ABSTRACT

INTRODUCTION: SELECT (Self Evaluation of Lovastatin to Enhance Cholesterol Treatment) was a self-selection study simulating consumer decision-making behavior in a real-world OTC setting.

METHODS: The self-selection study was divided into two components, self-assessment (SA) and purchase decision (PD). While thinking about these questions, participants could ask to talk to their doctors, pharmacists, have their cholesterol tested, or ask about other medications they were taking. Participants were asked a series of follow-up questions regarding their decisions, their eligibility criteria, their healthcare practices, and socio-economics. If a participant decided that MEVACOR® Daily was right for them when they were not eligible to use the product, they were asked questions to help understand the reasoning that led to the inappropriate decision. Because the eligibility criteria were so extensive and because the interview contained multiple pathways, the complex questionnaire was developed for electronic data capture (EDC) and its administration was enhanced by using screen prompts to guide investigators through the conduct of the interview. An abundance of verbatim open-ended data was collected, providing insight regarding participants’ reasoning and factors considered when making these decisions. In order to manage the collection and analysis of the data, various innovative data management and analysis strategies were employed. These included classification, mitigation, participant profiles, and hierarchies.

CONCLUSION: The data management and analysis strategies used for SELECT allowed for a “conversation-like” interview which looked into the reasons behind consumer decision-making and allowed for the data to be tabulated in an appropriate manner for a regulatory submission.

Key words: Lovastatin, Mevacor, self-selection, switch, OTC, consumer behavior

BACKGROUND

In the US, there is currently a wide range of prescription (Rx) only medications that have the potential for over-the-counter (OTC) self-treatment of common illnesses. Before the Food and Drug Administration (FDA), will reclassify a drug for OTC access, an assessment of the drug’s safety, effectiveness, and the consumer’s ability to correctly select and use the product is
required. Actual use (evaluation of how consumers will use a product in a real world setting) and self-selection studies (assessment of consumer thought processes when making decisions) are crucial components of the approval process. These studies must be designed in a way that convincingly demonstrates that consumers can self-determine the appropriateness of using a drug (self-selection) based on a set of drug label criteria and then make decisions leading to proper use over time.

While there are well-established design principles for assessing a drug’s safety and effectiveness, self-selection currently lacks an explicit scientific model. Without standardized methods for study conduct and evaluation of self-selection, study ‘success’ is often subject to interpretation.

MEVACOR® (lovastatin) was approved by the FDA as a prescription drug in 1987. Its indication was as adjunctive therapy for the reduction of elevated total cholesterol (Total-C) and low-density lipoprotein cholesterol (LDL-C) levels in patients with primary hypercholesterolemia. There has been mounting evidence of the benefits of cholesterol lowering in individuals at moderate risk of cardiovascular disease and growing interest of consumers to participate in their own healthcare decisions. Because of the well-established benefits of lowering cholesterol, and its proven efficacy and safety, lovastatin was developed for nonprescription use.

This report will examine the development and outcomes of the innovative study methodology designed to demonstrate consumer behavior in self-selection of OTC MEVACOR® used in the SELECT (Self Evaluation of Lovastatin to Enhance Cholesterol Treatment) study.

CUSTOM

The CUSTOM study preceded SELECT and was the primary actual use study for the MEVACOR® switch program (lovastatin 10 mg). CUSTOM was an open-label, long-term actual use study of MEVACOR® conducted to observe consumer self-selection and de-selection behaviors in a naturalistic OTC setting.

The CUSTOM study demonstrated that the majority of consumers could appropriately self-manage their treatment of cholesterol over time, including treatment to goal, compliance, and persistence, and could appropriately de-select usage based on changes in health status or drug effect (new prescriptions or new medical conditions, including unexplained muscle pain). Users also achieved beneficial lipid lowering with MEVACOR®. CUSTOM also demonstrated that MEVACOR® in a non-prescription setting is generally well tolerated, however, the self-selection behavior results were not optimal for certain label criteria. Specific areas in CUSTOM where a significant number of consumers did not comply with label restrictions were:

- **Women <55 years of age.** In CUSTOM, of the women <55 years of age who evaluated the product for potential use, 23.5% (161/685) elected to use MEVACOR™ OTC. Of the female User population, 37% (161/430) were women <55 years of age. For the SELECT label, color coded age guidance by gender was added to the front panel.
• **Women of childbearing potential.** Since women <55 years of age who used MEVACOR™ OTC in CUSTOM were not asked if they were menopausal, it was assumed that they were capable of conceiving a child. A question regarding childbearing potential was not asked in CUSTOM and there was no warning on the label against use in women of childbearing potential. For SELECT, “Do not use if you think you may become pregnant” was added to the label.

• **Low CHD risk users (<5% risk of CHD in 10 years).** In CUSTOM, 27.3% (289/1059) of the users were considered low risk based on personal characteristics as defined by the Framingham Risk Calculator. In the SELECT study label, consumers were told that if they do not meet specific criteria they might be at lower CHD risk and will have reduced benefit from the medicine.

While the CUSTOM study data did not result in an approval of MEVACOR® for OTC use, the lessons learned were used to help develop the methodology in the SELECT Self-Selection Study.

**METHODS:**

**STUDY DESIGN**

The purpose of the SELECT study was to demonstrate that a redesigned label improved the self-selection decisions made by consumers in CUSTOM, and to better understand the reasons behind these decisions. The SELECT study collected data demonstrating why participants made inconsistent or inappropriate decisions. Because use behavior had been adequately addressed in CUSTOM, SELECT did not include actual product usage and was focused on self-selection.

This “all-comers,” two-arm, multi-center, non-drug, self-selection study was conducted to observe, record, and query participants’ self-assessment and purchase decisions. Mass media advertising, targeted to reach a diversified study population, was used to recruit cholesterol-concerned individuals to call a toll free number and direct them to a study site in their area. The study was conducted in a storefront setting by nurse investigators. This study was designed to simulate the two-part self-selection process: self assessment and purchase decision. After reviewing the label, 1499 participants decided if the product was appropriate for them using the criteria on the label (self-assessment) and if they would like to buy it (purchase decision). A detailed questionnaire with multiple pathways for probing was used to understand behaviors associated with self-selection decisions that were not consistent with the label directions, especially in the areas that were targeted for improvement based on results from the CUSTOM study. Participants could not actually purchase the product, but in order to elicit an unbiased response, participants were led to believe that they would have an opportunity to purchase the product and were not told that they could not buy the product until the end of the interview. This methodology received approval from ASPIRE Independent Review Board in advance of the study.

Since consumer understanding and awareness of cholesterol varies, this study evaluated
participants’ understanding of eligibility criteria in two different label paradigms. One label paradigm was based on an LDL-C range of 130 to 170 mg/dL, which is based on National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III guidelines for lipid lowering therapy, and commonly used by physicians in making treatment determinations. The other label paradigm was based on a Total-C range of 200 to 240 mg/dL, a possibly more consumer-friendly surrogate for LDL-C. The Total-C range of 200 to 240 mg/dL was felt to be the appropriate lipid value eligibility range given the familiarity of this measure among consumers, consistency with national consumer initiatives, and its high concordance with the LDL-C 130 to 170 mg/dL range in the 1999-2002 National Health and Nutrition Examination Survey (NHANES).

SELECT participants evaluated the label focusing on 15 label elements in three categories:

**Absolute Safety Warnings** (Do Not Use)
- Allergy to lovastatin; Pregnant or breast-feeding; May become pregnant

**Relative Safety Warnings** (Ask a Doctor or Pharmacist Before Use)
- Have history of liver disease; Take potentially interacting medication; Take prescription lipid-lowering medication; Consume large quantities of grapefruit juice

**Benefit Guidelines**
- Age; No heart disease; LDL-C or Total-C in range; No stroke; HDL-C in range; No diabetes; CHD risk factors; Non-fasting cholesterol values

**OBJECTIVES**

1. Using either the LDL-C or the Total-C label paradigm as eligibility criteria, evaluate participants’ ability to make self-assessment decisions that are consistent with the label and appropriate purchase decisions. Participants’ self-assessment and purchase decisions were compared to their Eligibility Assessment to determine if their self-assessment decisions and their purchase decisions were correct.

2. To provide insight regarding participants’ reasoning and factors considered when making self-assessment and purchase decisions.

**Questionnaire/EDC Innovations**

A detailed questionnaire was used to understand behaviors associated with self-assessment or purchase decisions that were not consistent with the label directions. The interview contained numerous ‘skip patterns’ such that the response to one question could lead to up to eight different pathways. Based on the responses, these in turn could lead back to different questions in the questionnaire. Complex algorithms within the database determined the participant’s eligibility and asked probe questions based on the participant’s responses to the SA and PD questions.
1. Self-Assessment Decision (See figure 1)

After the participant indicated that they had completed the review of the product, the following self-assessment question was asked,

“Based on this label, is this product appropriate for you to use right now or not?”

In this segment, it was possible for participants to request a cholesterol test, ask for clarification regarding potentially interacting medications, ask to talk to a pharmacist, or ask to talk to a doctor. Under certain pre-defined circumstances the self-assessment question could be asked again.

2. Purchase Decision (see figure 1)

After the participant made a self-assessment decision, they were asked the following question to make a purchase decision,

“Would you like to pay for this right now for your own use or put it back in the display?”

In this segment, it was possible for participants to request a cholesterol test, ask for clarification regarding potentially interacting medications, ask to talk to a pharmacist, or ask to talk to a doctor. Under certain pre-defined circumstances the purchase decision question could be asked again.

At this point, regardless of additional information obtained, under no circumstance was the self-assessment question asked again as this would create bias.

If the participant decided to buy the product, they were asked the following open-ended question “After you buy this product, is there anything that you plan to do before you start using it?” This provided a better understanding of the participant’s intended behavior before taking the first dose of medication, including identifying the participants who still intended to talk to their doctor.

3. Questions from the Participants

Since participants were not able to consult with their personal physician or pharmacist in this study, it was important to simulate the type of pharmacist interaction a potential consumer would have in a real life purchase situation. The investigators were trained to answer questions that a pharmacist would be able to answer. The participants received answers to these general questions if they asked the questions any time prior to making their final purchase decision.

4. Eligibility Assessment (see figure 1)

The participants’ self-reported medical history as it related to the label was collected at this
point in the study in order to determine if a participant was eligible to use the product. These questions were scripted on the electronic Case Report Form (eCRF).

Figure 1: SELECT Question Flow

<table>
<thead>
<tr>
<th>Questions asked to all participants</th>
<th>Questions asked to specific participants based on answers to key SA and PD questions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SA: Self-Assessment Decision</strong></td>
<td><em>Among purchasers</em>探查：他们在使用前还会做什么？</td>
</tr>
<tr>
<td><em>(Participant can request cholesterol test or ask questions on meds and then be re-asked SA)</em></td>
<td></td>
</tr>
<tr>
<td><strong>PD: Purchase Decision</strong></td>
<td><em>Among non-purchasers</em>探查：为什么他们不会购买？</td>
</tr>
<tr>
<td><em>(Participant can request cholesterol test or ask questions on meds and then be re-asked PD)</em></td>
<td></td>
</tr>
<tr>
<td><strong>EA: Eligibility Assessment</strong></td>
<td><em>Among those who mention Dr. during SA or PD questioning</em>探查：特定问题会问Dr.</td>
</tr>
<tr>
<td><em>to collect all medical and personal factors listed on the label</em></td>
<td><em>Among ‘no’ self-assessors</em>列表自我评估不合格，基于对标签的理解</td>
</tr>
<tr>
<td><strong>Additional questions of interest</strong></td>
<td>*Among ‘yes’ self-assessors with 1 or more actual ineligibilities from EA:*探查：原因与EA不符</td>
</tr>
<tr>
<td><em>Level of interactions with own Dr.</em></td>
<td><em>Probe: reasons for discrepancies</em></td>
</tr>
<tr>
<td><em>Why not currently on cholesterol Rx</em></td>
<td></td>
</tr>
<tr>
<td><em>Health and Rx insurance</em></td>
<td><em>Among buyers with 1 or more self-assessed ineligibilities</em>探查：原因想买尽管已知不合格</td>
</tr>
<tr>
<td><em>Rapid Estimate of Adult Literacy in Medicine (REALM) test</em></td>
<td><em>Probe: reasons want to buy despite known ineligibilities</em></td>
</tr>
<tr>
<td><em>Education and Income</em></td>
<td></td>
</tr>
</tbody>
</table>

SA = Self-Assessment
PD = Purchase

© SELF CARE NOVEMBER 2010

Accepted for publication 26 November 2010
5. Situations Requiring Probe Questions

Based on the participants’ eligibility, questions were asked to probe these situations as they related to the self-assessment and purchase decisions:

- Discrepancy between self-assessment determination and Eligibility Assessment, i.e., participant stated that they meet the label requirements but the Eligibility Assessment indicated that they did not, for one or more characteristics.
- Discrepancy between self-assessment determination and purchase decision, i.e., participant stated that they do not meet the label requirements but they wished to purchase the product right now.
- Reasons that non-purchasers made their decision to not buy the product.

Data Management and Analysis Strategies

The majority of label eligibility errors made by SELECT participants were related to the benefits rather than the safety of the product. In order to understand consumers’ ability to comprehend the label and act appropriately, a detailed examination of the data was necessary. This was anticipated; hence, systems and tools were in place to allow the extensive open-ended data collected to be organized for analysis.

Specific probe or follow-up questions were asked to ensure the participants’ thoughts were fully explored. Verbatim responses were recorded in the database and were coded and classified into logical categories. In order to manage the collection and analysis of the data, various innovative data management and analysis strategies were employed.

Classification of Data

Various types of open-ended data were classified into concise categories with very specific guidelines for classification. For each type of open-ended data, there was a selection of categories. Each verbatim response could be classified with up to three codes if the participants’ open-ended response contained three important pieces of information.

For example, a participant may have responded, “I decided to purchase the product even though I have low cholesterol because both my parents have had heart attacks, I smoke, but I am planning on talking to my doctor first.” The following would have been the codes classified for this response, “Family history”; “Smoker”; “Talk to Doctor.” Each of these codes could be tabulated individually.

Mitigation of Unclear Participant Responses

Consumers do not always have the ability to verbalize their thoughts clearly or to follow questionnaire directions as written. However, consumers might still have well thought out and
appropriate reasons for their decisions. Therefore, there was a need to develop an adjudication process referred to as “mitigation” to accommodate for this imprecision in respondent communication. Multiple members of the analysis team participated in this process using pre-specified rules for the acceptability or non-acceptability of specific types of responses.

The responses to open-ended questions recorded on the eCRFs were reviewed for all participants who responded SA=Yes or PD=Yes but did not meet at least one label criterion. Three potentially mitigating factors included: a statement indicating that the participant intended to discuss MEVACOR® with his/her doctor; had other potentially mitigating factors; or had evidence of not understanding the SA question.

Because open-ended data were collected at multiple times during the interview, mitigation was done for the respondent based on the entirety of his/her data. A participant could have stated mitigating factors at multiple places during the interview and each participant’s data needed to be thoroughly reviewed in order to determine if mitigating factors existed. Fields in the database were set up so participants with mitigating factors could easily be tabulated.

For example, in the study approximately 70% of the participants made a correct SA decision. However, after mitigating the data, approximately 84% of the participants were placed in the correct category. For examples of mitigating responses, see Table 1.

Table 1

<table>
<thead>
<tr>
<th>Examples of Mitigating Responses for Participants that were “Too Young” to use the product:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age is Close</td>
</tr>
<tr>
<td>Talk to doctor (specific for this criterion)</td>
</tr>
<tr>
<td>Evidence of not understanding SA Question</td>
</tr>
<tr>
<td>Talk to doctor (general)</td>
</tr>
<tr>
<td>Told by doctor should be treated</td>
</tr>
</tbody>
</table>

Strategies for Analysis and Insight

Participant Profiles

Participant Profiles described and indexed key information for all participants who incorrectly self-assessed or incorrectly purchased MEVACOR®.

Participant Profiles were written for all participants that responded SA=Yes or PD=Yes and had at least one ineligibility criterion. A standard Participant Profile template was created in the database and an index was created electronically to organize the profiles according to the following attributes: factors related to the “Do Not Use” label elements; factors related to the “talk to your doctor before use label elements”; and factors related to label elements concerning persons who would not adequately benefit from the use of the product. A sample Participant Profile is shown in Figure 2.
Hierarchies

Through discussions with the FDA, it was determined that certain label criteria were deemed more important than others and needed to be prioritized. Thus, multiple hierarchies for label criteria were created, as shown in Table 2.
RESULTS

The SELECT study showed meaningful improvement in label compliant behaviour in women < 55 years of age and childbearing potential while performing similarly to CUSTOM regarding low CHD risk consumers.

Figure 3 is an example of how the correctness of participants’ self-assessment decisions could be displayed. Participants made a correct decision if they said “not appropriate for me” (SA=No) and had at least one reason for ineligibility, or if they said “appropriate for me” (SA=Yes) and had no ineligibilities. Participants who said SA=No but met all eligibility criteria were considered incorrect for self-assessment decision. Most of the data management and analysis strategies focused on understanding the participants that responded “appropriate for me” (SA=Yes), but had at least one reason for ineligibility.

Figure 3: Correctness of Self-Assessment Decision in Participants

<table>
<thead>
<tr>
<th>Label Criteria</th>
<th>Safety</th>
<th>Benefit</th>
<th>Combination Safety and Benefit</th>
<th>Benefit without Lipids</th>
<th>Expanded Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnant/Breast-Feeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>May Become Pregnant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interacting Medications</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipid Lowering Medications</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver Problem</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipid Values (LDL-C or Total-C)</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk Factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart Disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipid Lowering Medications</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Label Eligibility Criteria Included in Each Hierarchy
DISCUSSION

Demonstrating consumers’ ability to self-select appropriately for an asymptomatic, chronic condition, requires rigorous complex approaches to data collection, management, and analysis. In order to meet the challenge, the SELECT study team developed numerous innovative study design, data management, and analysis strategies. SELECT used an innovative approach to assessing consumer self-selection by realizing the thought processes of participants should be split into two separate and distinct entities: self-assessment and purchase decision. It is noteworthy that looking at self-selection in two parts (SA and PD) was critical but added substantial complexity to the data management and analysis. SA and PD needed to be compared to each other, as well as to the respondents’ eligibility assessment (EA), and this lead to analytic challenges.

During the paper-based pilot study it became apparent that experienced market research interviewers were unable to follow the complicated skip patterns and branching logic of the questionnaire. Further, the nurse investigators chosen for the SELECT would not have extensive market research experience enhancing the need for a computerized, scripted questionnaire with EDC. The development of the EDC system was extremely laborious. However, the system allowed the nurses to focus on the participant and following the correct procedures rather than determining the flow of the questionnaire and eligibility. This greatly enhanced the quality of the data collected and the flow of the interview.

One of the objectives of the SELECT study was to understand the consumer thought processes when making their self-assessment and purchase decisions. From the many years of testing MEVACOR™ for OTC suitability, it was apparent that many people intentionally made “incorrect” decisions by overriding the label eligibility criteria, and it was a key objective of SELECT to understand why. To achieve this objective, many open-ended questions were asked when consumers made decisions that would appear to be incorrect. These open-ended responses captured many of the reasons behind their decisions and show that there is a thought process that makes sense to them. Consumers are in fact interpreting the label with regard to their own personal histories.

In SELECT most of these decisions, in which the participant decided to “override” the label, were made based on benefit criteria, while only a few participants did so on safety criteria. This resulted in 100% correct decisions for absolute contraindications and over 90% correct decisions for relative contraindications for purchase decision. The advertising for the SELECT study targeted consumers who were concerned about cholesterol, many of these consumers have learned that they have high cholesterol and may be more apt to override the lipid values on the label and to try MEVACOR™. Furthermore, some participants said they would talk with their doctor about their ineligibility either before buying or before using the product. Participants felt they were still following the label when choosing to do this, since the label clearly stated, “Ask a doctor or pharmacist before using if...” for all label elements except for
Other reasons given that offer insight included “told by doctor I should be treated,” “I am close to (age, LDL-C, Total-C, HDL-C),” “I will get/check my cholesterol numbers before using,” and “I have a family history of heart disease.”

Other participants demonstrated clearly that they misunderstood the self-assessment question. A typical example of this occurred when a participant stated that they were appropriate for the product but that they did not want to buy the product. When asked why they decided not to buy the product, many responded that they did not meet an eligibility criterion, thus demonstrating that in fact they knew the product was not appropriate for them.

The additional complexities of the questionnaire and data management and analysis strategies, demonstrated that consumers often do act with knowledge even when deciding to “override” the label.

CONCLUSION

The data management and analysis strategies used for SELECT allowed for a “conversation-like” interview which delved deeply into reasons behind consumer decision-making and allowed for the data to be tabulated in an appropriate manner for an FDA submission. The data management and analysis strategies allowed the data to be tabulated in a structured and readily navigable manner to facilitate regulatory review. Although MEVACOR® is not yet on drugstore shelves, the lessons learned and innovations of SELECT can be applied to future studies and other innovative switch programs leading to increased consumer options for self-care.

Financial Support: All authors are employees of Merck & Co., Inc.
Declaration of Funding Interest: This study was funded in full by Merck & Co., Inc.
Correspondence to: Amy R. Replogle, M.S., Amy.Replogle@merck.com

REFERENCE