Panel Question 1: Clinical Trial Conduct Issues
The following clinical trial conduct issues were identified:
   a) Major Protocol Deviations
      o Early termination of the Alerts Clinical Study due to concerns of incomplete and unreliable ECG data
      o Adjudication of ST-depression/T wave change events as protocol-specified ST-elevation events
   b) Multiple look-back windows ranging from 7 days to 90 days from time of Guardian alarm to time of positive testing (ECG or stress test or biomarkers or angiography)
   c) Post-hoc change from single- to dual-ECG baseline for determination of new Q-waves
Please comment on whether or not these conduct issues individually and/or collectively affect the interpretation of the data, particularly pertaining to the effectiveness results. If so, how?

Panel Question 2: Effectiveness
The composite primary effectiveness results from the ALERTS Clinical Study are presented in the table below. Note that statistical significance was only reached using a 90-Day look-back window and dual baseline ECG analysis.

Composite Primary Effectiveness Endpoint Results		ECG Analysis Method					
		Single Baseline			Dual Baseline		
		Treatment Event Rate	Control Event Rate	Posterior Probability*	Treatment Event Rate	Control Event Rate	Posterior Probability*
Look-back Window	7-Day	3.8%	4.9%	0.7856	3.1%	4.7%	0.8833
	90-Day	3.8%	6.8%	0.9740	3.1%	6.5%	0.9908

* The significance threshold for the posterior probabilities of event reduction is 0.983 for the primary effectiveness endpoint.

In addition, 40% of the total treatment alarms were excluded from the PPV analysis measuring device's diagnostic performance for various reasons.

Given the above, and that the sponsor's proposed indication is to alert patients to "ST segment changes indicating acute coronary occlusion" please comment on the following;
   a) Does the endpoint assessing new Q waves on ECG adequately assess device effectiveness and is the dual baseline ECG approach for this endpoint reasonable?
   b) Is a 90-day look back window reasonable rather than a 7 day look back window for the time to door endpoint? Does the time to door endpoint adequately assess device effectiveness?
   c) Is it a concern when interpreting device effectiveness that 40% of alarms were excluded from the PPV analysis?

Panel Question 3: Safety
There were 31 system-related complication events in 30 subjects (3.3%) as defined for the primary safety endpoint. These data yielded a posterior probability of greater than 0.9999 that the proportion of subjects free from system-related complications is greater than 90%. Do these data provide a reasonable assurance of safety for the Guardian device?

Panel Question 4: Clinical Utility

The Guardian alarm in the ALERTS Study alerted subjects to seek medical attention when ST shifts were detected. Many of these alerts did result in a positive test for ischemia such as ECG changes, a positive stress test, positive cardiac biomarkers, or coronary disease present at angiography. However, some of these events were not positive for an ACS event by ACC/AHA definition criteria. Therefore, they may better be interpreted as silent ischemia, stress-induced ischemia or possibly other cardiac conditions that may cause ST shifts in the electrogram.

If the Guardian device detects and alarms for nonspecific cardiac events in addition to STEMI and NSTEMI ACS events, please comment on the clinical utility of the device. How do you envision it being used in patients?

Please comment specifically on the clinical benefit of reduction in time-to-door for patients without a STEMI or NSTEMI.

Panel Question 5: Indications for Use and Labeling

Based on the results of the IDE Study, the sponsor has proposed the following Indications for Use for the Guardian System:

> *The Guardian System is indicated to alert patients with prior acute coronary syndrome events to ST segment changes indicating acute coronary occlusion.*
>
> *Guardian System alerts reduce the overall time-to-door from a detected acute coronary occlusion until presentation at a medical facility independent of patient-recognized symptoms.*

The sponsor further proposes that that the Guardian System should be indicated for the following populations:
  a) Survivors of a previous Myocardial Infarction (STEMI or NSTEMI) also having one of the following, diabetes, renal insufficiency or a TIMI risk score of 3 or greater;
  b) Patients with any prior ACS event also having one of the following, diabetes, renal insufficiency or a TIMI risk score of 3 or greater; and
  c) Patients who have had or are scheduled for Coronary Bypass Surgery (CABG) also having one of the following, diabetes, renal insufficiency or a TIMI risk score of 3 or greater

Considering the secondary endpoint time-to-door clinical study results shown below, please discuss whether the proposed indications and intended populations are appropriate.

Time-to-Door Secondary Endpoint Results		Treatment Event Rate	Control Event Rate	Posterior Probability*
Look-back Window	7-Day	0.9%	1.8%	0.8614
	90-Day	0.9%	3.8%	0.9978

* The significance threshold for the posterior probabilities of event reduction is 0.975 for secondary effectiveness endpoints.

Please also comment on any concerns that you have with the proposed labeling for the device.

Panel Question 6: Post-Approval Study
Note: Discussion regarding a potential Post-Approval Study (PAS) should not be interpreted to mean that FDA has made a decision or is making a recommendation on the approvability of this PMA device. The presence of a post-approval study proposal or commitment does not in any way alter the requirements for premarket approval and a recommendation from the Panel on whether the risks outweigh the benefits. The premarket data must reach the threshold for providing reasonable assurance of safety and effectiveness before the device can be found approvable and any post-approval study could be considered. The consideration of the following question is predicated upon FDA finding the device approvable based upon the clinical premarket data.

Should the Guardian System be approved, please discuss whether a PAS would be of value and, if so, identify the outstanding questions that a PAS should be designed to answer.

Panel Question 7: Benefit & Risk
Putting trial design limitations and protocol deviations aside, do the effectiveness results and the totality of the data presented demonstrate that the Guardian device can accurately detect an ACS?

Given the device's safety profile, the totality of the evidence regarding effectiveness, and the clinical significance of these results, please comment on the benefit-risk profile of this device.

Panel Voting Questions
Following the panel discussion, CDRH will ask panel members to vote by ballot on the following questions:

> *The Guardian System is indicated to alert patients with prior acute coronary syndrome events to ST segment changes indicating acute coronary occlusion.*

> *Guardian System alerts reduce the overall time-to-door from a detected acute coronary occlusion until presentation at a medical facility independent of patient-recognized symptoms.*

The sponsor proposes that that the Guardian System should be indicated for the following populations:
   a) Survivors of a previous Myocardial Infarction (STEMI or NSTEMI) also having one of the following, diabetes, renal insufficiency or a TIMI risk score of 3 or greater;
   b) Patients with any prior ACS event also having one of the following, diabetes, renal insufficiency or a TIMI risk score of 3 or greater; and
   c) Patients who have had or are scheduled for Coronary Bypass Surgery (CABG) also having one of the following, diabetes, renal insufficiency or a TIMI risk score of 3 or greater

The following questions related to the approvability of the Guardian System. Please answer them based on your expertise, the information you reviewed in preparation for this meeting, and the information presented today:

- Voting Question 1: Is there reasonable assurance that the Guardian System is safe for the proposed indication for use (e.g. the device will not expose patients to an unreasonable or significant risk of illness or injury)?
- Voting Question 2: Is there reasonable assurance that the Guardian System is effective for the proposed indications for use?
- Voting Question 3: Do the benefits of the Guardian System for the proposed indications for use outweigh the risks of the Guardian System in patients who meet the criteria specified in the proposed indication?

Panel members will be asked to state how they answered each question and to explain their answers. If the panel member answered "no" to any question, he or she will be asked whether changes to labeling, restrictions on use, longer term follow-up, or other controls, would change his or her response

If the evidence provided is insufficient to allow for any of the determinations, the panel member should state this as the reason for answering "no." A description of any remedial studies or actions should be given.