

Study Synopsis

Protocol Title: An Observational Comparative Study Assessing Agreement Between Acuvera Capture and Paper-Based Methods for Best Corrected Visual Acuity (BCVA) Data Recording in Ophthalmic Clinical Trials

PROTOCOL NO.: OE-VALi-2025-001

Study Name: VALiCAPTURE

Study Phase: Observational, Prospective and Comparative Study

ClinicalTrials.gov No.: TBD

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1. Background and Rationale

Best Corrected Visual Acuity (BCVA) is the most widely accepted and clinically meaningful functional endpoint in ophthalmic clinical trials. It is routinely used to assess treatment efficacy, disease progression, and visual function across a broad spectrum of ocular diseases, including age-related macular degeneration (AMD), diabetic retinopathy, and inherited retinal diseases. Regulatory authorities such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) recognize BCVA as a primary endpoint in pivotal trials, and therapeutic approvals often hinge on statistically and clinically significant changes in BCVA outcomes (1–3).

Despite this critical role, BCVA data collection in clinical trials remains vulnerable when recorded on traditional paper forms. Common challenges include:

- **Calculation errors:** Manual determination of the total number of letters correctly identified during BCVA testing is prone to human error, particularly when partial lines are read or when examiners must manually apply line-by-line scoring rules. Miscounting or incorrect summation of letter scores can result in inaccurate BCVA values and distort subsequent data analyses. These errors are inherent to paper-based recording processes and highlight the need for standardized, automated systems capable of performing real-time calculations to ensure data accuracy and consistency across study sites (1,2,3).
- **Transcription Errors:** Manual transfer of BCVA scores from testing charts to case report forms can result in numerical misentries and calculation mistakes (4).
- **Omission and Misrecording:** Missed data points, illegible handwriting, or recording the wrong line/letter score can compromise data integrity (5).
- **Protocol Deviations:** Variations in testing procedures (e.g., incorrect testing distance, inappropriate prompting, or examiner bias) are not always detected in real time, introducing variability and bias (6).
- **Delayed Error Detection:** Errors are often identified only retrospectively, during central reading or data monitoring, causing delays in data cleaning, increased trial costs, and, in some cases, regulatory queries (7).

Digital capture solutions such as **Acuvera Capture** address these limitations by embedding real-time

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quality control at the point of care. The application incorporates automated error detection, warning systems for protocol deviations, and standardized workflow guidance, ensuring higher data fidelity. By minimizing calculation, transcription and protocol errors, **Acuvera Capture** has the potential to strengthen data reliability, streamline trial conduct, and increase regulatory confidence in BCVA endpoints.

Given that BCVA is the most critical functional endpoint in ophthalmic clinical trials, even small improvements in accuracy and reproducibility can substantially impact study outcomes, regulatory acceptability, and sponsor credibility. This study will directly compare **Acuvera Capture** against paper-based recording to validate data agreement and assess error rates, efficiency, and usability, thereby generating essential evidence to support digital transformation of BCVA data collection.

2. Study Purpose

To evaluate the level of agreement between the **Acuvera Capture** application and traditional paper-based methods for recording Best Corrected Visual Acuity (BCVA) in ophthalmic clinical trials. The study aims to determine whether the electronic capture system provides equivalent or improved accuracy, consistency, and error reduction compared with paper-based recording, thereby supporting its potential adoption as a reliable method for BCVA data collection in clinical research.

3. Study Objectives

Primary Objective:

1. To assess the agreement between BCVA data collected with paper forms and **Acuvera Capture**.

Secondary Objectives:

1. To compare the frequency and type of data discrepancies, calculation and transcription errors between paper and electronic capture.
2. To compare time to data entry and overall efficiency between paper and electronic capture.
3. To evaluate user feedback from certified examiners regarding usability and workflow.

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4. Study Outcomes

Primary Outcome:

Level of agreement in BCVA data recording between Acuvera Capture and paper-based methods, expressed using statistical measures of concordance (e.g., intraclass correlation coefficient [ICC], Bland-Altman limits of agreement, mean difference).

Secondary Outcomes:

a) Data discrepancies and errors

- Frequency and types of discrepancies between paper and electronic capture (e.g., calculation or transcription errors, missing data, protocol deviations).
- Error rates stratified by category (e.g., digit transposition, incomplete fields, illegible entries).

b) Efficiency metrics

- Time to complete BCVA data entry (per assessment and per session).
- Time to query resolution (if applicable).
- Overall workflow efficiency (average time saved per visit).

c) User feedback

- Usability ratings from certified examiners (measured through structured questionnaires or Likert scales) Questions 1 to 3 of the Acuvera Capture Survey (Appendix III)
- Qualitative feedback on workflow integration, ease of use, and error prevention features. Question 3 and 4 of the Acuvera Capture Survey (Appendix III)
- Examiner preference between electronic vs. paper methods. – Questions 5 to 7 of the Acuvera Capture Survey (Appendix III)

5. Study Design

- **Type:** Prospective, observational, comparative study
- **Number of Participants:** 90 adult participants (≈ 180 eyes), covering the entire spectrum of BCVA levels:
 - 30 participants (33%) in the normal/near-normal BCVA range (≤ 0.3 logMAR ≥ 70 letters); $\approx 20/40$ or better);

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- 30 participants (33%) with mid-range BCVA (0.4–0.9 logMAR (36-69 letters); 20/50 to 20/200)
 - 30 participants (33%) with low vision BCVA (≥ 1.0 logMAR (≤ 35 letters); worse than 20/200) including off-chart acuities using protocol low-vision procedures).
- **Number of Sites:** 2 ophthalmic clinical research centers Portugal)
 - **Number of Countries:** Portugal
 - **Number of Visits:** One study visit per participant
 - **Duration:** 2 months

Participants will undergo BCVA testing at a single visit using both paper-based recording and electronic capture with **Acuvera Capture**. Testing order will be randomized to minimize bias. Paper data will be inserted by the examiners or study coordinator into the study eCRF. Electronic capture data will be exported directly from the app.

6. Sample Size and Power Considerations:

This exploratory, two-site study, will enroll 90 adult participants (180 eyes), allocated to capture a broad acuity spectrum, to evaluate agreement between paper and electronic data capture. Approximately 30 participants (33%) in the normal/near-normal BCVA range , (≤ 0.3 logMAR ≥ 70 letters); $\approx 20/40$ or better); 30 participants (33%) with mid-range BCVA (0.4–0.9 logMAR (36-69 letters); 20/50 to 20/200) and 30 participants (33%) with low vision BCVA (≥ 1.0 logMAR (≤ 35 letters); worse than 20/200 including off-chart acuities using protocol low-vision procedures) will be enrolled. Being an exploratory study a formal sample size/power calculation was not performed.

With 180 paired BCVA recordings (paper vs. Acuvera Capture) each for OD and OS, precision for agreement metrics is expected to be adequate for feasibility/validation decisions. For example, if the true ICC for absolute agreement is in the 0.85–0.95 range typical of standardized BCVA procedures, 90 pairs yield an approximate 95% CI half-width of ~ 0.07 – 0.10 , sufficient to assess whether concordance meets a clinically acceptable threshold. For Bland–Altman analyses, assuming a conservative between-method SD of differences of 0.06–0.10 logMAR (≈ 3 – 5 letters), the 95% CI

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around the mean difference will be about ± 0.013 – ± 0.022 logMAR ($\approx \pm 0.65$ – ± 1.1 letters), supporting precise estimation of bias; limits-of-agreement will be presented with corresponding CIs. The sample also provides practical precision for secondary endpoints: if the true discrepancy (error) rate is $\sim 10\%$, an $n=90$ paired comparison yields a 95% binomial CI of roughly 4%–18%, and for efficiency outcomes the study has $\sim 80\%$ power (two-sided $\alpha=0.05$) to detect a within-participant standardized mean difference of ~ 0.32 (i.e., a small-to-moderate paired effect) in time-to-entry.

Overall, a total of **90 participants**, evenly distributed across **three BCVA strata** (normal/near-normal, mid-range, and low vision; approximately 30 participants per group), remains appropriate for this study's aims: it ensures representation across the acuity spectrum while providing decision-grade precision for concordance (ICC/Bland–Altman), informative bounds on error rates, and pragmatic sensitivity to workflow time differences, without over-scaling an observational validation.

7. General Statistical Analyses

A statistical analysis plan will be prepared to detail the statistical analyses that will be taking place. Since this is an exploratory study, data will be summarized descriptively, unless otherwise specified. Statistical tests will be performed at a two-sided significance level of 0.05 or one-sided significance level of 0.025, unless otherwise specified. Adjustments for multiplicity will not be made.

Continuous parameters will be descriptively summarized using number of observations with non-missing data, mean, standard deviation (SD), median, and range or inter-quartile range (IQR). Categorical parameters will be descriptively summarized using number and proportion of participants. Descriptive summaries will be presented separately for the right eye (OD), left eye (OS), and both eyes together (OU). Descriptive summaries for OU will not take into account correlation between participant eyes.

Demographics, ophthalmic history, BCVA and examiner feedback will be descriptively summarized. To analyze the primary objective, agreement between the two recording methods will be assessed separately for OD and OS using Bland–Altman plots, intraclass correlation coefficients (ICC), and mean differences with 95% confidence intervals (CI). As a supplementary analysis, a mixed effects model may be fit with both eyes from participants to determine the mean difference between the recording

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methods, accounting for correlation between participant eyes. Additional subgroup analyses may be conducted across different BCVA strata to explore potential differences in agreement at varying levels of visual acuity.

The frequency, type, and of discrepancies will be analyzed, with particular focus on calculation errors, transcription errors, missing data, and illegible entries. These will be compared between methods using chi-square or Fisher's exact test separately for OD and OS. Efficiency outcomes, including time to data entry and overall workflow duration, will be compared between methods using paired t-tests or non-parametric alternatives as appropriate separately for OD and OS.

Examiner feedback regarding usability and workflow will be evaluated qualitatively using an online survey (Appendix I). Structured questionnaire data will be summarized using frequency distributions, while open-ended responses will undergo thematic analysis to identify common patterns and perceptions of system performance.

All analyses will be performed using validated statistical software.

8. Study Population

Condition: Participants with any BCVA level, including those with underlying ocular disease

Inclusion Criteria:

- Adults ≥ 18 years old
- Able and willing to provide written informed consent
- Capable of performing BCVA testing procedures according to study requirements
- All BCVA ranges are eligible, including off-chart acuities (e.g., count fingers, hand motion, light perception) irrespective of the presence or absence of ocular disease.

Exclusion Criteria:

- Any condition preventing reliable completion of BCVA testing (e.g., severe cognitive impairment, language barriers)
- Inability or unwillingness to comply with study requirements

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- Non-ophthalmic condition that precludes safe or reliable testing (e.g., immediate post-operative systemic status preventing cooperation).
- Any circumstance that, in the investigator's opinion, makes the eye/participant unsuitable for accurate BCVA testing or for completing both data-capture methods during the same visit.

9. Study Eye Selection

Both eyes will be evaluated; however, only one eye will be designated as the Study Eye, according to the following criteria:

- The eye that determines the participant's eligibility for a specific BCVA group (i.e., normal, mid-range, or reduced BCVA) will be selected as the Study Eye.
- If both eyes have the same BCVA, the Study Eye will be assigned based on the participant's year of birth:
 - Right Eye (RE) if the year of birth is odd.
 - Left Eye (LE) if the year of birth is even.
 - Study Eye will always be performed first to ensure consistency in data collection.

10. Investigational and Control Treatment(s):

Not Applicable

11. Study Assessments

- Screening and consent prior to BCVA assessment
- Refraction testing performed by certified examiners by standardized ETDRS protocol
- BCVA testing performed by certified examiners using standardized ETDRS charts
- Each participant will be tested using both paper forms and Acuvera Capture (order randomized)
- Documentation of time to data entry, any errors flagged by Acuvera Capture or by the eCRF (paper-based results transcription), and user experience surveys completed by examiners

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12. Safety Assessments and reporting

This is a non-interventional study involving only standard Best Corrected Visual Acuity (BCVA) assessments performed using either traditional paper forms or the Acuvera Capture digital application. No investigational medicinal product or therapeutic intervention is used, and no adverse events are anticipated. Nevertheless, any incidents, discomfort, or unexpected events occurring during or immediately after BCVA testing (e.g., visual fatigue, dizziness, or procedural distress) will be documented in the source documents and case report form (CRF). The investigator will assess each event for severity and relationship to study procedures and ensure appropriate medical attention if necessary. Investigators are responsible for maintaining participant safety during all study activities. Any serious or unanticipated event judged related to study participation will be promptly reported to the sponsor and the Ethics Committee, in accordance with applicable EU and local regulatory requirements. The sponsor will review all reported events for completeness and compliance, and a safety summary will be included in the final study report.

13. Study Procedures / Data Acquisition

The technical procedures described in this section shall be performed according to the acquisition protocols / specific Standard Operational Procedures (SOPs) developed for the study and made available to sites before recruitment starts. Detailed instructions on how to perform the assessments will be given in the respective acquisition protocols or specific SOPs. Furthermore, the study procedures will be reviewed at site initiation visit which will take place prior to the initiation of the study. Study data that will be used for analysis will be recorded in the study electronic case report form (eCRF) (paper-based results) and downloaded from the Acuvera Capture solution (electronic data capture).

Study visit	Screening Visit
Visit Number	1
Procedure	
Informed Consent	X
Inclusion/Exclusion	X

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Medical History and Demographics	X
Refraction	OU
BCVA on paper ¹	OU
BCVA with Acuvera Capture ¹	OU
Adverse Events	X

¹ The sequence of testing on paper or with Acuvera Capture will be randomized to avoid bias

BCVA: Best Corrected Visual Acuity; **OU:** Both Eyes

13.1 Informed Consent and Participant Information

An Informed Consent Form (ICF) for the clinical study will be given to the participants.

13.2 Inclusion/Exclusion Criteria

During the visit, the investigator will check if all inclusion and none of the exclusion criteria are met.

13.3 Ophthalmological History and Demographics

The demographics and ophthalmological history will be documented at the screening visit (V1).

The following information will be collected:

- Age (year of birth)
- Sex
- Ethnicity
- Ophthalmic history (presence of ocular diseases and current or previous treatments like the use of eyedrops, laser, anti-VEGF injections, etc)

13.4 Refraction

Refraction will be obtained for each eye according to the ETDRS protocol, using standardized procedures to determine the best correction for visual acuity testing. All examiners will be certified by OptymEdge to conduct this and BCVA assessments. Testing will be performed at a distance of 4 meters in a sitting position, with reduction to 1 meter if acuity cannot be assessed at 4 meters. The final refraction result for each eye will be documented on the paper case report form and directly in

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the Acuvera Capture application, depending on the assigned recording method. This best correction will then be used for subsequent BCVA testing to ensure comparability between the two data capture approaches.

Detailed instructions on this procedure are provided in the study specific visual function procedure – VF Procedure Manual.

13.5 Best Corrected Visual Acuity (BCVA) on paper

BCVA will be assessed on both eyes by certified examiners, using best correction determined from protocol refraction. Measurements will be taken in a sitting position using ETDRS–like visual acuity testing charts at a starting distance of 4 meters. If vision cannot be assessed at 4 m, the testing distance will be reduced to 1 m. Patient response will be documented on provided paper-based worksheets. The overall BCVA score will be calculated manually according to the ETDRS letters score. Detailed instructions on this procedure are provided in the study specific visual function procedure – VF Procedure Manual.

13.6 Best Corrected Visual Acuity (BCVA) using Acuvera Capture

BCVA will be assessed on both eyes, using best correction determined from protocol refraction. Measurements will be taken in a sitting position using ETDRS–like visual acuity testing charts at a starting distance of 4 meters. If vision cannot be assessed at 4 m, the testing distance will be reduced to 1 m. Patient response will be recorded digitally in the provided Acuvera Capture platform. The overall BCVA score will be calculated automatically according to the ETDRS letters score.

Detailed instructions on this procedure are provided in the study specific procedure – Acuvera Capture VF Procedure Manual.

13.7 Randomization and allocation

Randomization will be implemented via the study’s RTSM module, which executes a pre-generated, site-stratified randomization grid. At each allocation, the RTSM (i) assigns the order of BCVA testing (Paper→Acuvera Capture or Acuvera Capture→Paper; 1:1 balance) to minimize order-related bias (fatigue, learning, memory effects, examiner preferences), and (ii) assigns the examiner–modality

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mapping, ensuring two different certified examiners are used and that the examiner performing the Paper assessment is not the examiner performing the Capture assessment. This approach preserves allocation of concealment, prevents copying of results between methods, and mitigates potential learning-curve bias with the app.

13.8 Participant Identification

Upon signing the ICF, participants will be identified by a unique code (Participant ID) used only for the purposes of this study. The code will consist of a combination of the first 4 letters from the study acronym (VALi) plus 2 fixed digits for the site number “01, etc” and 3 sequential digits for the participant number “001”. For instance, the first participant included will be VALi01001. Once assigned to a participant, the participant identification number will only be used to identify that specific participant and will not be reused for any other purpose.

13.9 Blinding / Unblinding Procedures

Not applicable.

14. Risks and Benefits

Risks: The study has minimal risk, as participants undergo standard BCVA testing already used in clinical practice. There is a slightly extended testing duration due to dual data entry methods

Benefits: Participants do not receive direct clinical benefit. The study may contribute to improved accuracy and efficiency of BCVA data capture in future clinical trials.

15. Ethical Considerations

The study will be conducted in accordance with the principles of the Declaration of Helsinki, International Council for Harmonisation Good Clinical Practice (ICH-GCP) guidelines, and all applicable local regulations. Written informed consent will be obtained from all participants prior to any study procedures. To protect confidentiality, data will be anonymized before analysis and reporting. As a minimal-risk study, its ethical justification rests on the potential to improve the quality of future ophthalmic clinical trials and to enhance patient safety through more accurate and reliable recording

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of Best Corrected Visual Acuity.

16. Dissemination of Results

Results will be submitted for peer-reviewed publication and may be presented at ophthalmology conferences. Findings are expected to support product validation, regulatory acceptance, and sponsor credibility.

17. References

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APPENDIX I

ACUVERA CAPTURE SURVEY

Acuvera Capture Experience Survey

On a scale of 1-5 (one being the worst and 5 being the best)

1. Ease of Use

How easy was it to use the Capture App compared to paper worksheet input?

- 1) Very difficult
- 2) Somewhat difficult
- 3) About the same
- 4) Somewhat easy
- 5) Very easy

2. Navigation & Layout

How intuitive was the Capture App's layout and navigation?

- 1) Very confusing
- 2) Somewhat confusing
- 3) Neutral
- 4) Somewhat intuitive
- 5) Very intuitive

3. Speed & Efficiency

Using the Capture App, how would you rate the time it took to complete data entry and file docs?

- 1) Much slower than paper
- 2) A little slower than paper
- 3) About the same
- 4) A little faster than paper
- 5) Much faster than paper

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4. Accuracy & Reliability

Were the Capture App's reminders (i.e. stopping rule reminder) handy compared to paper input?

- 1) Strongly disagree
- 2) Disagree
- 3) Neutral
- 4) Agree
- 5) Strongly agree

5. Overall Satisfaction

Overall, how satisfied are you with using the Capture App?

- 1) Very dissatisfied
- 2) Dissatisfied
- 3) Neutral
- 4) Satisfied
- 5) Very satisfied

6. Likelihood to Continue

If given the option, would you prefer to use the Capture App instead of paper going forward?

- 1) Definitely no
- 2) Probably no
- 3) Not sure
- 4) Probably yes
- 5) Definitely yes

7. Feedback

What's one thing you liked most about the app, and one thing you would improve?

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Suite 700
Rockville, MD 20850

Project Manager:

**Coordinator
Investigator:**

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Investigator Protocol Acceptance Form

Protocol Number	OE-VALi-2025-001
Protocol Title	
Observational, prospective, and comparative study assessing agreement between Acuvera Capture (digital capture) and paper-based methods for BCVA data recording in ophthalmic clinical trials	
Document	
Protocol Version	
1.0_FINAL_07NOV2025	
<p>I have read and understood this study synopsis. Having fully considered all the information available, I consider that it is ethically justifiable to perform the study according to the above protocol.</p> <p>In addition, I agree to conduct this protocol and any amendment and/or supplements according to applicable national laws and regulations relevant to perform this study, to ICH GCP Guidelines and in a manner consistent with the declaration of Helsinki.</p> <p>Furthermore, I agree to make no additions and/or changes without the consent of the sponsor, except when necessary to protect the safety of the subjects.</p> <p>Investigator Name: _____</p> <p>Clinical Site: _____</p> <p>_____</p> <div style="display: flex; justify-content: space-between;"> <div style="width: 45%; text-align: center;"> Investigator's Signature </div> <div style="width: 45%; text-align: center;"> Date </div> </div>	

Upon completion, file a copy in Master File and retain the original in the Investigator File.