A strategy for measuring patient preferences to incorporate in benefit-risk assessment of new ophthalmic devices and procedures

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Abstract. The U.S. Food and Drug Administration recently released guidance documents explaining that measurement of patient preferences should be considered during the pre-market approval process to specify patients’ tolerances for risk and perspectives on benefit when assessing the benefit-risk profile of new medical devices. For ophthalmological patients, the typical primary clinical outcome is a visual impairment measure. Especially for surgically-implanted devices, the benefit a specified improvement in vision measures must be translated to a patient-specific benefit of the improvement in ability to function in everyday life. We developed, and validated with simulations, a strategy for measuring an individual patient’s ability to function and the overall benefit to that patient of specified improvements in functional ability. Our strategy employs Rasch analysis to measure changes in functional ability; multidimensional scaling to measure patient-specific benefits of changes in functional ability; and structural equation modeling to cross-walk patient preferences for functional ability changes to changes in visual impairment measures.
1. Introduction
Recently the U.S. Food and Drug Administration (FDA) issued guidelines for industry and FDA staff on the consideration of patient preferences when evaluating the benefit-risk profiles of medical devices during the pre-market approval process [1-2]. In ophthalmology, the potential benefits of surgically-implanted devices designed to improve vision (e.g., intraocular lens, retinal stimulator for prosthetic vision), typically are evaluated psychophysically with clinical visual impairment measures (e.g., visual acuity, visual fields). Measures of medical device benefits and risks to the patient necessarily entail potentially idiosyncratic personal preferences when judging the value of what is to be gained as a consequence of improved visual impairment measures. For example, visual acuity loss means different things to different people depending on which of the patient’s activities are limited or precluded by the vision loss and the value to the patient of being able to perform those activities with a criterion level of ease. The challenge in addressing this problem has three parts: 1) identify which activities are important to the patient and are limited or precluded by the patient’s visual impairment; 2) measure how much value the patient assigns to different levels of improvement of his or her ability to perform the identified activities; and 3) cross-walk the values assigned by the patient to improved ability to perform his or her self-selected activities to corresponding improvements in clinical visual impairment measures. Here we present our strategy for solving this three-part problem.

2. Background to Our Strategy
Relevant to part 1 of the problem, we have developed and routinely employ an adaptive rating scale instrument designed to measure a patient’s functional ability to perform vision-dependent activities. This instrument, the Activity Inventory (AI), consists of an item bank with 510 items that describe everyday activities within a hierarchical framework [3-5]. At the top level of the hierarchy, the activities are organized according to the objective they serve (Daily Living, Social Interactions, or Recreation). Fifty of the 510 items are classified as “Goals”, which describe what the person is intending to accomplish (e.g., prepare daily meals, manage personal finances, entertain guests). The other 460 items in the bank, which are nested under the Goals, are classified as “Tasks”. Tasks describe specific cognitive and motor activities that must be performed to accomplish their parent Goal (e.g., cut food, read recipes, measure ingredients, read bills, write checks, sign name). First, the patient is presented a Goal item and asked to rate how important it is for them to be able to accomplish it without depending on another person (ranging from “not important” to “very important”). If the patient responds “not important” the interviewer moves on to the next Goal. If the Goal is of non-zero importance to the patient, the patient is then asked to rate how difficult the Goal is to achieve without depending on another person (ranging from “not difficult” to “impossible”). If the patient responds “not important” the interviewer moves on to the next Goal, otherwise the patient is asked to rate the difficulty of Tasks nested under that Goal. Difficulty ratings of AI items were obtained from 3200 low vision patients (disabling chronic visual impairments in both eyes) and item measures and response category thresholds were estimated from Rasch analysis for all 510 items in the AI item bank [6].

With respect to part 2 of the 3-part problem, we must estimate the utility (i.e., a variable representing value, benefit, satisfaction, happiness, etc.) assigned by each patient to a hypothetical risk-free intervention that would make each of the identified important and difficult Goals in the AI not difficult to that patient. Psychometric tools that have been used in the past to estimate utilities include stated-preference methods such as partial profile discrete choice [7], pairwise comparison [8], best-worst scaling [9], and iterative bidding games [10]. The pairwise comparisons methods are inspired by and analysed within the framework of Thurstone’s law of comparative judgment [11]; discrete choice methods are loosely grounded in conjoint measurement theory [12]; iterative bidding games are framed by game theory [13]; and best-worst scaling is justified by post hoc probabilistic measurement models.
The underlying theory is important because the lack of consensus about the value of items requires that utilities be estimated from efficient repeated measures on each person, as opposed to the “crowd-sourcing” approach of Rasch analysis.

To solve the third part of the 3-part problem, we must be able to predict changes in the difficulty of Goals and Tasks in the AI from changes in visual impairment measures. From our previous work, we have learned that correlations between person measures estimated from difficulty ratings of AI Goals and different subsets of AI Tasks are the result of two independent vision factors – one factor represents visual processing underlying the recognition and identification of objects (the ventral stream or “what” visual pathway) and the other factor represents visual processing underlying perception of spatial relations and motion (the dorsal stream or “where” visual pathway) [6,11].

The first factor is affected by changes in visual acuity and the second factor is affected by visual field loss and scotomas (blind spots). By determining how much of each factor is demanded by each item in the AI, and specifying the patient’s visual ability on each factor from visual impairment measures, we will be positioned to predict the change in difficulty of each Goal as a result of intervention that causes changes in the patient’s visual impairment measures. A model giving us that capability will enable us to crosswalk utilities attached to the importance and difficulty ratings of activities back to clinical visual impairment measures.

3. Simulation of the Estimation of Utilities from Triadic Comparisons of Differences

The utility to an individual patient of an intervention that makes an activity easy to perform will depend on both the importance (I) and difficulty (D) of that activity to the patient, i.e., U(I,D). The marginal utilities are then mU(I)=dU(I,D)/dI and mU(D)=dU(I,D)/dD. Relative utilities of individual activities range from 0 (when I=0 or D=0) to 1.0 (when I=I_{max} and D=D_{max}). Activities in the AI having unique combinations of importance and difficulty ratings, i.e., (I_{A},D_{A}), (I_{B},D_{B}), (I_{C},D_{C}), are presented to the patient three at a time and the patient is asked to rank-order the activities according to the amount (money, time, effort, pain, etc.) he/she is willing to invest in making the activity easy to perform. The patient is then asked if the amount he/she is willing to invest to improve the middle-ranked activity, (I_{B},D_{B}), is closer to the amount for the top-ranked activity, (I_{A},D_{A}), or to the amount for the bottom-ranked activity, (I_{C},D_{C}). If the response is (I_{C},D_{C}), then rank scores are assigned to the differences in utilities between each pair of activities, i.e., 3 for (I_{A},D_{A})- (I_{C},D_{C}), 2 for (I_{A},D_{A})- (I_{B},D_{B}), and 1 for (I_{B},D_{B})- (I_{C},D_{C}) and entered into the appropriate cells of a dissimilarity matrix. All possible combinations of activities with unique (I,D) ratings are presented 3 at a time are presented in this way and difference ratings in each cell of the dissimilarity matrix are averaged. Multidimensional scaling (MDS) is used to estimate the position of each activity on a number line (or in a multidimensional space), which represents a continuous utility scale. These data collection steps were simulated with a computer program that had marginal utilities assigned to each importance rating and to each difficulty rating (ranging from 0 to 1). Total utility of each activity was defined as the product of the marginal utilities. The simulation proved that MDS applied to the dissimilarity matrix generated by ranking differences between pairs of utilities in triadic comparison trials can estimate the assigned marginal and total utilities.

4. A Structural Equation Model to Crosswalk Visual Impairments to Visual Ability

The primary outcomes from the ophthalmologist’s perspective are visual impairment measures such as visual acuity, contrast sensitivity, and scotoma maps. For the ophthalmologist to interpret these measures in terms that are meaningful to the patient, they must be mapped onto visual ability. To crosswalk visual impairments to visual ability, we need to develop a model that explains how vision factors 1 and 2 are related to visual impairments.

To evaluate how well the two vision factors can predict visual ability, we employed confirmatory factor analysis (i.e., a structural equation model). The model we constructed has seven latent variables: the two independent vision variables identified with the exploratory factor analysis and five health state variables estimated from a wide variety of measures and indicators. The model for the two vision
variables included visual acuity, contrast sensitivity, a variety of ocular and visual system disease diagnoses, and visual symptoms. The weights on the paths from the latent vision variables to the functional ability measures were set to the values estimated from the exploratory factor analysis, so that the health state variables were restricted to modeling the unexplained variance.

Vision factor 1 is equal to log binocular visual acuity and explains 73% of the observed variance in visual acuity. Vision factor 2 depends on the spatial distribution of binocular blind spots in the visual field relative to the area of retina in the dominant eye used for fixation (i.e., preferred retinal locus or PRL). The precise nature of this dependence is currently an active area of research. The aim of this work is to use clinical measures of visual impairments (binocular visual acuity and binocular scotoma maps) to predict the values of vision factor 1 and vision factor 2. Psychometric measures of psychological state, cognitive state, physical functioning ability, and diagnostic indicators (i.e., clinical signs from tests and examinations and symptoms from a structured health history survey) are used to estimate the 5 latent health state variables (effect modifiers). Using the estimated latent vision and health state variables, the structural equation model is then employed to predict patient difficulty ratings of AI Goals and Tasks. The distribution across patients of the ratio of mean square residuals (observed uncertainty variance) to the expected uncertainty variance (i.e., information weighted) is used to assess the validity of the structural equation model.

5. Discussion
A structural equation model is used to estimate the two latent visual ability variables ("what" and "where" components of visual processing in the cortex) from clinical visual impairment measures, as well as estimating latent visual ability effect modifiers from other health state data. These estimates are then used to predict patient difficulty ratings of activities in the AI. Given a particular patient’s \((I,D)\) ratings of activities in the AI, and population-based marginal utilities on \(I\) and \(D\) ratings and on their combinations, the model can be used to predict the utility to the patient of improvements in clinical measures of visual impairments.

6. References
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