Use of Cognitive Testing to Optimise Questionnaire Wording and Mode of Administration in the Evaluation of Risk Minimisation Activities

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CONFLICT OF INTEREST

L. Zografos, E. Andrews, and D. Whalley are full-time employees of RTI Health Solutions, which received funding from Bayer Pharma AG to conduct this study. The contract between RTI Health Solutions and the sponsor includes independent publication rights. RTI conducts work for government, public, and private organisations, including pharmaceutical companies.

Z. Vassilev and P. Petraro are full-time employees of Bayer Healthcare Pharmaceuticals Inc., the funder of this study.

ABSTRACT

Background: As part of the evaluation of risk minimisation measures for aflibercept, for intravitreal injection, a questionnaire was developed to assess patient knowledge and understanding of key safety information contained in aflibercept's EU educational materials. Interviews were conducted to test the questionnaire with patients prior to the start of data collection.

Objectives: To ensure that patients understood and consistently interpreted the questions and response options and to determine the most appropriate mode of data collection given the potential for visual impairment in the target population.

Methods: Two rounds of interviews were first conducted in English (in the UK) with 11 patients to identify issues and optimise wording. Interviewers trained in cognitive debriefing methods asked patients to complete the questionnaire while describing their thought processes aloud. Additional probe questions elicited more information on how patients interpreted and chose their answers and the format and usability of the questionnaire. The questionnaire was revised after each round of interviews and translated into 4 additional languages (for France, Germany, Italy, and Spain). Cognitive interviews were then conducted with l4 patients per country to confirm wording and cultural acceptability.

Results: Across all countries, 56% of patients were aged 50 to 75 years, and 37% were 76 years or older. Early results indicated that some patients likely could have difficulty completing the questionnaire without support due to visual impairment and cognitive difficulties. Based on these findings, the questionnaire was shortened, the language simplified, and the format changed to be interviewer administered. Subsequent interviews in the UK and other countries supported the length and wording of the revised questionnaire, as well as the mode of administration.

Conclusion: Appropriate questionnaire design is essential to optimise data quality. Careful pretesting is critical to ensure appropriate wording and administration format, particularly when there is potential for visual and/or cognitive impairment within the target population.

BACKGROUND

Surveys to Evaluate Risk Minimisation Measures

- Aflibercept (Eylea), administered via intravitreal injection, is a fusion protein specifically designed to bind all forms of vascular endothelial growth factor A (VEGF-A) and placental growth factor, two proteins involved in the abnormal growth of new blood vessels.[1] At the time of this study, aflibercept had been approved by the European Medicines Agency (EMA) for the treatment of neovascular (wet) age-related macular degeneration (wAMD), visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO), and visual impairment due to diabetic macular oedema.[1]
- As part of the risk minimisation measures (RMMs) for aflibercept, Bayer Pharma AG (Bayer) developed materials to help educate physicians and patients on the key safety information for and safe use of aflibercept.
- Surveys are a common research method to evaluate patient understanding of key safety information communicated as part of RMMs. These studies are considered post-authorisation safety studies under the EMA Good Pharmacovigilance Practices guidance.
- A survey questionnaire was developed to evaluate patient knowledge of the following concepts contained in the aflibercept educational materials:
  - Conditions that patients should tell their doctor about before receiving aflibercept
  - Possible aflibercept side effects
  - Appropriate actions a patient should take if a symptom or a suspected side effect is experienced
  - Receipt and use of the patient booklet, patient information leaflet, and audio CD
  - Patient and treatment characteristics (e.g., age, sex, education, time since first aflibercept treatment, and number of aflibercept injections received)

Importance of Cognitive Testing

- Despite best efforts and scientific expertise devoted to questionnaire design for risk minimisation evaluation, newly developed questions should also be tested among members of the target population through cognitive interviews. Potential sources of measurement error can be identified and minimised via thorough pretesting of the instructions, questions, and response options presented in questionnaires.[2,3]
- Cognitive interviews permit researchers to optimise survey instructions and refine question wording, response options, and overall questionnaire format through observing and evaluating the cognitive processes that respondents use to answer questions, including item comprehension, information retrieval, and response selection.[2,4,5]
- In addition, cognitive pretesting also helps facilitate consistency not only across respondents but also with the researcher's intentions for measurement.[6]
- Particular care must be taken when developing survey items for special populations to ensure that resulting questions are easily read and understood and that the question formats and administration modes are appropriate for the intended population.[7]
- For this study, cognitive interviews were conducted with patients in 5 European countries (the United Kingdom, France, Germany, Italy, and Spain) to test the draft questionnaire prior to the initiation of data collection for a full study to evaluate RMMs.

OBJECTIVE

- To ensure that patients understood and consistently interpreted the questions and response options in the aflibercept risk minimisation evaluation questionnaire and to determine the most appropriate mode of data collection given the potential for visual impairment in the target population.

METHODS

Questionnaire Development

- A paper questionnaire was developed using best practices for instrument development and was tested through cognitive interviews with patients in each country.
- The aim of the interviews was to identify issues with the questionnaire and optimise wording of the instructions, items, and response options, as well as to elicit patients' input on the mode of questionnaire administration.

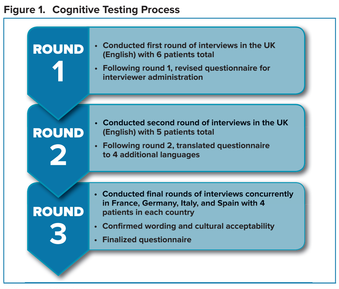
Eligibility Criteria

- Participants who were invited to take part in the cognitive interviews were selected to represent the range of patients who might be prescribed aflibercept.
- Eligible patients were required to meet the following criteria:
  - Had been administered aflibercept or another anti-VEGF intravitreal injection at least once within the last 6 months for an aflibercept indication approved at the time of the interviews
  - Aged 18 years or older
  - Able to understand and sign the consent form
  - Able to understand the native language of the country in which the study was being conducted
  - Had not participated in a clinical trial for an approved aflibercept indication in the past 12 months

Cognitive Testing Process

- Figure 1 summarises the steps in the cognitive testing process.
- Experienced interviewers trained in cognitive debriefing methods conducted in-person interviews in each country with patients using a semistructured interview guide.
- After reviewing and signing the informed consent form, participants were asked to provide feedback on the draft questionnaire. Interviewers asked patients to complete the questionnaire while describing their thought processes aloud. Additional probe questions elicited more information on how patients interpreted and chose their answers.
- For the first round of interviews, interviewers were trained to let the patient read the paper questionnaire on their own unless the patient had trouble reading due to visual impairment, in which case the interviewer read the questions to patient. In subsequent rounds, the questionnaire was administered to the patient as an interview.
- The cognitive testing phase of the study was conducted from 2013 to 2014.

Figure 1. Cognitive Testing Process



UK = United Kingdom.

RESULTS

Patient Characteristics

- Across interviews in all countries (N = 27), the participants were predominantly older than 50 years (Table 1).
- Most participants had a secondary school education or higher.
- Over half of participants were female.
- Three participants had received an aflibercept injection. The other participants had received other types of anti-VEGF intravitreal injections.
- Most participants were being treated for wAMD.

Table 1. Summary of Patient Characteristics

Patient Characteristics	N = 27[a]
Age, years, n (%)	
< 50	1 (3.7%)
50-75	15 (55.6%)
≥ 76	10 (37.0%)
Not available	1 (3.7%)
Mean (range)	74 (47-92)
Sex, n (%)	
Female	16 (59%)
Male	11 (41%)
Education, n (%)	
Less than secondary school education	6 (22%)
Secondary school education or higher	21 (79%)
Indication, n (%)	
wAMD	25 (93%)
CRVO	2 (7%)
Prescription, n (%)	
Eylea	3 (11%)
Lucentis	21 (78%)
Avastin	3 (11%)
Macugen	0 (0%)

[a]Total percentage by category may not sum to 100% due to rounding.

Cognitive Interview Findings

- Results from the first round of cognitive interviews with patients in the UK indicated that the target patient population for the full study may have cognitive difficulties (e.g., slow thinking, poor concentration, and memory issues) in addition to visual impairment. Results suggested that some patients may struggle to complete the questionnaire on their own.
- Some participants indicated that they were not familiar with completing questionnaires, and some experienced difficulty with understanding and completing the questions. Interviewers suggested simplifying long sentences and shortening the introductory paragraphs. In addition, the interviewers suggested that the questions should be phrased in the second-person singular form so that a participant would feel directly addressed.
- Ultimately, it was determined that a patient-completed paper questionnaire would not be suitable for the full study. Completion of the questionnaire via the Internet was also ruled out, as patients would face similar challenges as with paper administration and moreover would be required to have computer and Internet access. Telephone administration was not considered given the length and number of response options. Therefore, it was determined that the most suitable format was an interviewer-administered questionnaire using trained study site staff to collect data.
  - As potential biases and an "intervention effect" can arise from interviewer-administered questionnaires, it is essential that such potential issues are mitigated through rigorous training of site personnel who are responsible for administering the questionnaire to patients.
  - Therefore, in the full risk minimisation evaluation study for aflibercept, site personnel were trained to ensure a thorough understanding of the importance of and processes for conducting an objective interview.

Modifications to the Questionnaire

- Based on the results of the first round of UK interviews, the following modifications were made to the questionnaire to simplify wording, reduce length, and adapt the questionnaire to an interviewer-administered mode of data collection before proceeding with the remaining interviews:
  - The introductory instruction text and question stems were shortened to make them easier to read and understand.
  - Individual questions were revised to use the second person singular form.
  - Individual questions were converted to a tabular format to make the questions easier for the interviewer to administer.
  - Interviewer instructions, cues, and potential probes were included in a margin alongside the questions to provide the interviewer with specific guidance when administering the questionnaire.
- Excerpts from the original paper questionnaire (prior to formatting) and from the revised interviewer-administered questionnaire are presented in Figure 2 and Figure 3.
- Subsequent interviews in the UK and other countries supported the length and wording of the revised questionnaire, as well as the mode of administration.

Figure 2. Excerpt of Questionnaire Prior to Cognitive Testing

Q4. Which of the following conditions should patients tell their doctor or nurse about before starting treatment with Eylea?

Tick all that apply.

- ❑ An infection in or around the eye
- ❑ Current pain or redness in the eye
- ❑ An allergy to iodine, any painkillers, or any of the ingredients in Eylea
- ❑ Any issues or problems with previous eye injections
- ❑ Glaucoma or a history of high pressure in the eye
- ❑ Seeing flashes of light or 'floaters' in the eye
- ❑ Any use of medications, with or without a prescription
- ❑ Previous or planned eye surgery within 4 weeks before or after Eylea treatment
- ❑ Pregnancy, plans to become pregnant, or breastfeeding
- ❑ None of the above
- ❑ I don't know

Figure 3. Excerpt From Final Reorganised and Reformatted Questionnaire With Interviewer Instructions

Inform the patient that the questions reference information that they might communicate with their ophthalmologist or anyone in the ophthalmologist's eye clinic, such as a nurse.

If needed, repeat the question.

Provide hard copy of table to patient as reference.

Q1. Which of the following issues or health conditions should you tell your ophthalmologist about before you have an Eylea injection?

Please answer:

- ☐ "Yes" if you think you need to tell your ophthalmologist, *OR*
- ☐ "No" if you think you do not need to tell your ophthalmologist, *OR*
- ☐ "I don't know" if you do not know or you are not sure.

What information should you tell your ophthalmologist about?		Yes	No	I don't know
a.	Any current eye problems (for example, infection, pain or redness in the eye)	☐	☐	☐
b.	Any allergies to medications (for example, iodine or painkillers)	☐	☐	☐
c.	Any problems with eye injections in the past	☐	☐	☐
d.	If you have glaucoma or have had issues with feeling of high pressure in the eye in the past	☐	☐	☐
e.	If you see flashes of light	☐	☐	☐
f.	If you see moving spots (known as floaters) in your eye	☐	☐	☐
g.	Any medications that you have used	☐	☐	☐
h.	If you have had (or are going to have) an eye operation in the 4 weeks before or after the Eylea injection	☐	☐	☐
i.	If you are pregnant, are planning to become pregnant, or are breast feeding	☐	☐	☐

CONCLUSIONS

- To optimise data quality for survey studies conducted in the context of RMMs, appropriate questionnaire design and rigorous processes for implementation are essential.
- Careful pretesting is critical to ensure appropriate wording and administration format, particularly when there is potential for visual and/or cognitive impairment within the target population.
- Cognitive pretesting for this study resulted in a different mode of administration than originally planned and important revisions to wording of instructions, question stems, and response options for the full study.
- Additional study procedures were introduced for the full study to ensure that interviewers were well trained on best practices for conducting an objective, standardised interview.
- The changes made to the survey design as a result of the cognitive testing process will support more accurate reporting of patient knowledge of the safe use of aflibercept.

ACKNOWLEDGEMENTS

- The authors would like to thank Mark Price and Kelly Hollis of RTI Health Solutions for their contributions to the poster.

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