



# **PCSK9 Inhibitors for Treatment of High Cholesterol: Effectiveness, Value, and Value-Based Price Benchmarks**

## **Meeting Summary and Policy Recommendations**

**November 24, 2015**

**Completed by:**

**Institute for Clinical and Economic Review**



## About the New England CEPAC Process

During public meetings of the New England CEPAC, the Council deliberates and votes on key questions related to the systematic review of the clinical evidence, an economic analysis of the applications of the medical technologies or treatments under examination, and the supplementary information presented. Council members are selected for three year terms and are intentionally selected to represent a range of expertise and diverse perspectives. To maintain the objectivity of New England CEPAC and ground the conversation in the interpretation of the published evidence, members are not pre-selected based on the topic being addressed. Acknowledging that any judgment of evidence is strengthened by real-life clinical and patient perspectives, clinical representatives with expertise in the subject matter are recruited for each meeting topic and provide input to Council members before the meeting to help clarify their understanding of the interventions being analyzed in the evidence review. The same clinical experts serve as a resource to the Council during their deliberation, and they help form recommendations with the Council on ways the evidence can be applied to policy and practice.

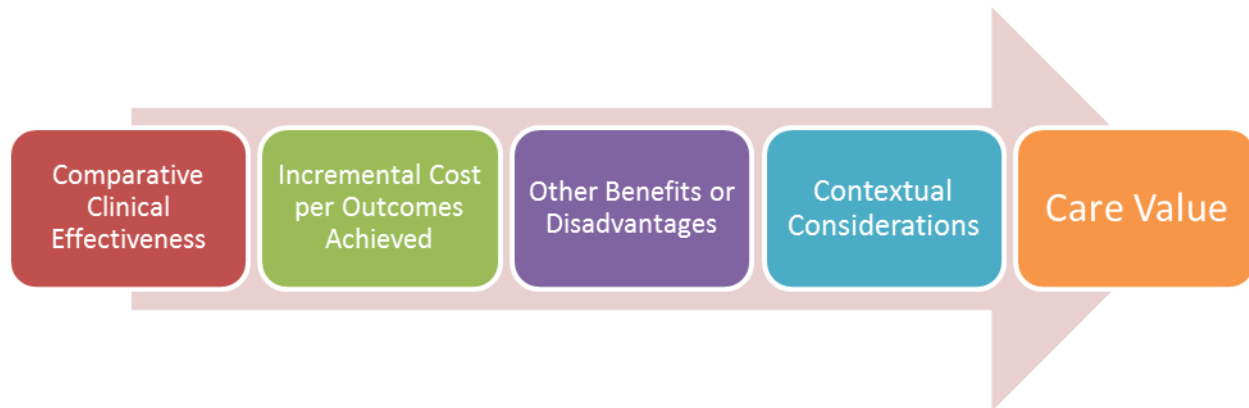
At each meeting, after the Council votes, a Policy Roundtable discussion is held with the Council, clinical experts, and representatives from provider groups, payers, and patient groups. This is intended to bring stakeholders into the discussion on how best to apply the evidence to guide patient education, clinical practice, and coverage and public policies. Participants on Policy Roundtables are selected for their expertise on the specific meeting topic, are different for each meeting, and do not vote on any questions.

At the October 27, 2015 meeting, the Council discussed issues regarding the application of the available evidence to help patients, providers, and payers address the important questions related to the management of high cholesterol. Following an evidence presentation and public comments, the Council voted on key questions concerning the clinical effectiveness and value of PCSK9 inhibitors alirocumab and evolocumab. These questions are developed by the ICER research team for each assessment, with input from the New England CEPAC Advisory Board to ensure that the questions are framed to address the issues that are most important in applying the evidence to support clinical practice and medical policy decisions. The voting results are presented in the section below, along with comments reflecting considerations mentioned by the Council members during the voting process.

In its deliberations and voting related to value, the Council made use of a value assessment framework with four different components of *care value*, a concept which represents the long-term perspective, at the individual patient level, on patient benefits and the incremental costs to achieve those benefits. The four components of care value are comparative clinical effectiveness, incremental cost per outcomes achieved, additional benefits or disadvantages, and contextual considerations regarding the illness or therapy (see Figure 1 on the following page).

Once they made an overall assessment of care value as low, intermediate, or high considering these four components, the New England CEPAC then explicitly considered the affordability of PCSK9 inhibitors in assessing *provisional* health system value as low, intermediate, or high (see Figure 2 on the next page, as well as the detailed explanations that follow below).

**Figure 1. Care Value Framework**



There are four elements to consider when deliberating on care value:

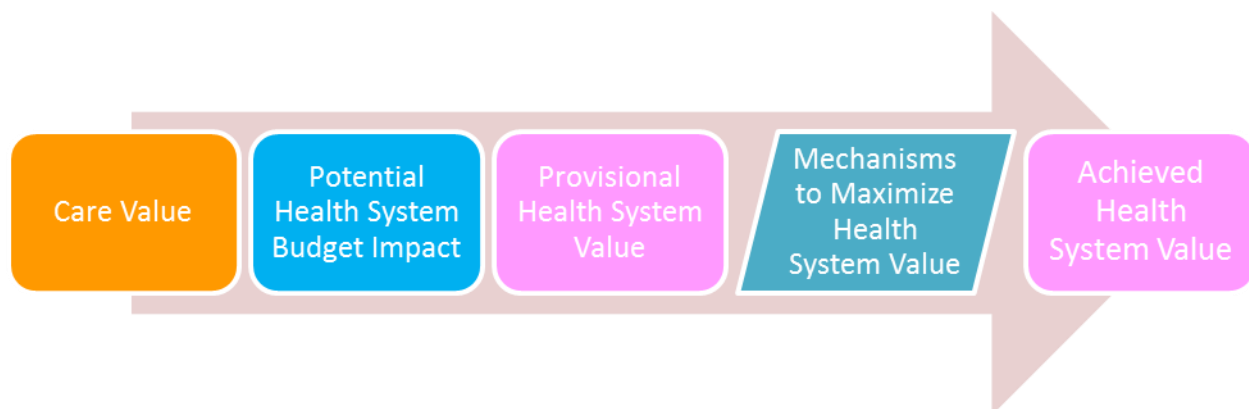
1. **Comparative clinical effectiveness** is a judgment of the overall difference in clinical outcomes between two interventions (or between an intervention and placebo), tempered by the level of certainty possible given the strengths and weaknesses of the body of evidence. The Council uses the ICER Evidence Rating Matrix as its conceptual framework for considering comparative clinical effectiveness.
2. **Incremental cost per outcomes achieved** is the average per-patient incremental cost of one intervention compared to another to achieve a desired “health gain,” such as an additional stroke prevented, case of cancer diagnosed, or gain of a year of life. Alternative interventions are compared in terms of cost per unit of effectiveness, and the resulting comparison is presented as a ratio: a “cost per outcome achieved.” Relative certainty in the cost and outcome estimates continues to be a consideration. As a measure of incremental costs per outcomes achieved, ICER follows common academic and World Health Organization (WHO) standards by using cost per quality-adjusted life years (QALYs) and adopting thresholds at \$100,000 per QALY and \$150,000 per QALY as guides to reasonable ratios of incremental costs per outcomes achieved.
3. **Other benefits or disadvantages** refers to any significant benefits or disadvantages offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. Examples of additional benefits include mechanisms of treatment delivery that require many fewer visits to the clinician’s office, treatments that reduce disparities across various patient groups, and new potential mechanisms of action for treating clinical conditions

that have demonstrated low rates of response to currently available therapies. Additional disadvantages could include increased burden of treatment on patients or their caregivers. For each intervention evaluated, it will be open to discussion whether additional benefits or disadvantages such as these are important enough to factor into the overall judgment of care value. There is no quantitative measure for additional benefits or disadvantages.

4. **Contextual considerations** include ethical, legal, or other issues (but not cost) that influence the relative priority of illnesses and interventions. Examples of contextual considerations include whether there are currently any existing treatments for the condition, whether the condition severely affects quality of life or not, and whether the condition affects priority populations. There is no quantitative measure for the role of contextual considerations in an overall judgment of care value.

In assessing provisional health system value, the Council was asked to vote whether interventions represent a “high,” “intermediate,” or “low” value.

**Figure 2. Health System Value Framework**



1. **Potential Health System Budget Impact** is the estimated *net* change in *total* health care costs over a 5-year time-frame.
2. **Provisional “Health System Value”** represents a judgment integrating consideration of the long-term care value of a new intervention with an analysis of its potential short-term budget impact if utilization is unmanaged. The Council votes reflect a judgement on the provisional health system value of an intervention.
3. **Mechanisms to Maximize Health System Value** is an action step, ideally supported by enhanced early dialogue among manufacturers, payers, and other stakeholders.
4. **Achieved Health System Value** is the real-world result of health care stakeholder efforts to maximize the value of a given intervention.

Usually, the care value and the provisional health care system value of an intervention or approach to care will align, whether it is “high,” “intermediate,” or “low.” For example, a treatment that is judged to represent high care value from the perspective of per-patient costs and benefits will almost always represent a high health system value as well. But health system value also takes into

consideration the short-term effects of the potential budget impact of a change in care across the entire population of patients. Rarely, when the additional per-patient costs for a new care option are multiplied by the number of potential patients treated, the short-term budget impact of a new intervention of intermediate or even high care value could be so substantial that the intervention would be “unaffordable” unless the health system severely restricts its use, delays or cancels other valuable care programs, or undermines access to affordable health insurance for all patients by sharply increasing health care premiums. Under these circumstances, unmanaged change to a new care option could cause significant harm across the entire health system, in the short-term possibly even outweighing the good provided by use of the new care option itself.

Provisional health system value builds upon the judgment of care value by integrating consideration of the potential short-term budget impact of a new intervention, a figure highly dependent upon an estimation of the potential uptake of the new drug across the entire population. In the ICER framework, the theoretical basis for the budget impact threshold is based on societal willingness to pay. This foundation rests upon the assumption that society would prefer health care costs to grow at a rate that does not exceed growth in the overall national economy. ICER has used estimates based on data from the World Bank, the Centers for Medicare & Medicaid Services (CMS), and other public sources to calculate a budget impact threshold for individual new drugs or devices that would identify those whose potential budget impact would contribute significantly to excessive health care cost growth.

It should be noted that if, after considering potential budget impact, a health intervention judged to have high care value receives a judgment of “low” provisional health system value from the Council, this does not imply that the health system should not adopt the intervention; rather, the vote indicates that policy makers should consider implementing mechanisms related to patient selection, step therapy, pricing, and/or financing to ensure that the short-term budget impact of a high care value intervention does not lead to more harm than good. New England CEPAC votes on provisional health system value will therefore serve an important function by highlighting situations when policymakers need to take action and work together to align care value with health system value.

## Comparative Clinical Effectiveness Voting Results

1. Is the evidence adequate to distinguish between the overall net health benefits of the PCSK9 inhibitors Praluent® and Repatha™, excluding use in homozygous familial hypercholesterolemia for which only Repatha has an indication?

*Council Vote:*  Yes (0%)  No (100%)

### ***Sub populations include:***

- Individuals with heterozygous familial hypercholesterolemia (HeFH) who are not at goal (LDL <160mg/dL)
- Individuals with a history of atherosclerotic cardiovascular disease who cannot take statins or who take statins but are not at goal (LDL < 70mg/dL)

### **For individuals with heterozygous familial hypercholesterolemia (HeFH) who are statin intolerant or who take statins but are not at goal (<160mg/dL):**

2. Is the evidence adequate to demonstrate that adding PCSK9 inhibitors to treatment improves net health benefits?

*Council Vote:*  Yes (58%)  No (42%)

**Comments:** Council members voting yes noted that their votes assumed that lower LDL-C is a sufficient indicator for improved outcomes. It was also noted that the higher risk in FH populations was an important consideration and that this vote is based only on evidence available at present. Members voting no suggested that while the early evidence looks promising, more data is needed before conclusions can be drawn. They also expressed concerns that lower LDL-C may not be a sufficient endpoint to indicate improved outcomes.

### **For individuals with a history of atherosclerotic cardiovascular disease who are statin intolerant:**

3. Is the evidence adequate to demonstrate that adding PCSK9 inhibitors to treatment improves net health benefits?

*Council Vote:*  Yes (33%)  No (67%)

**Comments:** CEPAC members voting no pointed primarily to the uncertainty around the LDL hypothesis (whether a lower LDL-C leads to improved outcomes) given that this population may not have risks as high as patients who have FH and therefore high cholesterol from birth. Uncertainty was also discussed surrounding possible harms of the drugs given that LDL-C levels as low as those produced by these drugs have not been seen before and may have unknown long-term consequences.

**For individuals with a history of atherosclerotic cardiovascular disease who take statins but are not at goal (LDL < 70mg/dL):**

4. Is the evidence adequate to demonstrate that adding PCSK9 inhibitors to treatment improves net health benefits?

*Council Vote:* 3 Yes (25%) 9 No (75%)

**Comments:** Similar to the previous question, Council members voting no cited a lack of evidence that lowering LDL-C below 70mg/dL ultimately improves outcomes. Without this evidence, many Council members felt unable to conclusively vote that PCSK9 inhibitors improve net health benefit for this population. Council members voting yes noted the LDL is a central mechanism of disease, and efforts should be taken to lower it when possible.

## Care Value Voting Results

**For individuals with heterozygous familial hypercholesterolemia (HeFH) who are statin intolerant or who take statins but are not at goal (LDL <160mg/dL):**

5. Given the available evidence, what is the *care value* of adding **PCSK9 inhibitors vs. no additional treatment**?

*Council Vote:* 0 High (0%) 8 Intermediate (67%) 4 Low (33%)

**Comments:** A majority of the council found PCSK9 inhibitors to have an intermediate care value for patients with HeFH. Members of the Council voting for an intermediate care value acknowledged the high incremental cost-effectiveness ratios but were persuaded not to vote “low” value because of the perceived increased risk and limited treatment options for patients with FH in whom statins have not been sufficiently effective. It was suggested that PCSK9 inhibitors help to fill a critical unmet need for this population. Members voting for a low value were persuaded by the high cost-effectiveness ratios in light of the residual uncertainty about clinical benefits.

**For individuals with a history of atherosclerotic cardiovascular disease who are statin intolerant:**

6. Given the available evidence, what is the *care value* of adding **PCSK9 inhibitors vs. no additional treatment**?

*Council Vote:* 0 High (0%) 5 Intermediate (42%) 7 Low (58%)

**Comments:** CEPAC found PCSK9 inhibitors to present a low to intermediate care value for this population. Members felt that this population is not at as high of a risk as those with FH.

**For individuals with a history of atherosclerotic cardiovascular disease who take statins but are not at goal (LDL < 70mg/dL):**

7. Given the available evidence, what is the *care value* of adding **PCSK9 inhibitors vs. no additional treatment**?

Council Vote: 0 High (0%) 2 Intermediate (17%) 10 Low (83%)

**Comments:** Rationale for a majority “low” vote was similar to that for the previous question; council members also noted that this population has several alternative treatment options at their disposal.

**For the combined population of all patients in these groups**

8. Given the available evidence, what is the *care value* of adding **PCSK9 inhibitors vs. no additional treatment**?

Council Vote: 0 High (0%) 3 Intermediate (25%) 9 Low (75%)

**Comments:** Council members questioned the utility of lumping all patient populations together into a single group; however, it was recognized that in real-world situations, policy makers may not be able to tease out each sub-population.

## Provisional Health System Value Voting Results

**For individuals with heterozygous familial hypercholesterolemia (HeFH) who are statin intolerant or who take statins but are not at goal (LDL <160mg/dL):**

9. Given the available evidence, what is the provisional *health system value* of adding **PCSK9 inhibitors vs. no additional treatment**?

Council Vote: 0 High (100%) 2 Intermediate (17%) 10 Low (83%)

**Comment:** Council members voting for a low provisional health system value emphasized the need to consider the high short-term costs from a societal perspective. Council members emphasized that paying high prices for PCSK9 inhibitors will create the need for cuts in other areas.

**For Individuals with a history of atherosclerotic cardiovascular disease who are statin intolerant:**

10. Given the available evidence, what is the provisional *health system value* of adding **PCSK9 inhibitors vs. no additional treatment**?

Council Vote: 0 High (100%) 0 Intermediate (0%) 12 Low (100%)



**For Individuals with a history of atherosclerotic cardiovascular disease who take statins but are not at goal (LDL < 70mg/dL):**

11. Given the available evidence, what is the provisional *health system value* of adding **PCSK9 inhibitors vs. no additional treatment**?

Council Vote:  High (100%)  Intermediate (0%)  Low (100%)

**For the combined population of all patients in these groups**

12. Given the available evidence, what is the provisional *health system value* of adding **PCSK9 inhibitors vs. no additional treatment**?

Council Vote:  High (100%)  Intermediate (0%)  Low (100%)

# Roundtable Discussion and Key Policy Recommendations

Following New England CEPAC’s deliberation on the evidence and subsequent voting, ICER convened a Policy Roundtable intended to bring stakeholders into the discussion on how best to apply the evidence to guide patient education, clinical practice, and coverage policies. The Roundtable was composed of clinical experts, a patient, a representative from a national pharmacy benefit management company, a regional insurer, a purchaser of state based health insurance, and a representative from an academic medical center. Participants on Policy Roundtables are selected for their expertise or experience related to the specific meeting topic, are different for each meeting, and do not vote on any questions. The Policy Roundtable participants are displayed below.

**Table 23. Policy Roundtable Participants**

Policy Roundtable Participants
<p><b>Leslie Fish, PharmD</b> Vice President of Pharmacy, Fallon Health</p>
<p><b>Jonathan Karas</b> Patient Representative</p>
<p><b>Dolores Mitchell,</b> Executive Director, Group Insurance Commission</p>
<p><b>Patrick O’Gara, MD</b> Senior Physician, Brigham and Women’s Hospital Professor of Medicine, Harvard Medical School</p>
<p><b>William Shrank, MD, MSHS</b> Senior Vice President, Chief Scientific Officer and Chief Medical Officer, Provider Innovation and Analytics, CVS Health</p>
<p><b>Thomas Siepka, RPh, MS FACHE</b> Vice President, System Pharmacy and Outreach, Dartmouth Hitchcock</p>
<p><b>Paul Thompson, MD</b> Chief of Cardiology, Hartford Hospital Professor of Medicine, University of Connecticut</p>

The Roundtable discussion explored the implications of New England CEPAC’s votes for clinical practice and medical policy, considered real life issues critical to developing best practice recommendations in this area, and identified potential avenues for applying the evidence to improve patient care. The main themes and recommended best practices from the conversation are summarized below. The Policy Roundtable discussion reflected multiple perspectives and opinions; therefore, none of the recommendations below should be taken as a consensus view held by all participants.

**1. Professional societies should take prompt action to update clinical guidance, including a likely need to return to treatment goals based on target LDL-C levels.**

Members of the Roundtable highlighted the need to link the dialogue surrounding PCSK9 inhibitors to a broader discussion about clinical guidelines made by professional societies. Physicians rely on clinical guidelines when making decisions about a particular diagnostic or therapeutic procedure. Guidelines are intended to direct everyday clinical decision-making and reinforce the practice of evidence based medicine. Roundtable participants noted that the emergence of PCSK9 inhibitors has unveiled an urgent need for action from professional societies. As mentioned earlier in this report, guidelines for the treatment of cholesterol have changed in recent years. In 2013, the ACC/AHA released a guideline that moved away from recommending specific LDL-C levels as treatment targets.<sup>5</sup> While both the 2013 guideline and previous guidelines include strong recommendations for use of statin therapy to treat individuals with cardiovascular disease, the updated guideline does not recommend specific LDL-C targets. This guideline was developed when little clinical evidence was available for treatment with PCSK9 inhibitors. Clinical participants on the Roundtable voiced that LDL-C goals serve as a mechanism to measure patient progress.

Without specific treatment goals, clinicians may face challenges when prescribing statin therapy as a preferred treatment. They may feel pressured to prescribe PCSK9 inhibitors to yield lower LDL-C levels despite a lack of evidence supporting the hypothesis that lower LDL-C leads to improved outcomes. An updated guideline that stratifies patients by their cardiovascular risk, includes treatment goals based on target LDL-C levels, and titrates medication use to reach a specified target would provide clinicians with a basis for discussion when examining treatment options with patients. In order to remain relevant and effective within the context of a changed treatment landscape, professional societies should produce updated guidelines that recommend specific LDL-C targets based on patient characteristics.

**2. Payers should use prior authorization to enhance health system value by limiting treatment to patients for whom extended trials of high-dose statins combined with ezetimibe have been unsuccessful.**

Due to the high cost of PCSK9 inhibitors, payers will likely administer utilization management techniques to control aggregate health care costs. Specifically, prior authorization and step therapy are used to stratify patients by risk and previous treatment in order to ensure that coverage policies align with prudent clinical practice options. These coverage policies typically require patients to first try a lower-cost, evidence based therapy to achieve a clinical goal. If a patient is unable to achieve a goal with a specified therapy, a physician may escalate a patient to a more intensive and costly option.

For high cost drugs, prior authorization criteria are generally based on an FDA indication, and treatment is limited to patients for whom the evidence demonstrates greatest benefit. In addition

to the FDA indications, PCSK9 inhibitors will likely be limited to patients whose LDL-C has not reached target levels after extended trials (likely 60-90 days) of high-dose statins combined with ezetimibe. Clinical expert participants on the Roundtable felt that it was practical and reasonable for patients to fail at least 2 statins, with one at the lowest dose, prior to use of PCSK9 inhibitors. Statin non-adherence was also raised as a point of concern; one clinical expert expressed that providers do not always know when a patient is taking statins as prescribed. Another participant expressed that as part of coverage policies, payers may want to consider using results of lab tests to demonstrate that 2 statins have been tried. If executed appropriately, these measures will enhance the health system value of PCSK9 inhibitors. As noted earlier, unless the current treatment guideline is updated, payers will likely face challenges when developing criteria and will be limited in their ability to administer these tools. Discussion also turned to managing use of PCSK9 inhibitors in key subpopulations as described below:

#### Patients with FH

There was consensus throughout the meeting that there is a significant unmet need among patients with FH who are unable to lower cholesterol sufficiently using statins or ezetimibe. The patient participant on the Roundtable shared his experience in dealing with FH as a patient and as a parent of a child with FH, noting that some patients with FH must endure intensive and expensive treatment like apheresis. Other Roundtable participants mentioned that for those patients with clearly identified unmet need (e.g., homozygous FH or very high LDLs on treatment) the discussed criteria could be relaxed. Roundtable participants also stated that identifying patients with FH can be difficult. The clinical experts acknowledged that LDL-C measures are most useful for understanding risk; specifically noting that they would consider a patient to have clinical FH if they presented with an LDL > 190 mg/dL without any treatment. Measures such as genetic testing were deemed unnecessary for most patients, as these tests can be costly and there are 1700 genetic mutations that can cause FH.

#### Primary Prevention and Off-Label Use

In the discussion of off-label use, there was general consensus that PCSK9 inhibitors should not be used for primary prevention or for patients with comorbidities such as diabetes; participants considered off-label use to be a slippery slope within the context of this discussion.

**3. Prior authorization criteria may need to require most patients who believe they are statin intolerant to be re-tried on statins.**

Many patients report adverse effects associated with statin therapy; however, the field lacks consensus on a definition of statin intolerance. Based on feedback from the clinical expert participants and a review of existing definitions, it may be considered reasonable by some to operationalize the recent National Lipid Association (NLA) definition of statin intolerance when making treatment decisions. In June 2014 National Lipid Association Expert Panel on Statin Intolerance suggested the following definition for statin intolerance:

Statin intolerance is a clinical syndrome characterized by the inability to tolerate at least 2 statins: one statin at the lowest starting daily dose AND another statin at any daily dose, due to either objectionable symptoms (real or perceived) or abnormal lab determinations, which are temporally related to statin treatment and reversible upon statin discontinuation, but reproducible by re-challenge with other known determinants being excluded (such as hypothyroidism, interacting drugs, concurrent illnesses, significant changes in physical activity or exercise, and underlying muscle disease). Specifically, the lowest starting statin daily dose, is defined as rosuvastatin 5 mg, atorvastatin 10 mg, simvastatin 10 mg, lovastatin 20 mg, pravastatin 40 mg, fluvastatin 40 mg, and pitavastatin 2 mg<sup>1</sup>.

This definition may prove useful in clinical practice, but it is important to note that there are limitations to understanding statin intolerance. The prevalence of true statin intolerance is uncertain and ‘perceived symptoms’ are not always related to statin therapy. One clinical expert participant shared that many people who think they have statin intolerance actually can tolerate the medications. Two studies referenced in this report examined statin intolerance; one found a 10% incidence of mild to moderate muscle symptoms for patients on high intensity statin therapy<sup>17</sup> and the second a 9.4% incidence of muscle symptoms in statin-naïve patients treated with atorvastatin 80 mg daily compared to a 4.6% incidence in patients randomized to placebo.<sup>18</sup>

Also of note, the precise measurement of statin intolerance is difficult. As noted earlier in our report, often statin intolerance is primarily associated with muscle pain, which can arise from a number of other causes, particularly in older individuals. This was echoed by one clinical expert participant of the Roundtable who conveyed that statin intolerance is primarily a clinical diagnosis; there is no genetic marker to identify it.

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<sup>1</sup> An assessment by the Statin Intolerance Panel: 2014 update  
John R. Guyton, MD, FNLA correspondence email, Harold E. Bays, MD, FNLA, Scott M. Grundy, MD, PhD, FNLA, Terry A. Jacobson, MD, FACP, FNLA Received: March 3, 2014; Accepted: March 4, 2014;

**4. Management of patients with possible statin intolerance and other complexities of decision-making regarding PCSK9 inhibitors suggest that it is reasonable to restrict prescribing of PCSK9 inhibitors to specialists in lipid management.**

Currently, there is variation in how payers define statin intolerance; it will likely take work to define the concept. One way to ensure that possible statin intolerance and other complexities are appropriately managed would be to limit prescribing authority of PCSK9 inhibitors to specialists in lipid management. This was emphasized during the Roundtable when one participant noted that it is difficult to account for grey areas when releasing a very expensive drug; even among specialists there is great variability in expertise. Given that cardiologists are likely to see the majority of the high risk patients it may be reasonable to restrict prescribing of PCSK9 inhibitors to specialists.

**5. If the pricing for PCSK9 inhibitors were to fall 50%-85% to a level that aligns with the benefit to patients and with a reasonable short term affordability, payers would likely consider lifting many elements of proposed prior authorization requirements.**

During the Policy Roundtable, there was a focused discussion on the price of PCSK9 inhibitors as it relates to other public health expenditures. One participant vocalized that other services are being starved to pay for these and other drugs. The participant included pointed statements towards the morality associated with prices charged for new treatments and society's willingness to pay. There was an urge for stakeholders to understand how to apply balance between the cost of care versus other services that must be financed such as public health, education, safety, and other public programs. When the pharmacy benefit management representative was asked about the price he responded that if PCSK9 inhibitors were priced lower, the conversation about cost and value would not be taking place.

The high cost of the pharmaceuticals was also noted by participants both on the payer and provider side when discussing the administrative burden associated with prior authorization and other utilization management techniques. These mechanisms are necessary to reduce the budgetary impact of PCSK9 inhibitors at the current price. However, Roundtable participants noted that if the drugs were priced near ICER's value-based price benchmark, the focus on utilization management, and perhaps the entire discussion surrounding the value and budgetary impact of PCSK9 inhibitors, would not be taking place. In the future, pharmaceutical companies should join a broader discussion with payers and other stakeholders about how the current approach to the pricing of drugs can change to help address the negative impact of rising health care costs on patients and on other important societal goals.

**6. Future research needs will be strongly influenced by the results of current clinical outcomes studies, but additional research in adherence and long-term safety will be important to guide practice and policy in the future.**

Discussion during the October 27, 2015 meeting highlighted the need for more information about efficacy and safety of PCSK9 inhibitors. It was evident that there is an unmet need among patients with FH, but evidence pertaining to other sub-populations is less clear. When voting on the evidence, the majority of the council concluded that there was not adequate evidence to demonstrate that PCSK9 inhibitors improve net health benefits in patients with a history of cardiovascular disease. In addition to general uncertainty around long-term effectiveness and safety, most Council members were unable to completely accept the so-called “LDL hypothesis”. This hypothesis assumes that any lowering of LDL cholesterol would also lower the risk of heart attacks and strokes. Council members were reluctant to embrace the hypothesis likely because this has been demonstrated for some drugs (statins, ezetimibe) but not for others (niacin, fibrates). It will be necessary to revisit the discussion surrounding the direct effects of PCSK9 inhibitors on rates of heart attack and stroke when results of ongoing trials are released in 2017.

There may also be a need to examine real world data related to difference in treatment adherence between PCSK9 inhibitors and statins. As noted earlier, it is difficult to measure treatment adherence among patients who have been prescribed statins. It remains unclear whether treatment adherence would improve if a patient were to switch from an oral statin to a less frequent, but injectable, PCSK9 inhibitor. PCSK9 inhibitor adherence was referenced during the evidence review in the context of clinical trial data. Some felt that there may be differences between adherence rates observed in RCTs versus those experienced by patients that are not participating in trials. Some argue rates of adherence found outside of clinical trials will most certainly be lower than those reported during clinical trials. Adherence rates for PCSK9 inhibitors versus statins will likely need to be studied further.

There appeared to be consensus among participants of the Roundtable that clinicians should try multiple statin options before seeking alternative treatments for patients with elevated LDL-C. There may be opportunity in this area to develop tools to help physicians educate patients about statin intolerance. One physician shared that patients are often afraid that any experienced muscle pain while taking statins will be permanent and therefore discontinue use of the medication. As direct to consumer marketing campaigns are executed for the new LDL-C lowering therapies, statin intolerance-related muscle pain will likely be used as means of attracting patients to PCSK9 inhibitors. In this environment, it is imperative that patients be equipped with accurate information pertaining to evidence based therapies in order to make well informed treatment decisions.