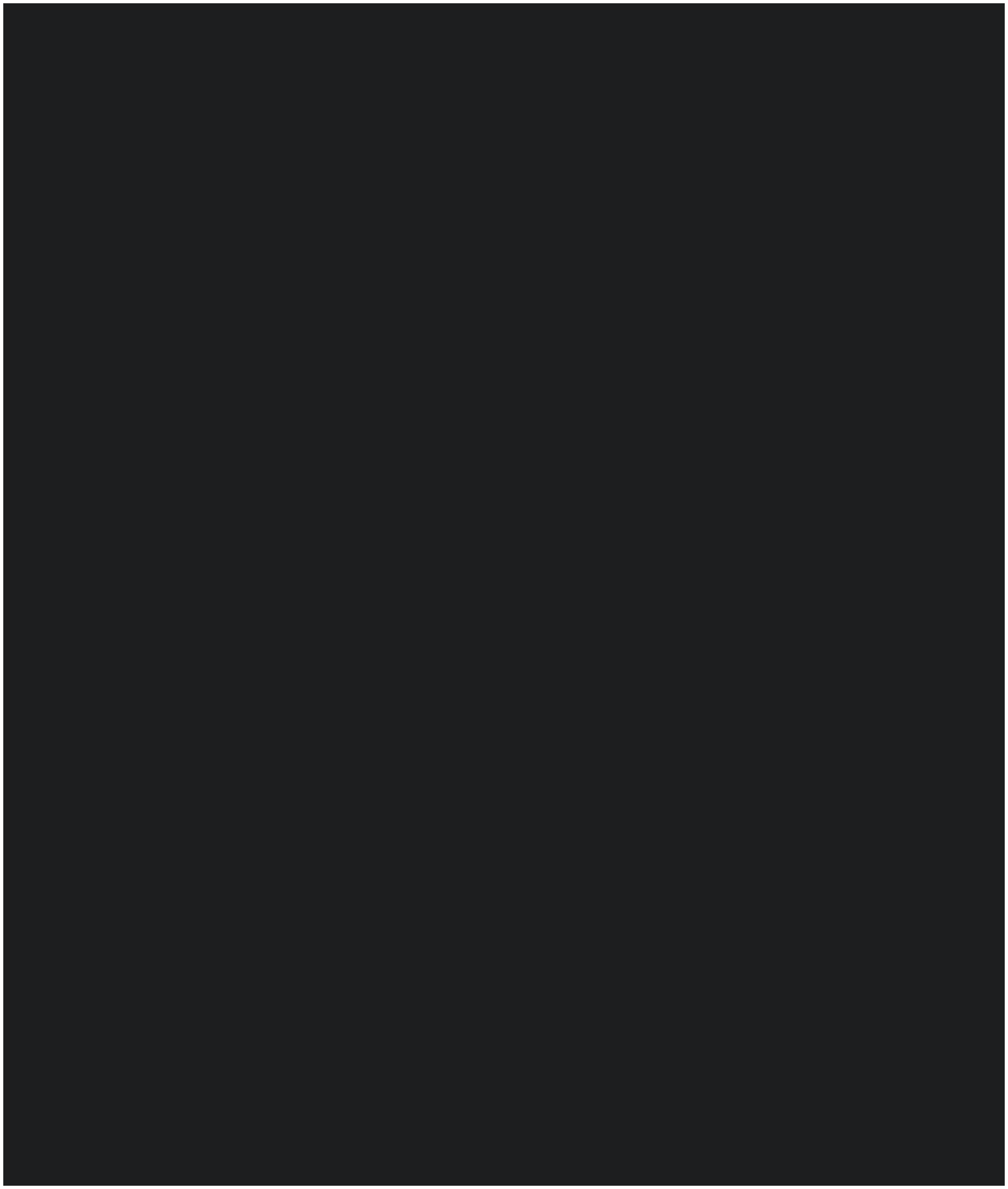

APPENDIX B: ECP REGISTRATION FORM

[redacted]

[redacted]

APPENDIX C: IRIS COLOR SCALE

APPENDIX D: [redacted] PATIENT REPORTED OUTCOMES

[redacted]

PROTOCOL COMPLIANCE INVESTIGATOR(S) SIGNATURE PAGE

Protocol Number and Title: CR-6334 ACUVUE® OASYS with Transitions™ Light Intelligent Technology™ Clinical Performance Registry

Version and Date: v4.0, 24 November 2020

I have read and understand the protocol specified above and agree on its content.

I agree to conduct this study according to ISO 14155,[1] GCP and ICH guidelines,[2] the Declaration of Helsinki,[3] United States (US) Code of Federal Regulations (CFR),[4] and the pertinent individual country laws/regulations and to comply with its obligations, subject to ethical and safety considerations. The Principal Investigator is responsible for ensuring that all clinical site personnel, including Sub-Investigators adhere to all ICH [2] regulations and GCP guidelines regarding clinical trials during and after study completion.

I will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants.

I am responsible for ensuring that all clinical site personnel including Sub-Investigators adhere to all ICH[2] regulations and GCP guidelines regarding clinical trials during and after study completion.

All clinical site personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all clinical site personnel involved in the conduct of this study are informed about their obligations in meeting the above commitments.

I shall not disclose the information contained in this protocol or any results obtained from this study without written authorization.

Principal Investigator: _____

Signature Date

_____

Name and Professional Position (Printed)

Institution/Site: _____

Institution/Site Name

_____

Institution/Site Address