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Duke Clinical Research Institute

From Thought Leadership to Clinical Practice

Quantifying Patient Preferences for Leadless Pacemakers

Prepared for Abbott Laboratories

[redacted]

Duke Clinical Research Institute, Duke University

Protocol

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[redacted]

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ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
BMI	Body mass index
CDRH	Center for Devices and Radiological Health
DHHS	Department of Health and Human Services
DCE	Discrete choice experiment
DCRI	Duke Clinical Research Institute
[redacted]	[redacted]
FDA	Food and Drug Administration
IDE	Investigational Device Exemption
MAR	Maximum-acceptable risk
OHRP	Office for Human Research Protections
[redacted]	[redacted]
PAG	Patient Advisory Group
PHI	Protected health information

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1. RESPONSIBLE PARTIES

The persons accountable for the design and implementation of the study protocol are listed in Table 1.

Table 1. Responsible Parties

Name	Title	Affiliation
[redacted]	[redacted]	Duke Clinical Research Institute Durham, NC

2. AMENDMENTS AND UPDATES

[redacted]

3. SYNOPSIS

Abbott's dual chamber leadless pacemaker (Leadless DR System) will offer an alternative to traditional dual chamber pacemakers among patients in need of dual-chamber rate-responsive bradycardia pacing therapy. Relative to conventional transvenous pacemakers, the Leadless DR System offers advantages including that it is totally self-contained and does not require separate components (leads and generator), thereby eliminating complications associated with transvenous pacemakers, for example pocket infection, lead fracture, and lead dislodgment. In addition, because the device is placed directly in the heart, it is not visible, and does not necessitate a lump and scar on the chest. However, its drawbacks relative to transvenous pacemakers include a potentially higher rate of complications like cardiac perforation, shorter battery life requiring more frequent replacement procedures, and less historical evidence about its safety and efficacy. Obtaining scientific information on the relative importance of the advantages and disadvantages of both types of pacemakers from the patient perspective will provide valuable information to regulators, providers, and patients.

A quantitative patient preference survey, using a discrete-choice experiment (DCE), will be developed, tested and fielded amongst individuals undergoing evaluation for a cardiac pacemaker at US clinical sites participating in Abbott's single-arm Investigational Device Exemption (IDE) trial for the Aveir dual-chamber leadless pacemaker. Adult patients who are referred to the study site for evaluation for a pacemaker or with a known indication for a de-novo pacemaker will be eligible to complete the patient-preference survey via online administration. All participants will complete the patient-preference survey before being approached about their potential interest in enrolling in the trial, and thus before they receive information about dual-chamber pacemakers and before they receive their pacemaker. [redacted]

The primary objective of the study is to quantify patient preferences for pacemaker device features. The secondary objective is to explore and characterize heterogeneity in patient preferences. [redacted]

4. RATIONALE FOR PATIENT PREFERENCY STUDY

Abbott's dual chamber leadless pacemaker will offer an alternative to traditional dual chamber pacemakers. The dual chamber leadless implantable pacemaker system, henceforth referred to as the "Leadless DR System", is a programmable system comprising two implanted leadless pacemaker devices that monitors and regulates the patient's heart rate by providing dual chamber rate-responsive bradycardia pacing therapy. Each leadless pacemaker device of a Leadless DR System is a self-contained pulse generator with built-in battery and electrodes that provide bradycardia therapy (sensing and pacing). As a leadless pacemaker, it does not require a pacing lead or its associated connector, nor does it require a pulse generator pocket. Instead, it is intended for direct implantation into the right ventricle and/or the right atrium.

The Leadless DR system eliminates complications associated with the leads, surgical pocket, and connectors required with a traditional dual chamber pacemaker (e.g. pocket infection, lead fracture, and lead dislodgment). Among leadless pacemaker systems, Abbott's system is unique in its ability to upgrade from a single to a dual chamber leadless configuration and the retrievability of the dual chamber system. The system also provides other important, non-clinical benefits. First, a leadless system may improve patient comfort because it is implanted directly in the heart; therefore, patients cannot feel the device. With a traditional pacemaker, some patients report pain or discomfort around the generator pocket.[i] Second, the leadless system eliminates the visible lump and scar at a traditional pacemaker's pectoral implant site. A leadless system also minimizes the need for activity restrictions after surgery, which are required following traditional pacemaker surgery to prevent lead dislodgement.

At the same time, the Leadless DR system presents certain disadvantages compared to a traditional pacemaker. First, although the Leadless system avoids risks associated with leads, pockets and connectors, it increases the risk of cardiac perforation during implantation. Second, the battery life of the two generators in a Leadless DR system will be shorter than the battery life of the generator in a traditional pacemaker, meaning the Leadless generators will have to be replaced more often than a traditional generator. The Leadless DR system is also a new technology, while traditional pacemakers have been commercially available for over 50 years. As such, there is less evidence available regarding physicians' and patients' experience with leadless systems, particularly in the longer term, compared to traditional pacemakers.

Conventional transvenous pacemakers provide significant improvements in physical functioning and outcomes in individuals with bradyarrhythmia. Although generally well tolerated, serious adverse events, including pocket-related issues (i.e. infections, hematomas, skin erosion, twiddler's syndrome) and lead-related issues (i.e. infections, fractures, connector issues, lead-induced tricuspid regurgitation, venous obstruction or thrombosis), pose

significant risks to patients, especially as these devices are frequently implanted in older and frail patients. Patients also report chest discomfort, physical restriction, and cosmetic concerns with traditional pacemakers.[ii, iii] The advent of leadless pacemakers offers patients the same benefits of conventional pacemakers, but without the visible scar and lump of a traditional pacemaker. Leadless pacemakers also offer the possibility of lower infection risks and less chest discomfort than traditional pacemakers, but possibly higher risks of complications during placement and extraction. Patients may place different levels of importance on the features of transvenous pacemakers and leadless pacemakers and their associated risks.

The Investigational Device Exemption (IDE) clinical trial that will be used to support market approval for the Leadless DR System is currently under development. It will be conducted in a global patient population with cardiovascular issues in which a pacemaker is indicated. The purpose of the global IDE study is to evaluate the clinical safety and efficacy of a dual chamber leadless pacemaker in patients indicated for dual chamber pacing.

Abbott is conducting a patient preference study among sites participating in the trial, in collaboration with the Duke Clinical Research Institute's (DCRI) [redacted], to quantify patient preferences pertaining to risks and features of conventional transvenous pacemakers and leadless pacemakers. The preference study is designed to elicit patient preferences for risks and features that vary between a dual chamber leadless pacemaker system and a dual chamber transvenous pacemaker system, to quantify their relative importance. The results of the patient preference study will inform technology development, support regulatory review, and potentially support Abbott dual-chamber leadless system product labeling to provide patients' perspectives on perceived advantages versus the risks of a leadless dual chamber system compared to a dual chamber transvenous pacemaker.

5. OBJECTIVES

5.1. Primary

The primary objective of the study is to quantify patient preferences for pacemaker device features. This includes estimates of the following:

- The conditional relative importance of device features included in the DCE
- Maximum percentage-point increases in the acceptable risk of complications or infection for an improvement in another attribute (for example: to get a preferred device type, to avoid discomfort, or to have a device with longer battery life)

- Other value equivalents (for example: What patients will give up in terms of years of battery life to move from a less-preferred device type to a more-preferred device type).
- Predicted choice probabilities for product profiles relative to specified comparators (i.e. the likelihood that an average respondent in the sample would choose a device profile with specific features, compared with a profile with different features)
- Mean ranking of select device features not included in the DCE (i.e. insertion procedure, visible lump of the generator, and scar on chest or groin)

5.2. Secondary

The secondary objectives of the study include the following:

- Use latent-class analysis to investigate whether there are classes of respondents with systematically different preferences and to investigate whether these differences in preferences are correlated with self-reported characteristics
- Test for differences in preferences in the following subgroups:
  - Participants who agreed (verbal or written) to be screened for participation in the IDE study compared with those who did not (see Section 7)
  - Gender
  - Age 65 years and older compared with those younger than 65 years
  - Body mass index (BMI) stratified by CDC definition of obesity (i.e. BMI≥ 30 versus >30)
  - History of major surgery (self-report) requiring a hospital stay of 2 or more nights in the past 5 years
  - Those with a sedentary lifestyle compared with those with a non-sedentary lifestyle where sedentary is defined as not exercising and non-sedentary is any amount of daily exercise.

6. METHODS

6.1. Study Design

In the DCE, respondents will be asked to select their preferred device alternative in a series of experimentally controlled pairs of hypothetical device alternatives. The alternatives will be defined in terms of specific levels of device features (attributes).

6.2. Attribute Selection

The DCRI team, which includes an expert clinical researcher and electrophysiologist, collaborated with Abbott and patient advisors (see Section 6.3) to select the study attributes. Selection of attributes and corresponding levels were informed by a scoping review of the published literature, scientific abstracts, and product information available from manufacturers of traditional and leadless pacemaker devices. Priority was given to treatment features thought to be of concern to patients and those that differentiate device alternatives.

The final attributes included in the DCE are listed in Table 2. They include pacemaker type (with leads or leadless), whether the device is removable (applies only to leadless pacemaker), length of battery life (i.e. replacement frequency), years since government approval, whether the device causes a mild level of discomfort for six months, risk of a complication requiring an operation and risk of infection requiring removal and antibiotics.

Table 2. Attribute Table

Attributes	Levels
Pacemaker type	• Pacemaker with leads • Leadless pacemaker removable • Leadless pacemaker not removable
Years of battery life	• 5 years • 8 years • 12 years • 15 years
Years since government approval	• 2 years • 10 years
Discomfort for 6 months	• No discomfort • Discomfort
Chance of complication requiring an operation	• 1% • 5% • 10% or 20%*
Risk of Infection requiring removal and antibiotics	• 1% • 5% • 10% or 20%*

*Scope test –each respondent will be assigned to either 10% or 20% as the highest risk level for infection and complication risks.

To gain insights about device features that are inextricably linked to a specific type of pacemaker and thereby not amenable to inclusion in a DCE, a ranking exercise will be used to elicit information on participants' relative concern for these device features. These features include the insertion procedure, where the device is implanted/resides in the body, the need for leads, whether the device is externally visible, and duration of activity restrictions after the device is implanted (Table 3). In a ranking exercise, it is important that all features included in the exercise are either positive or negative. Because the options pertaining to the insertion procedure, presence of leads and location are not clearly positive or negative, survey respondents are first asked to indicate which specific aspect of a pacemaker attribute is of greater concern for these three features (see first three rows of Table 3 below). For example,

regarding leads, respondents could choose “having a pacemaker without leads” or “having a pacemaker with leads”, as shown in Table 3. The chosen feature of greater concern is then transferred to the ranking exercise so that all features shown in the ranking exercise represent negative aspects of pacemakers from the patient perspective.

Table 3. Items in the Ranking Exercise

Insertion procedure • Pacemaker inserted through cut in skin on the chest • Pacemaker inserted using tube through the groin
Leads • Having a pacemaker with leads • Having a pacemaker without leads
Pacemaker location • Having a pacemaker placed under the skin on the chest • Having a pacemaker attached to the walls inside the heart
No heavy lifting is allowed for 6 weeks (versus limited activity for 2 weeks)
Scar on chest (versus no scar)
Lump on chest (versus no lump)

6.3. Patient Advisory Group

[redacted]

6.4. Pretesting the Survey Instrument

[redacted]

6.5. Survey Instrument

The final survey instrument includes the following sections:

- Screening questions to confirm eligibility (Section 7)
- Informed consent (Section 14.2)
- Patient-reported information on personal health and sociodemographic characteristics
- Attribute descriptions
- Tutorial on risks presented graphically
- Practice questions to familiarize respondents with the DCE question format
- Comprehension questions
- DCE questions
- Ranking exercise

The DCE survey is expected to take 25-30 minutes to complete. The survey will be administered online.

6.6. DCE Experimental Design

A D-efficient experimental design representing 48 choice questions was generated using design algorithms in SAS (Kuhfeld 2010).[iv] The design was divided into 6 blocks of 8 choice questions. Each participant will be randomized to complete one block of 8 questions. Participants also will be asked if they are willing to complete an additional 4 choice questions. To generate those choice questions, an additional D-efficient design was

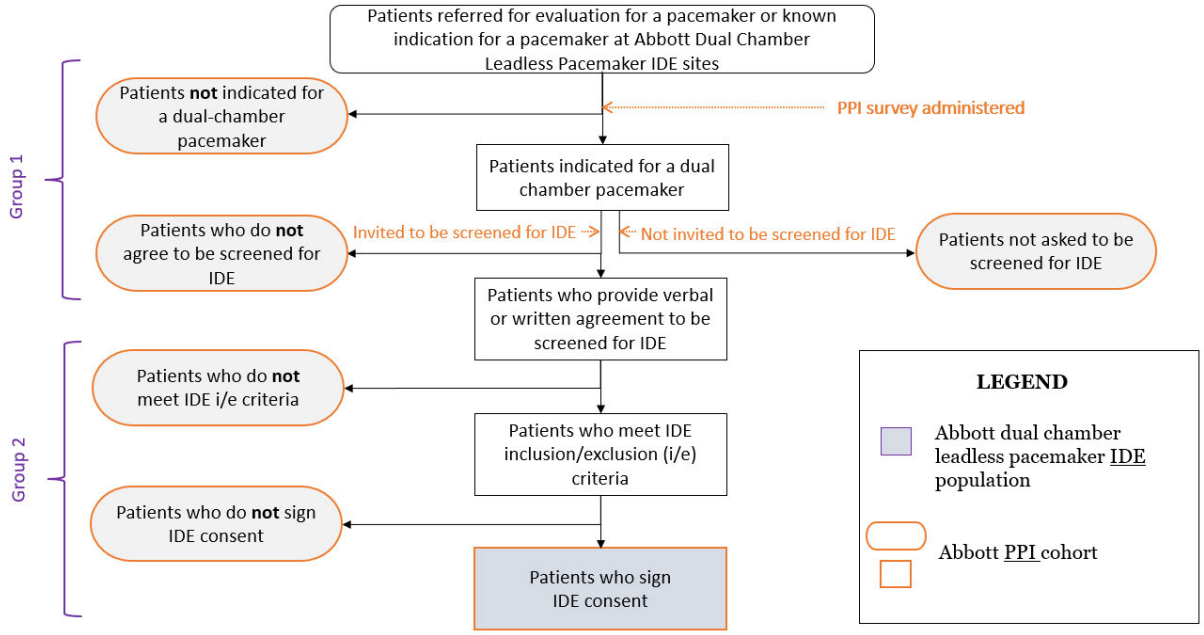
generated representing 24 choice questions, divided into 6 blocks of 4 choice questions each. Survey participants will be randomized to complete one block of 4 choice questions. Additional information about the experimental designs are included in the Statistical Analysis Plan from the DCRI PrefER Group.

6.7. Survey Programming

[redacted] Access to the survey will require entry of unique passcodes by participants.

7. Study Population and Recruitment

Figure 1. Flowchart for Recruitment in PPI and IDE Studies



Adult patients who are referred to Leadless DR System IDE clinical trial sites for evaluation for a pacemaker or with a known indication for a de-novo pacemaker will be eligible to complete the patient-preference survey via online administration (Figure 1). Only IDE study sites in the United States will participate.

To be eligible to complete a PPI survey, patients must meet the following eligibility criteria:

- Adult patients age 18 years or older
- Reside in the United States
- Able to read and speak English, consent to participate in the PPI survey
- Willing and able to use a tablet or computer to complete the survey

- Scheduled to undergo evaluation for a de-novo cardiac pacemaker at the study site (patient may or may not have a known indication for a pacemaker at the time they complete the survey)

To minimize selection bias, individuals will be asked and those who agree to participate will complete the patient-preference (i.e. PPI) survey before being approached about their potential interest in enrolling in the IDE trial. Thus, they will complete the patient-preference survey before they receive information about dual-chamber pacemakers and/or the Aveir DR IDE trial and before they receive their pacemaker (if they ultimately receive one).

This recruitment approach affords preference measurement among a broader set of patients representing people in the US who may soon have to make a real-world decision about choosing de-novo pacemaker. Additionally, it will allow for a comparison of patient preferences between two groups. The first group includes: 1) individuals who are not candidates for a dual-chamber pacemaker; 2) not asked to be screened for participation in the IDE trial; or 3) asked to be screened for the IDE trial and decline (verbal or written) (Group 1 in Figure 1). The second group includes all patients who agree (verbal or in writing) to be screened in the IDE trial, including individuals who are later found to be ineligible to participate and individuals who are eligible but ultimately choose do not consent and enroll in the ICE trial (Group 2 in Figure 1). Comparisons between these groups will test whether individuals who initially agree to consider participating in an investigational device trial are less risk averse than individuals who do not. For patients who verbally consent to be screened for participation in the IDE trial, a case report form will be used to record PPI passcodes, whether the patient met eligibility criteria, and whether the patient ultimately enrolled in the IDE trial. Thus, patients with passcodes in the trial data will be used to identify patients in Group 2. All other PPI respondents will be included in Group 1.

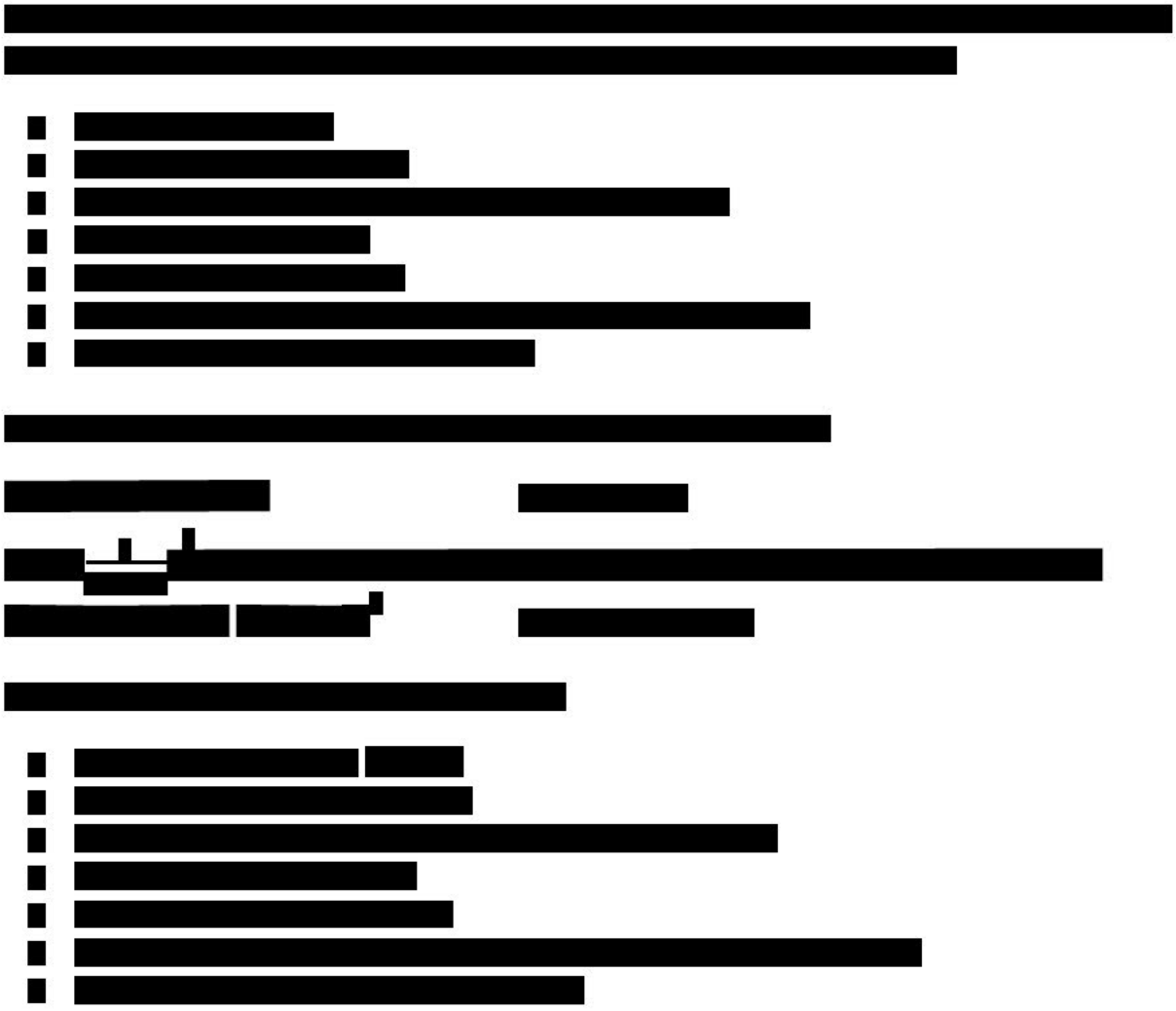
Abbott will take primary responsibility for working with operational teams and study sites to develop training materials for recruitment and assist with their dissemination to study sites.

8. Sample Size

The target sample size is a minimum of 300 patients from US IDE sites. For maximum statistical power, nearly equal enrollment in Group 1 and Group 2 (n=150 each) is ideal. However, as it is not known beforehand who will ultimately participate in the IDE trial and who will not, a specific number of individuals in each group cannot be guaranteed.

Formal sample size calculations for DCEs are not possible without priors for respondents' preferences. In addition, the information needed to identify all relevant preference weights can vary significantly across instruments and populations. [redacted]

[redacted]



The expected necessary sample size ranges between 83 (based on Orme (2010)) and 227 (based on Yang et al. (2015)). Thus, the proposed n=150 in each group should be adequate for aggregate patient-preference modeling. However, if it is possible to exceed the proposed sample size, estimated preference weights will be more precise and statistical power for comparisons will be greater.

9. Survey administration

DCRI will generate unique passcodes that will be provided to study sites recruiting patients to participate in the patient-preference study. Each passcode will include a prefix to indicate the study site followed by a code that will be unique for each potential participant.

Study sites will maintain crosswalks linking the passcodes and all patient identifiers. These crosswalks can also be used by sites to track which patients ultimately complete the PPI survey. Also, as described in Section 7, sites will enter information in the IDE trial case report

[1] Average design efficiency in Yang et al. (2015).

form for patients who verbally consent to participate in the IDE trial. This information will be used to differentiate among: 1) patients who verbally consented to be screened but did not meet inclusion/exclusion criteria; 2) patients who met eligibility criteria but declined to participate in the IDE trial; and 3) patients who ultimately enrolled in the trial and received a leadless pacemaker.

DCRI will send Abbott passcodes along with information indicating whether the survey was completed or partially completed, and Abbott will transfer the passcodes to study sites. Using this method, DCRI will not receive any patient protected health information (PHI).

Participants should complete the survey using a tablet or PC. Participants should be strongly discouraged from using a mobile phone to complete the survey.

10. Participant Compensation

As described in Section 9, study sites will maintain crosswalks linking passcodes for the patient preference survey with patient identifiers in order to track who has completed the survey and to pay any incentives that may be due to the participant. It is assumed that Abbott or study sites will process incentive payments.

11. Data Management

[redacted]

11.1. Survey Variables

The survey will collect:

- Years since diagnosis with heart problems
- Actions taken to manage heart problems
- Years since first pacemaker received
- Number of times pacemaker replaced
- Years since last pacemaker replacement
- Type of pacemaker
- Experience with pacemaker discomfort, complications, and infections
- Experience with major surgery
- Age
- Gender
- Height and weight (to compute BMI)
- Lifestyle activity level
- Marital status
- Race/ethnicity
- Source of health insurance
- Highest education completed
- Employment status
- Responses to comprehension questions
- Respondents' treatment choices in the DCE questions
- Respondents' ranking of items in the ranking exercise

The survey will not collect any protected health information (PHI).

11.2. Additional Variables

Additional participant-level variables not collected in the survey will be tracked by participating IDE study sites. These data will later be merged with survey data for analysis. Variables that will be transferred to Duke are limited to the following:

- Participants' passcodes to access the survey
- Whether the participant completed or partially completed the preference survey
- Whether the individual agreed to participate in the IDE clinical trial
- Study site identifier

11.3. Study Endpoints

Study endpoints will include a set of log-odds preference weights for all attribute levels included in the DCE. From these preference weights, the following endpoints will also be calculated:

- The conditional relative importance of device features included in the DCE
- Percentage-point increases in the maximum-acceptable risk (MAR) of complications or infection for an improvement in another attribute (for example: to get a preferred device type, to avoid discomfort, or a have a device with longer battery life)
- Other value equivalents (for example: What patients will give up in terms of years of battery life to move from a less-preferred device type to a more-preferred device type)
- Predicted choice probabilities for product profiles relative to specified comparators (i.e. the likelihood that an average respondent in the sample would choose a device profile with specific features, compared with a profile with different features)

Mean ranking of select device features not included in the DCE (i.e. insertion procedure, visible lump of the generator, and scar on chest or groin) will be estimated.

12. Analysis

Discrete-choice experiments generate complex cross-section/time-series choice data for each respondent. These data include a dichotomous dependent variable and are analyzed using advanced statistical methods. The basis for the analysis is the model specification assumed when generating the experimental design prior to survey implementation. That specification considers a categorical main-effects model for all study attributes. However, the specification assumed in the experimental design takes into account only statistical considerations. The statistical analysis of choices will provide a measure of the impact of changes in the attribute levels on the likelihood that treatments are selected by respondents, also referred to as attribute-level preference weights.

Respondents' reactions to the stimuli in DCE questions generally involve complex decision processes, and the final model specification must account for the pattern of choices as observed in the data set. The Statistical Analysis Plan from the DCRI [redacted] lays out the initial analyses that will be conducted to assess the quality of the data and describes exploratory analytic strategies that will inform the final model specification.

The design and study specifications have been developed to support a robust analysis and reporting that will include the following:

- Summary statistics of respondents' demographic characteristics, sociodemographic characteristics, experience with heart problems and treatment for heart problems

- An evaluation of data quality including respondents' performance on survey comprehension questions, time to complete the survey, response non-variance, and attribute dominance
- A scope test to evaluate whether respondents are sensitive to actual levels of risk presented
- Subgroup analysis for pre-specified subgroups
- An analysis of preference heterogeneity among respondents and associations with different demographic, clinical, and treatment characteristics
- Selection of the most appropriate preference model specification and reporting of the relative importance of device features included in the DCE, equivalence values (including MARs), and predicted choice probabilities
- Results of a ranking exercise for additional device features not included in the DCE

Additional, detailed descriptions of planned study analyses are included in the Statistical Analysis Plan from the DCRI [redacted].

13. Limitations of the Research Methods

Although the study will follow good survey practices to elicit truthful responses from participants, choices obtained with DCE questions do not have the same consequences as real-world treatment decisions.

The use of a fractional-factorial D-efficient design will not allow the estimation of individual-level preferences or higher-order interaction likely effects between attributes. This, however, is offset by the fact that such a design will allow us to ask respondents to complete a more reasonable number of DCE questions.

The study design can be limited by the task complexity and cognitive fatigue. However, to address, the study employs accepted best practice survey design strategies such as low reading level text, a risk tutorial, color, and graphics to engage respondents and the inclusion of comprehension questions to evaluate respondents who are sufficiently well prepared to provide valid preference data.

14. Protection of Human Subjects

14.1. Institutional Review Board/Independent Ethics Committee

The [redacted] will be the IRB of record for this study. The [redacted] has oversight of 10 convened IRBs, of which 8 meet monthly. The [redacted] holds a Federal-Wide Assurance [redacted]

[redacted] from the Department of Health and Human Services (DHHS) Office for Human Research Protections (OHRP) that allows us to review and approve human subject procedures through our IRB committees. These committees are also registered with OHRP for both DHHS and Food and Drug Administration-regulated research. The FWA requires IRB review for all studies conducted by Duke that involve human subjects, regardless of the funding source.

14.2. Informed Consent

An electronic consent document will be provided by site research staff via website link. The consent document will provide information about the study and instruct participants that they may contact their study doctor and/or the IRB should they have any questions about the study. Site research staff are responsible for providing the contact information along with the link to the consent form. Participants will be asked to read this information, and they will be given the option to agree or not agree to continue with the PPI survey.

14.3. Confidentiality

While it is impossible to guarantee perfect data security given the electronic nature of data collection, every effort to ensure security will be made and this will be explained to respondents as part of their informed consent. The online patient preference survey will not collect individually identifying information. The only information that will be collected that could be used to identify an individual is the passcode used to access the survey. However, the crosswalk between the passcode and personal identifying information will be maintained at IDE study sites. Information from study sites transmitted back to Duke will be limited to variables described in Section 11.2.

Further, to ensure data privacy, data will be collected on secure data systems by the survey vendor and stored and analyzed on secure Duke systems. No data will be intentionally disclosed to third parties.

All data and records will be kept confidential in accordance with institutional policies and HIPAA on subject privacy and that the Investigator and other site personnel will not use such data and records for any purpose other than those specified and use upon analysis for potential publication purposes. Any data analyzed for publication will remain de-identified.

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