Clinical Outcome Assessments (COA) Qualification Program
DDT COA #000127: Functional Vision Questionnaire (FVQ) ObsRO
Letter of Intent

Administrative Structure:

This proposal is being submitted by Novartis Pharmaceuticals Corporation, which is the sponsor of the ObsRO. Novartis has contracted with Adelphi Values, a health outcomes agency commissioned to conduct research supporting the development of the ObsRO. Please direct correspondence to Orin Tempkin.

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Concept(s) of Interest (COI) for Meaningful Treatment Benefit:

The concepts of interest are visual function and functional vision in pediatric (3-11 years) patients with a clinical and genetic confirmed diagnosis of Retinitis Pigmentosa (RP), as observed and reported by their parent or primary caregiver.

Currently in qualitative development, the Functional Vision Questionnaire (FVQ) Observer-Reported Outcome (ObsRO) includes domains targeted to assess those concepts in pediatric (3-11 years) patients. The current version of the ObsRO (version 2.0) includes 2 items in the visual function domain, 16 items

in the functional vision domain and 8 items in the distal health-related quality of life (HRQoL) domain. The distal HRQoL domain is not intended to support product label claims and so qualification of that domain is not being sought.

It should be noted that an associated FVQ Patient-Reported Outcome (PRO) instrument is also being developed for use in adolescent (12-17 years) and adult (18+ years) patients and is being submitted as part of a separate, parallel COA Qualification Letter of Intent.

Conceptual framework

Table 2-1 below provides a conceptual framework for the functional vision and visual functioning domains of the current FVQ ObsRO instrument representing the current development (version 2.0). The draft FVQ ObsRO is designed to assess functional vision by measuring the level of difficulty or frequency experienced by RP patients, as observed by their parent or primary caregiver, when in specific situations or performing a variety of activities of daily living (ADLs) that significantly rely on visual function.

The draft 26-item FVQ ObsRO currently consists of three domains assessing visual function symptoms (2 items; light/dark adaptation, difficulty seeing color) and impacts on functional vision (16 items; including daily activities and mobility). There are also 8 items assessing distal impacts on distal HRQoL (social functioning/independence, emotional wellbeing, work and education and leisure activities), but qualification of those domains is not being pursued. The conceptual framework will be refined and updated if the ObsRO is modified after the completion of the qualitative interviews.

Table 2-1 Conceptual framework for the domains of the FVQ ObsRO (version 2.0)

Domain	Sub-domain	Concept	Item
Visual function symptoms	Light/dark adaptation		1. Difficulty adjusting to new light conditions
	Difficulties seeing color		2. Difficulty telling the difference between different colours
Impacts on functional vision	Daily activities	Finding things	3. Difficulty finding things
		Reading normal print	4. Difficulty identifying letters, numbers or small pictures in a room with good lighting
			5. Difficulty identifying letters, numbers or small pictures in a dimly lit room
		Viewing digital screens	6. Difficulty seeing things on a computer
			7. Difficulty seeing things on a mobile phone or tablet
			8. Difficulty when watching TV
		Household chores	9. Difficulty when tidying up toys or clothes
		Eating	10. Difficulty finding food on their plate
	Mobility	Going up/down steps and stairs	11. Difficulty when going down steps, stairs, or stepping off a curb in good lighting without help from someone else
			12. Difficulty when going down steps, stairs, or stepping off a curb in dim lighting without help from someone else
		Bumping into objects/people	13. Bump into objects or people when walking in unfamiliar environments in good lighting
			14. Bump into objects or people when walking in unfamiliar environments in dim lighting
			15. Bump into objects or people when walking in familiar places in good lighting
			16. Bump into objects or people when walking in familiar places in dim lighting
		Falling/tripping	17. Trip or fall when walking in familiar outdoor places in daylight
			18. Trip or fall when walking in familiar outdoor places in dim lighting
Impacts on distal HRQoL	Leisure activities		19. Difficulty doing outdoor leisure activities in daylight
			20. Difficulty doing outdoor leisure activities in dim lighting
			21. Difficulty doing indoor leisure activities in good lighting
			22. Difficulty when doing indoor leisure activities in a dimly lit room
	Social functioning/ Independence	Taking part in social activities	23. Difficulty taking part in social activities without help from a parent or carer
		Upset	24. Become upset

Table 2-1 Conceptual framework for the domains of the FVQ ObsRO (version 2.0)

Domain	Sub-domain	Concept	Item
	Emotional wellbeing	Frustration	25. Become frustrated
	Work and school		26. Difficulty doing school work or homework
			26a. Person who observed difficulties.

Grey cells - qualification is not being pursued for these items.

Context of Use for COA Qualification:

Targeted study population

The FVQ ObsRO instrument is intended to be used to assess visual function, functional vision and distal HRQoL in pediatric (3-11 years) patients with a clinical and genetic confirmed diagnosis of RP, as reported by their parent or primary caregiver. The target population includes pediatric patients with different RP gene mutations, including *RLBP1* and *RPE65*, with the exception of Usher Syndrome as this subtype is associated with both visual and aural impairments. Clinical trial samples are expected to include pediatric patients with demographically and clinically diverse characteristics including diversity in terms of age, RP subtype, patient-reported severity, visual acuity and country. The FVQ ObsRO is intended to be used in RP clinical trials to evaluate the efficacy of RP treatments (most likely gene therapies) across multiple countries and languages.

As noted above, a PRO is also being developed for use in adolescent (12-17 years) and adult (18+ years) patients which is being submitted in a separate parallel Letter of Intent. While it is recognized that a PRO could also be developed for use in older children (e.g. those aged 8-11 years), this is not being pursued, as it is expected that relatively few children aged <12 are expected to be included in RP trials; hence, if multiple instrument covering the <12 years age range were included in a given trial, each completed for a very small sample of patients, it would make pooling data and interpretation challenging.

RP refers to a group of inherited degenerations of the photoreceptor cells (rods and cones) of the retina leading to gradual loss of vision and ultimately blindness. Patients with RP typically lose night vision in adolescence, peripheral vision in young adulthood, and central vision in later life, all of which affect patients' ability to perform vision-dependent functions of everyday life [1]. Mutations in any of a wide variety of genes can cause RP.

Targeted study design and statistical analysis plan

Following completion of the current qualitative phase of instrument development, an observational, non-interventional study will be conducted with the parents/caregivers of pediatric patients (aged 3-11 years) with RP to support initial assessment of the psychometric properties of the FVQ ObsRO for use in this context of use. A psychometric analysis plan (PAP) will be developed and finalized prior to database lock detailing the psychometric analyses which will assess the performance of the FVQ ObsRO. Ability to detect change over time and anchor and distribution-based analyses to support estimation of within-patient responder definitions and between-group meaningful change thresholds will then be evaluated in the first clinical trial(s) in which the instrument is included. The visual function and impact on functional vision scores results from the FVQ ObsRO instrument are expected to be used as secondary endpoints in RP clinical trials, with results used to provide evidence of treatment benefit and support product label claims. Other endpoints in RP trials are expected to include Performance-Reported Outcome (PerfO) assessments such as the Multi-Luminance Mobility Test (MLMT) and Clinician-Reported Outcome (ClinRO) assessments of concepts such as visual acuity or visual field.

Applicable study settings for future clinical trials

The FVQ ObsRO is being developed in English, German and French with qualitative research being conducted in the US, Canada (Newfoundland), France and Germany to help ensure the content is appropriate and applicable across cultures. It is intended for use in multinational clinical trials. Following completion of the qualitative development of the FVQ ObsRO it will be translated and linguistically validated for use in other non-English speaking languages. This process will follow best practice for linguistic validation, as detailed in the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Translation and Cultural Adaptation Task Force best practice guidelines [2].

COA Type: Observer-Reported Outcome (ObsRO)

References:

1. Hartong, D.T., E.L. Berson, and T.P. Dryja, *Retinitis pigmentosa.* The Lancet, 2006. **368**(9549): p. 1795-1809.

2. Wild, D., et al., *Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: report of the ISPOR Task Force for Translation and Cultural Adaptation.* Value Health, 2005. **8**(2): p. 94-104.