Virtual Reality Assessment of Functional Vision in Patients with Achromatopsia.

Achromatopsia is an inherited retinal disorder characterised by congenital visual impairment, significant photophobia, and reduced visual acuity. Normal background lighting can be debilitating for these patients, with huge emotional, social and activity of daily living implications. Traditional clinical assessments, such as best-corrected visual acuity (BCVA) and contrast sensitivity, often failed to capture the full extent of visual challenges experienced in everyday environments—particularly those involving variable or bright lighting.

With therapeutic interventions such as gene therapy and optogenetics progressing toward clinical implementation, there is a critical need for objective, ecologically valid endpoints to measure functional vision. The multi-luminance mobility testing (MLMT) that was used as the end point for the clinical trial for Voretigene neparvovec (AAV2-hRPE65v2) for Leber Congenital Amaurosis, the one gene therapy approved in Australia, is time and space consuming. It required a room to be set up with obstacles, such as tables, chairs and open cupboard doors that the study participant needed to walk through under different light conditions. The primary efficacy endpoint of the study, that ultimately led to the therapy's approval and use within Australia, was improvement in the participants mobility on this course.

This clinical study, conducted at the Save Sight Institute, University of Sydney, investigated the use of a novel virtual reality (VR) mobility task to assess functional vision in individuals with achromatopsia. The VR take involved wearing a VR headset and using hand joysticks to walk through a virtual room (Figure 1). The VR environment was looking to imitate the MLMT and assess functional vision in a more reproducible and space efficient manner. The VR task involved navigating a simulated environment with obstacles and changing light conditions, designed to emulate real-world challenges faced by individuals with these conditions and the MLMT (Figure 2). This VR tool was tested in this study, to see if it can be an efficacious outcome measure, in the hope that it would be easier to replicate in international clinical trial centres with the need for less clinic space and provide reproducible testing.

Figure 1: The commercial Oculus® rift virtual reality headset and handpieces/joystick.

Figure 2: Screen shots from the virtual navigation task. An indoor room which patients navigate through where the furniture, objects and illumination can be randomised to 1 of 7 different scenarios and 2 of 7 light levels illustrated.

We enrolled individuals with genetically confirmed achromatopsia and age-matched individuals with normal vision. Each participant underwent a comprehensive set of assessments, including:

- Clinical measures (BCVA, contrast sensitivity, and light sensitivity testing)
- The VR mobility task, which recorded performance metrics such as navigation time, obstacle collisions, and eye/head movement patterns under different lighting conditions (Figure 2) [Phase 1 & 2]
- MonCvOne® to measure photosensitivity and quantify patient's level of photoaversion (avoidance of light due to discomfort) (Figure 3) [Phase 3]

The primary objective was to evaluate the **feasibility, reliability, and ecological validity** of the VR task. Secondary aims included identifying candidate endpoints for future interventional clinical trials.

In Phase 1, ten healthy controls tested various versions of the VR mobility protocol to assess learning effects and refine the task. Most participants required approximately five training runs to achieve consistent performance. Some experienced motion sickness, particularly with both eyes open, prompting a shift to testing with one eye for initial phases. Iterative changes were made, including the introduction of an "Objects Only" course and the exclusion of the difficult mazes from test trials.

Healthy controls showed good test-retest reliability, while achromatopsia patients exhibited greater variability. This was attributed to inconsistent path following and difficulty perceiving directional arrows at high luminance. Additional training and

potential modifications to arrow design or luminance may mitigate these issues in future trials.

The VR mobility test was generally well-tolerated across a broad age range. Participants with prior gaming experience adapted quicker to joystick controls, and the learning curve was steeper in older individuals unfamiliar with such gaming systems.

In Phase 2, patients with achromatopsia were tested with the VR mobility test. Time to complete and number of collisions with objects were significantly greater in these patients compared to healthy controls, especially at higher luminance levels.

Phase 3 found the MonCvOne® as a reproducible measure of photosensitivity. The brighter luminance correlated with smaller palpebral aperture measurements, meaning that in brighter settings there was more squinting.

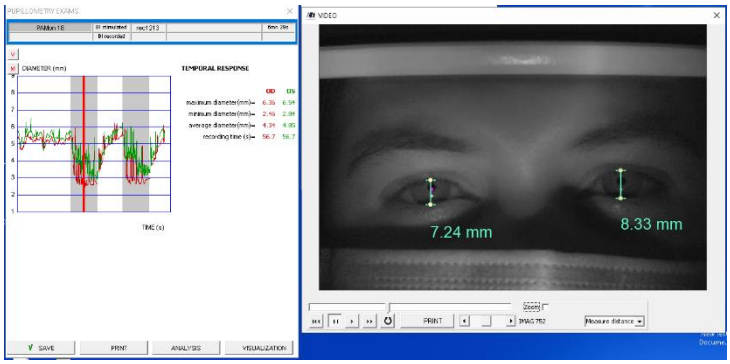

Figure 3: MonCvOne® palpebral aperture measurement (PAM) after light stimulus. Measured in this patient as 7.24mm & 8.33mm of the right and left eye respectively.

The results demonstrated that VR-based mobility testing offered a scalable and patient-friendly approach to evaluating real-world visual performance of patients with achromatopsia, with potential utility as a surrogate endpoint in upcoming clinical trials for novel therapies. MonCvOne® also proved to be a measurable and repeatable measure of light sensitivity in healthy subjects as well as those with achromatopsia.