APR 23 2001

SUMMARY OF SAFETY AND EFFECTIVENESS

I. General Information

Device Generic Name:	Dual Chamber Implantable Cardioverter Defibrillator System
Device Trade Name:	Medtronic® Model 7250 Jewel® AF Implantable Cardioverter Defibrillator System ("AF Only" indication) Medtronic Model 9465 InCheck™ Patient Assistant Medtronic Transvene® CS/SVC Model 6937A Lead
Applicant Name and Address:	Medtronic, Inc. 7000 Central Avenue, N.E. Minneapolis, MN 55432
PMA Number:	P980050/S1
Date of Panel Recommendation:	December 5, 2000
Date of Notice of Approval to Applicant:	APR 6 2001

NOTE: In this and future device labeling, "o" = New device feature or information; and "•" = Previously specified information

II. Indications and Usage

The Model 7250 Jewel® AF Implantable Cardioverter Defibrillator (ICD) System is intended to provide pacing, cardioversion, and defibrillation for treatment of patients with:

- symptomatic drug refractory atrial fibrillation and/or
- life-threatening ventricular tachyarrhythmias.

Notes: Associated with atrial tachyarrhythmia treatment:

1. Use of the ICD System has not been demonstrated to decrease the morbidity related to atrial tachyarrhythmias.
2. The effectiveness of high Frequency Burst pacing (A-50Hz Burst therapy) in terminating device classified atrial tachycardia (AT) was found to be 11.7%, and in terminating device classified atrial fibrillation (AF) was found to be 18.2%, in the patient population studied.

III. Device Description

The Model 7250 Jewel® AF Implantable Cardioverter Defibrillator System (hereafter referred to as the Jewel®AF) is a multiprogrammable implantable cardioverter defibrillator that monitors and regulates a patient's heart rate by providing atrial and ventricular arrhythmia therapy, and single or dual chamber bradycardia pacing.

- Therapies: The Jewel®AF is an implantable medical device that automatically detects and treats episodes of atrial fibrillation (AF), atrial tachycardia (AT), ventricular fibrillation (VF), ventricular tachycardia (VT), and bradycardia. When an arrhythmia is detected, the implantable device delivers defibrillation, cardioversion, antitachycardia pacing, or bradycardia pacing therapy.

- Leads: The Jewel® AF, along with the Medtronic Transvene® CS/SVC Model 6937A Lead, and other compatible commercially available pace/sense leads and cardioversion/defibrillation leads, constitutes the implantable portion of the system. The lead systems for the Jewel® AF system are implanted using either transvenous or transthoracic techniques. The Model 9790C Programmer, Model 9961 Software, the Model 9466 Patient Magnet, a telemetry programming head and the Medtronic Model 9465 InCheck™ Patient Assistant constitute the external portion of the system.

Jewel® AF

The nominal specifications of the Jewel® AF are listed below:

Table 1. Specifications

Model #	Defibrillation Lead Connection	Pacing Lead Connection	Dimensions WxHxD	Volume	Mass
7250G	2 DF-1 (3.2mm)	2 IS-1 bipolar (3.2mm)	76 x 55x16 mm	56 cc	95 g
7250H	3 DF-1 (3.2mm)	2 IS-1 bipolar (3.2mm)	79 x 55x16 mm	57 cc	96 g
Maximum Shock Energy		27 Joules			
Case Material		Titanium			
Header Materials		Polyurethane, silicone Rubber			
Power Supply		Lithium silver vanadium oxide (6.4V nominal)			

- Therapies: The Jewel® AF uses standard ICD therapies, e.g., defibrillation, cardioversion and antitachycardia pacing to treat VT and VF. The outer case of the Jewel® AF is an Active Can® that serves as one high voltage electrode. The Jewel® AF uses the ventricular VT/VF detection criteria (intervals and number of intervals to detect).

- Atrial Tachyarrhythmia Detection: The major difference between the Jewel® AF and previous Medtronic® ICDs is the capability for detection and treatment of atrial tachyarrhythmias. The Jewel® AF classifies atrial tachyarrhythmia episodes into one of two atrial detection zones: (1) AT or (2) AF. These zones may be programmed to overlap. Episodes falling in the overlap zone are differentiated as AT or AF through cycle length regularity. Therapies for atrial tachyarrhythmias include antitachycardia pacing, high frequency burst pacing and defibrillation shock therapies.

- Bradycardia Pacing: The Jewel® AF has dual chamber bradycardia pacing. The Jewel® AF does not have rate responsive pacing modes.
- Atrial Rate Stabilization: The Jewel® AF has atrial rate stabilization pacing (ARS) which is a rate smoothing function that gradually returns the heart rate to the programmed or intrinsic rate following a pacing pause, e.g., a premature atrial contraction.
- Mode Switching: The Jewel® AF has mode switching which switches the device from an atrial tracking mode to a non-tracking mode, thereby preventing tracking of high atrial rates in the ventricle.
- Ventricular Safety Pacing: The Jewel® AF has ventricular safety pacing (VSP) which prevents the inhibition of ventricular pacing due to oversensing of a non-ventricular event.

AT Detection: Tiered Therapy Programming Options

- Up to six automatic AT therapies are available for device-detected AT:

AT Therapies 1 – 2	Programmable to AntiTachycardia Pacing (or Skip)
AT Therapy 3	Programmable to 50 Hz Burst Pacing (or Skip)
AT Therapies 4 – 6	Programmable to A-Defib (or Skip)

- AT therapy programming sequence options:
  - Anti-tachycardia Pacing only
  - Anti-tachycardia Pacing → 50 Hz Burst Pacing
  - Anti-tachycardia Pacing → 50 Hz Burst Pacing → A-Defib
  - 50 Hz Burst Pacing only
  - 50 Hz Burst Pacing → A-Defib
  - A-Defib only

AF Detection: Tiered Therapy Programming Options

- Up to six automatic AF therapies are available for device-detected AF:

AF Therapy 1	Programmable to 50 Hz Burst Pacing (or Skip)
AT Therapies 2-6	Programmable to A-Defib (or Skip)

- AF therapy programming sequence options:
  - 50 Hz Burst Pacing only
  - 50 Hz Burst Pacing → A-Defib

- A-Defib only

Model 9961 Application Software

The Model 9961 (Jewel® AF) software contains the programmer application for the Jewel® AF system. It is used with the commercially available Model 9790C Programmer to program the Jewel® AF. The Model 9961 Application Software runs on the commercially available Models 9886, 9891, and 9952 baseline software.

Model 6937A Transvene® CS/SVC Lead

The Medtronic Transvene® CS/SVC Model 6937A Lead is a modified Model 6937 SVC lead. The modifications include a shorter defibrillation coil and the addition of urethane tubing overlay to increase lead body stiffness. These modifications allow placement in the Coronary Sinus (CS) in addition to the Superior Vena Cava (SVC).

Medtronic Model 9465 InCheck™ Patient Assistant

The Medtronic Model 9465 InCheck™ Patient Assistant is a hand-held, battery-operated communicator that may be prescribed for a patient by their physician for use in enabling pre-programmed implantable devices (Model 7250 Jewel AF) capable of detecting and/or treating atrial arrhythmias. The Model 9465 is a downsized version of the Model 9464 Patient Activator.

Commercially Available System Components

The commercially available components used as part of the Jewel® AF System include endocardial or epicardial pace/sense and cardioversion/defibrillation leads, the Model 9790C Programmer, and the Models 9886, 9891, 9952 baseline software. The Jewel® AF System is compatible with commercially available implant support instruments and accessories used with previous Medtronic ICDs, including the Model 5358 Defibrillation Implant Support Device (DISD), Model 5705/5426 Active Can Emulator and Header (ACE) implant support device, Models 54520 and 55421 Patient Cables, Model 5429 Cable, the Model 5311 Pacing System Analyzer, and the Model 9466 Patient Magnet.

IV. Contraindications

Do not use the Jewel® AF System in:

- Patients whose tachyarrhythmias may have transient or reversible causes, such as:
  - acute myocardial infarction
  - digitalis intoxication
  - drowning
  - electrocution
  - electrolyte imbalance
  - hypoxia
  - sepsis
- Patients with incessant VF, VT, or chronic atrial tachyarrhythmias

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- Patients who have a unipolar pacemaker
- Patients whose primary disorder is bradyarrhythmias

V. Warnings and Precautions

- Anti-Coagulation – Use of the ICD System should not change the application of established anticoagulation protocols.
- Resuscitation availability. Do not perform ICD testing unless an external defibrillator and medical personnel skilled in cardiopulmonary resuscitation (CPR) are readily available.
- Lead system. Do not use another manufacturer's lead system without demonstrated compatibility as undersensing of cardiac activity and failure to deliver necessary therapy could result.
- Electrical isolation during implantation. Do not permit the patient to contact grounded equipment which could produce hazardous leakage current during implantation. Resulting arrhythmia induction could result in the patient's death.
- Avoiding shock during handling. Program the ICD to OFF during surgical implant and explant, or post-mortem procedures, because the ICD can deliver a serious shock if you touch the defibrillation terminals while the ICD is charged.
- Suspension of ventricular pacing. There is no back-up bradycardia pacing in the ventricle during atrial antitachycardia pacing (ATP).
- Occurrence of stroke. Following an ischemic or cerebrovascular accident, disable atrial defibrillation therapies until the patient has stabilized.

Sterilization, Storage, and Handling

- Resterilization. Do not resterilize and re-implant an explanted ICD.
- "Use Before" Date. Do not implant the ICD after the "Use Before" date, because the battery's longevity could be reduced.
- If package is damaged. Do not use the ICD or accessories if the packaging is wet, punctured, opened, or damaged, because the integrity of the sterile packaging might be compromised. Return the ICD to Medtronic.
- ICD storage. Store the ICD in a clean area, away from magnets, kits containing magnets, and sources of electromagnetic interference to avoid ICD damage. Store and transport the ICD between -18 to 55 °C (0 to 131 °F), because temperatures outside this range could damage the ICD.
- Equilibration. Allow the ICD to reach room temperature before programming or implanting the ICD, because rapid temperature changes could affect initial ICD function.

Implantation and ICD Programming

- Infrequent charging of the high voltage capacitors could extend the ICD charge time. Program the ICD to condition the capacitors automatically, or perform a test charge

to form the capacitors manually every six months (if the ICD has not charged to its maximum energy).

- Use only Medtronic programmers, application software, and accessories to communicate with the ICD.
- Positioning a magnet or the programming head over the ICD suspends detection and treatment. The magnet does not alter bradycardia therapy.
- End of Life (EOL). Replace the ICD when the programmer displays an EOL message and a battery voltage of 4.50 volts or less. Immediate replacement is recommended if the programmer displays a Charge Circuit Timeout or Charge Circuit Inactive message.
- Program ICD parameters such as sensitivity thresholds and detection intervals according to the recommendations in the technical manual.
- Program the first atrial defibrillation therapy to two times the atrial defibrillation threshold (aDFT), or the maximum output.
  Note: Limit the number of automatic atrial defibrillation therapies in patients who experience frequent episodes of atrial tachyarrhythmias.

o Suspension of ventricular pacing. There is no backup bradycardia pacing in the ventricle during atrial antitachycardia pacing (ATP). The "Initial # Pulses" parameter should not be set to large values for ventricular pace dependent patients.

Lead Evaluation and Lead Connection

- For lead resterilization, use ethylene oxide only. Do not resterilize more than one time.
- Do not tie a ligature directly to the lead body, tie it too tightly, or otherwise create excessive strain at the insertion site as this can damage the lead.
- Do not immerse leads in mineral oil, silicone oil, or any other liquid.
- Do not grip the lead with surgical instruments.
- Do not use excessive force or surgical instruments to insert a stylet into a lead.
- Use the same polarity evaluated during testing when connecting the leads to the AMD to ensure defibrillation effectiveness.
- Do not use ventricular transvenous leads in patients with tricuspid valve disease or a mechanical prosthetic tricuspid valve. Use with caution in patients with a bioprosthetic valve.
- Use the correct suture sleeve (when needed) for each lead to immobilize the lead and protect it against damage from ligatures.
- Ensure that the defibrillation lead impedance is greater than 10 ohms. An impedance below 10 ohms could damage the ICD.
- Do not kink the leads. Kinking leads can cause additional stress on the leads, possibly resulting in lead fracture.
- Do not suture directly over the lead body as this may cause structural damage. Use the lead anchoring sleeve to secure the lead lateral to the venous entry site.

- Lead or Active Can® electrodes in electrical contact during a high voltage therapy could cause current to bypass the heart, possibly damaging the ICD and leads. While the ICD is connected to the leads, make sure that no therapeutic electrodes, stylets, or guidewires are touching or connected by an accessory low impedance conductive pathway. Move objects made from conductive materials (e.g., an implanted guidewire) well away from all electrodes before a high voltage shock is delivered.
- If a pacing lead is abandoned rather than removed, it must be capped to ensure that it is not a pathway for currents to or from the heart.
- If a header port is unused on the ICD, the port must be plugged to protect the ICD.
- Refer to the lead technical manuals for specific instructions and precautions.

Follow-up Testing

- Ensure that an external defibrillator and medical personnel skilled in cardiopulmonary resuscitation (CPR) are present during post-implant ICD testing should the patient require external rescue.
- Be aware that changes in the patient's condition, drug regimen, and other factors may change the defibrillation threshold (DFT), which may result in non-conversion of the arrhythmia post-operatively. Successful conversion of ventricular fibrillation or ventricular tachycardia during testing is no assurance that conversion will occur post-operatively.

ICD Explant and Disposal

- Interrogate the ICD, and program the ICD to OFF and disable ICD functions prior to explanting, cleaning, or shipping the ICD to prevent unwanted shocks.
- Return all explanted pulse generators and leads to Medtronic.
- Never incinerate the ICD due to the potential for explosion. The ICD must be explanted before cremation.

Environmental and Medical Therapy Hazards

Patients should be directed to avoid devices that generate strong electric or magnetic interference (EMI). EMI could cause malfunction or damage resulting in non-detection or delivery of unneeded therapy. Moving away from the interference source, or turning it off, usually allows the ICD to return to its normal mode of operation.

Hospital and Medical Environments

- Electrosurgical cautery could induce ventricular arrhythmias and/or fibrillation, or may cause device malfunction or damage. If use of electrocautery is necessary, the bipolar configuration is recommended whenever practical. Also, the current path and (if monopolar electrocautery is used) the ground plate should be kept as far away from the ICD and leads as possible (minimum of 15 cm [six inches]).
- External defibrillation may damage the ICD or may result in temporary and/or permanent myocardial damage at the electrode tissue interface as well as temporary or permanent elevated pacing thresholds. Minimize current flowing through the ICD

and lead system by following these precautions when using external defibrillation on a patient with an ICD:

- Position defibrillation paddles as far from the ICD as possible (minimum of 13 cm [five inches]). Minimize current flowing through the ICD and lead system by positioning the defibrillation paddles perpendicular to the implanted ICD-lead system.
- Use the lowest clinically appropriate energy output (watt seconds).
- Confirm ICD function following any defibrillation.

- High radiation sources such as cobalt 60 or gamma radiation should not be directed at the ICD. If a patient requires radiation therapy in the vicinity of the ICD, place lead shielding over the device to prevent radiation damage and confirm its function after treatment.
- Lithotripsy may permanently damage the ICD if it is at the focal point of the lithotripsy beam. If lithotripsy must be used, keep the ICD at least 2.5 to 5 cm [one to two inches] from the focal point of the lithotripsy beam.
- Magnetic Resonance Imaging (MRI) should not be used on patients who have an ICD because of the potential damage to the ICD.
- Radio frequency ablation procedure in a patient with an ICD could cause ICD malfunction or damage. RF ablation risks can be minimized by:
  - Programming the ICD to Off.
  - Avoiding direct contact between the ablation catheter and implanted lead or ICD.
  - Positioning the ground plate so that the current pathway does not pass through or near the ICD system; i.e., place ground plate under the patient's buttocks or legs.
  - Having defibrillation equipment available.

Home and Occupational Environments

- High voltage power transmission lines could generate enough EMI to interfere with ICD operation if approached too closely.
- Communication equipment such as microwave transmitters, line power amplifiers, or high power amateur transmitters could generate enough EMI to interfere with ICD operation if approached too closely.
- Commercial electrical equipment such as arc welders, induction furnaces, or resistance welders could generate enough EMI to interfere with ICD operation if approached too closely.
- Home appliances which are in good working order and properly grounded do not usually produce enough EMI to interfere with ICD operation. There are reports of ICD disturbances caused by electrical hand tools or electric razors used directly over the ICD implant site.
- Static magnetic fields. Patients should avoid equipment or situations where they would be exposed to static magnetic fields (greater than 10 gauss or 1 millitesla) magnetic fields since it could suspend detection. Examples of magnetic sources that

could interfere with normal ICD operation include: stereo speakers, bingo wand, extractor wand, magnetic badges, or magnetic therapy products.

Electronic Article Surveillance (EAS)

- Electronic Article Surveillance (EAS) equipment such as retail theft prevention systems may interact with the ICD. Patients should be advised to walk directly through, and not to remain near an EAS system longer than is necessary.

Cellular Phones

- The ICD has been tested to the frequency ranges used by the cellular phones included in Table 2. Based on this testing, the ICD should not be affected by the normal operation of such cellular phones.
- The ICD contains circuitry that allows usage without interaction (when programmed to nominal sensitivity) of all cellular phones having one of the transmission technologies listed in Table 2. These transmission technologies represent most of the cellular phones in use worldwide. Patients can contact their local cellular phone service provider to confirm that the provider uses one of these technologies.

Table 2. Cellular Phone Transmission Technologies

Transmission Technology	Frequency Range
Analog	
FM (Frequency Modulation)	824 - 849 MHz
Digital TDMA[a]	
North American Standards	
NADC[b] (TDMA - 50 Hz)	824 - 849 MHz
PCS[c] 1800	1850 - 1910 MHz
International Standards	880 - 915 MHz
GSM[d]	
[minimum of 2.5 cm from AMD recommended]	
DCS[e]	1710 - 1785 MHz
Digital CDMA	
CDMA – DS[f]	824 - 849 MHz

[a] Time Division Multiple Access
[b] North American Digital Cellular
[c] Personal Communication System
[d] Global System for Mobile Communications
[e] Digital Cellular System
[f] Code Division Multiple Access - Direct Sequence

VI. Alternative Practices and Procedures

Alternative therapies include the use of antiarrhythmic medication, electrical ablation and cardiac surgery, and other commercially available implantable cardioverter defibrillators, including in combination with pacemakers.

VII. Marketing History

The Jewel® AF has been commercially available in Europe and Canada. There were no reported instances where the device was withdrawn from the marketplace due to safety and effectiveness.

VIII. Adverse Events

The clinical study of the Model 7250 Jewel® AF System for AF-Only patients is summarized below.

Table 3. Patient Enrollment, Device Implantations, and Follow-up

Patient enrollment (worldwide)	146 patients
Patients implanted with Jewel ®AF	144 patients
Cumulative patient follow-up	1838 months
Average individual patient follow-up	12.6 +/- 6.2 months

Patient Deaths: There have been eight deaths (5.5%) in the 146-patient clinical study. Causes of death were classified by the investigator and the independent clinical events committee.

Table 4. Cause of Patient Deaths

Cause of Death	Patients	Days Post-Implant
Ventricular Fibrillation Arrest	1	37
Hyperkalemia	1	476
Congestive Heart Failure	1	89
Pneumonia	1	251
Cardiogenic Shock/Respiratory Failure	1	454
Post-Heart Transplant Complications	1	390
Refractory Heart Failure and Respiratory Failure	1	444
Unknown	1	466

The following table indicates the incidence of three types of adverse outcomes (cerebovascular accident, death, and new onset ventricular tachyarrhythmias) among patients in the 7250 "AF Only" PMA Clinical Report Update population (N=146). This table has been stratified by patients' ejection fraction (EF) as measured within six months prior to enrollment. Results of a statistical analysis of the above numbers indicate a significant difference in rate of adverse outcomes among the three groups (Pearson chi-square test, $p=0.002$), with patients in the low EF group (EF = 40%) suffering significantly more adverse outcomes than those in the other two groups ($p<0.001$). The high EF group (EF > 40 %) and the unknown EF group did not differ significantly ($p=0.26$)

Table 5. Incidence of Adverse Outcomes

Patients Experiencing Adverse Outcomes by Ejection Fraction (N=146)				
EF Group	CVA	Death	New VT/VF	Total*
EF = 40% (N=28)	1 (3.6%)	4 (14.3%)	6 (21.4%)	10 (35.7%)
EF > 40 % (N=67)	3 (4.5%)	1 (1.5%)	1 (1.5%)	5 (7.6%)
EF Unknown (N=51)	0 (0.0%)	3 (5.9%)	4 (7.8%)	7 (13.7%)
Total (N=146)	4 (2.7%)	8 (5.5%)	11 (7.5%)	22 (15.1%)

* Note: One patient who experienced new onset VT/VF subsequently died, so row totals do not all add up.

Table 6 summarizes adverse events experienced during the clinical investigation.

Table 6. Adverse Event Summary

Adverse Events Summary (N=146)[1]	Number	Patients	Percent
Adverse Events at Implant	11	11	7.5%
Complications	26	23	15.8%
Observations	221	97	66.4%
Non System-Related Adverse Events	322	95	65.1%
Total Adverse Events	580	131	89.7%
[1]Over a cumulative follow-up of 1838 months			

Table 7 reports system-related adverse events at implant.

Table 7. Adverse Events Related to ICD System at Implant (N=146)

Adverse Event	Number of Events	Number of patients (%)
Early Recurrence of AF (ERAF)	4	4 (2.7%)
Shoulder Pain	2	2 (1.4%)
Congestive Heart Failure	1	1 (0.7%)
Inappropriate Detection	1	1 (0.7%)
No Device Implanted (atrial myopathy)	1	1 (0.7%)
No Device Implanted (high ventricular DFT)	1	1 (0.7%)
Oversensing	1	1 (0.7%)
Total	11	11(7.5%)

Table 8 reports system-related complications post-implant. Table reports system-related observations. Each adverse event was reviewed by an independent clinical events committee to determine whether it was related to the ICD system.

Table 8. Complications Related to ICD System Post-implant (N=146)

Adverse Event	Number of events	Number of patients (%)
Lead Dislodgment	11	10 (6.8%)
Atrial Fibrillation	3	3 (2.1%)
Hematoma	2	2 (1.4%)
Infection	2	2 (1.4%)
Allergic Reaction	1	1 (0.7%)
Anxiety	1	1 (0.7%)
Inappropriate Detection	1	1 (0.7%)
Lead Failure	1	1 (0.7%)
Pacemaker Syndrome	1	1 (0.7%)

Adverse Event	Number of events	Number of patients (%)
Patient Unable to Tolerate Therapy	1	1 (0.7%)
Skin Irritation	1	1 (0.7%)
Undersensing	1	1 (0.7%)
Total	26	23 (15.8%)

Table 9. Observations Related to ICD System (N=146)

Adverse Event	Number of events	Number of patients (%)
Inappropriate Detection	41	27 (18.5%)
Failure To Cardiovert/Defibrillate	26	19 (13.0%)
Incisional Pain	23	22 (15.1%)
Atrial Fibrillation	17	15 (10.3%)
Oversensing	16	16 (11.0%)
Patient Activator	12	11 (7.5%)
Anxiety	10	7 (4.8%)
Shoulder Pain	9	9 (6.2%)
Hematoma	8	8 (5.5%)
Undersensing	6	4 (2.7%)
Bleeding/Hemorrhage	4	4 (2.7%)
Defibrillation Therapy	4	4 (2.7%)
Nausea	4	4 (2.7%)
Failure To Capture	3	3 (2.1%)
Pacing Therapy	3	3 (2.1%)
Other (Number of Events < 3)	35	30 (20.5%)
Total	221	97(66.4%)

IX. Potential Adverse Events

Adverse events associated with ICD systems, in addition to those reported in the above table, include cardiac perforation, coronary sinus perforation, cardiac tamponade, erosion through the skin, extrusion, false sensing, fibrotic tissue growth, fluid accumulation, formation of hematomas or cysts, inappropriate pulsing or inhibition of normal electrical conduction, infection, keloid formation, lead dislodgment, loss of sensing, muscle and nerve stimulation, myocardial irritability at implant, pericarditis, psychological effects, including psychological intolerance to the ICD, imagined therapies, dependency, fear of inappropriate therapies, and fear that therapeutic capability may be lost, rejection phenomena (local tissue reaction and fibrotic tissue formation), and venous perforation.

X. Summary of Studies

A. Nonclinical Laboratory Testing

Nonclinical laboratory testing of the Jewel® AF System was performed and included:

component and subassembly qualification testing;

device qualification testing; and

- firmware, software and system testing

The sample sizes used in the tests ranged from 10 to 77 depending upon the nature of the test and the similarity of the part to those used in previous devices.

The nonclinical laboratory testing demonstrated that the device performed according to specification.

1. Component and Subassembly Testing

All of the components and subassemblies of the Jewel® AF ICD were qualified for use in ICD applications. The qualification testing of the critical Jewel® AF ICD components and subassemblies qualification is summarized in Table . The qualification demonstrated that components and subassemblies performed according to specification and are of acceptable quality and reliability for use in the Jewel® AF ICD

Table 10. Jewel® AF ICD Component/Subassembly Qualification Testing Summary

Component or Subassembly	Sample Size	Tests Performed and Acceptance Criteria	Results
Connector Module Subassembly (G and H configuration)	24 "G" 14 "H"	Meets all applicable requirements of the IS-1 (ISO 5841-3) and (DF-1 ISO 11318) international standards for connectors	Meets Acceptance Criteria
Low Power Hybrid Electronic Module Subassembly	95	Accelerated life testing shall not cause hybrids to cease operation or exhibit parametric shifts that would prevent correct performance in end application.	Meets Acceptance Criteria
High Power Hybrid Electronic Module Subassembly	77	Accelerated life and charging life testing shall not cause hybrids to cease operation or exhibit parametric shifts that would prevent correct performance in end application.	Meets Acceptance Criteria
Charger Board Assembly	22	High voltage pulse testing shall not cause the charger board assembly to cease operation or exhibit parametric shifts that would prevent correct performance in end application.	Meets Acceptance Criteria
Lithium-Silver Vanadium Battery	16	Accelerated discharge testing, environmental (shock, vibration, temperature extremes, constrained short-circuit at 35°C.) Batteries must conform to capacity, charge time, and dimensional requirements initially and following environmental exposures. Short-circuit samples must not lose hermetically.	Meets Acceptance Criteria

Component or Subassembly	Sample Size	Tests Performed and Acceptance Criteria	Results
High Voltage Output Capacitors	125 (GEM®) 10 (Jewel® AF)	The high output capacitors are the same chemistry and are functionally the same as those used in the GEM, Jewel family of ICDs. Electrical requirements include capacitance, leakage current, charge time, and charge/discharge characteristics. These requirements must be met both before and after environmental exposure and continuous voltage application life testing.	Meets Acceptance Criteria

2. Device Qualification Testing

Device qualification testing was performed to ensure that the Jewel® AF ICD performs adequately in typical shipping, handling and operating environments. The device qualification testing is summarized in Table . The test results demonstrated that the Jewel® AF ICD will perform adequately in typical environments and is qualified for its intended use.

Table 11. Jewel AF ICD Device Qualification Testing Summary

Test	Sample Size	Acceptance Criteria	Results
Environmental	22	Temperature Storage: Meets Section 26.2 of European Standard EN 45502-1 Mechanical Vibration: Meets Section 23.2 of European Standard prEN45502-2-2 Mechanical Shock: Meets Section 23.7 of European Standard prEN45502-2-2.	Meets Acceptance Criteria
Electromagnetic Compatibility	22	Electromagnetic interference: Meets requirements of the 1975 AAMI Pacemaker Standard. Also meets performance standards at additional frequencies, including radiated continuous wave and pulsed electromagnetic fields and conducted continuous wave sinusoidal currents. Cellular Phone: Not susceptible to interference from analog or digital cellular telephones, including the following systems: AMPS, TDMA-50 (NADC), GSM, PCS, and CDMA. X-ray: Must withstand diagnostic levels (minimum 35 Rads). Electrosurgical Cautery: Must withstand spark cutting; spark coagulating and sine cutting modes and energies. Transthoracic Defibrillation: 1000V and 1500V.	Meets Acceptance Criteria
Design Verification Testing	3	The electrical design, pacing and sensing, and delivered energy stability were evaluated by subjecting the ICD to various conditions (e.g. different loads, voltages, and temperatures) prior to testing. Device must perform appropriately over a broad range of conditions.	Meets Acceptance Criteria

3. Firmware, Software and System Testing

The Jewel® AF firmware, software, and system performance were evaluated under typical and unusual user scenarios, and stress and abuse testing, including feature interaction testing. Table describes the Jewel® AF firmware verification testing, software verification testing, and system testing. All of the more than 300 Jewel® AF firmware requirements and more than 1000 Jewel® AF (Model 9960) software requirements were met.

System testing of the Jewel® AF system (Jewel® AF ICD, Model 9961 application software, Model 9790C programmer, accessories and support instruments) was performed to ensure that all system components work together appropriately under simulated clinical situations. The Jewel® AF system performed appropriately during system testing.

The Jewel® AF System was analyzed to verify that hazard-mitigating actions were implemented for all components of the Jewel ® AF system. The system hazard analysis verified that all mitigating actions were implemented.

Table 12. Jewel AF Firmware, Software and System Testing

Test	Acceptance Criteria	Results
Firmware Verification Testing	Each firmware requirement must be met. The Jewel® AF has over 300 firmware requirements that specify the ICD functional performance.	Meets Acceptance Criteria
Software Verification Testing	Each software requirement must be met. The Model 9961 (Jewel® AF) software has over 1,000 requirements that specify the software functional performance.	Meets Acceptance Criteria
System Testing	Jewel® AF system (Jewel® AF ICD, Model 9961 application software, Model 9790C programmer, accessories and support instruments) must perform appropriately during simulated clinical situations, including typical and unusual user scenarios, stress and abuse testing, an feature interaction testing.	Meets Acceptance Criteria
System Hazard Analysis	Must verify that mitigating actions were implemented for all hazards identified during a system-level review of all components of the Jewel® AF system (including environmental or physiological factors, ICD, firmware, software, labeling, lead connector system and programmer system).	Meets Acceptance Criteria

B. Biocompatibility

The biocompatibility of the tissue-contacting materials used in the Jewel® AF has been established in previous PMA applications. These materials include polyurethane, silicone, silicone rubber, and titanium. These materials are all currently used in Medtronic's commercially available ICDs (including the Models 7219, 7220, 7221, 7223 Jewel® and MicroJewel®, and Model 7227 and 7271 GEM® ICDs) and have a proven track record of biocompatibility. No new materials or processes were introduced with the Jewel® AF that would introduce new issues of biocompatibility.

C. Animal Studies

An animal study was conducted to analyze the performance of the Jewel® AF under conditions simulating actual human use. The study was performed in accordance with Good Laboratory Practice (GLP) regulations (21 CFR 58). The features evaluated in the animal studies included: dual chamber bradycardia pacing functions, atrial rate stabilization, automatic mode switching, VT/VF detection and therapy, AF/AT detection and therapy, patient activated therapy, impedance measurements, and noninvasive EP study. Also evaluated were the effects of external transthoracic defibrillation and radio-frequency telemetry on system operation. The animal study demonstrated appropriate functioning of the Jewel® AF system.

D. Clinical Study

Jewel® AF AF-Only Clinical Study Design

A global (USA, Europe and Canada), multicenter, prospective non-randomized clinical study was performed to evaluate the safety (incidence of system-related complications) and effectiveness (termination of spontaneous atrial tachyarrhythmias) of the Model 7250 Jewel® AF System in 146 patients.

Patient Population

The study specified that patients eligible for enrollment included those who evidenced symptomatic, drug-refractory atrial arrhythmias. Specifically, the inclusion criteria were:

- The patient must have had at least 2 atrial fibrillation and/or atrial flutter episodes within the last 3 months.
- One episode must have had electrocardiographic documentation.
- The episodes must have been symptomatic.
- The patient must have been drug refractory or intolerant (defined as failure of ≥ 1 antiarrhythmic drug(s) because the drug was deemed ineffective by the Investigator or not tolerated by the patient).
- The patient must have been in sinus rhythm (SR) at the time of implant, or it must have been possible to cardiovert an atrial arrhythmia to SR. Post-cardioversion the patient must be in SR for ≥ 1 hour.

Crossover Study

The Jewel® AF AF-Only clinical trial included a two-period, two-arm, crossover design to have atrial prevention therapies programmed ON vs. OFF during the first 3 months of follow-up, then reversed during the second 3 months of follow-up (with patients acting as their own controls). This design was intended to assess the ability of the prevention therapies to reduce the frequency of atrial arrhythmias. From the sixth month onward, these therapies were programmed at the discretion of the investigator.

Primary Objectives

- Assess the relative risk of system-related complications following implant of the Model 7250 Jewel® AF ICD compared to the Model 7219D system.
- Estimate the efficacy of the atrial treatment therapies of the Model 7250 in terminating spontaneous atrial tachyarrhythmias.

Secondary Objectives

- Determine the impact of the Model 7250 system on patients' quality of life (SF-36 and Symptom Checklist Assessment).
- Estimate the relative risk of death of patients enrolled in the Model 7250 study compared to those enrolled in the Model 7219D study.
- Estimate the positive predictive value of the Model 7250's AT/AF detection algorithm.
- Estimate the efficacy of atrial shock treatment therapy in terminating spontaneous AF episodes.
- Estimate the efficacy of ATP and high-frequency burst (HFB) in terminating spontaneous atrial tachycardias.
- Estimate the effect of atrial prevention therapies on the frequency of atrial tachyarrhythmia episodes.
- Estimate the mean atrial defibrillation threshold at implants and 3 months post-implant.
- Estimate the incidence of documented atrial shock-induced ventricular arrhythmia.

Control Devices

The Model 7219D was prospectively identified as the control device for comparisons involving the primary objectives.

Follow-up

The study specified that patients were to be followed up with an office visit at 1, 3 and 6 months, and every 6 months thereafter until completion of the study.

Clinical Results

Patient Population

Table 13. Patient Population

Demographics	Patient Population (N=146)	
Gender	104 (71%) Male; 42 (29%) Female	
Age	62.1 years (22 – 83 years)	
LV Ejection Fraction	51.1% (15% – 91%)	
History of AT/AF	146 (100%)	
NYHA Classification	Class I	54%
	Class II	34%
	Class III	12%
Left Atrial Diameter	46.1 mm (11.0 – 60.0 mm)	

Primary Indication	History of symptomatic atrial fibrillation	74%
	History of symptomatic atrial fibrillation and flutter	23%
	History of symptomatic atrial flutter	3%
Primary Cardiovascular History (non-exclusive)	Hypertension	45%
	Mitral valve disease/disorder	34%
	Coronary artery disease	32%
	Cardiomyopathy	30%

Table 14. Implant Experience

ICD and Lead Implant Success (N=146)	Patients
Patients in whom Model 7250 was implanted	99%
Patients who received a two-lead system	39%
Reasons Not Implanted (2 pts, 1.4%)	
High ventricular defibrillation threshold	1
Atrial myopathy	1

Ten patients (6.8%) had the Jewel AF explanted for the following reasons:

Table 15. Device Explants (N=10)

N	Reason	ICD Assessment
3	AV nodal ablation, needed rate-responsive pacemaker/higher upper rate	ICD operating within specification.
2	Pocket infection	ICD operating within specification.
1	AV nodel ablation, developed persistent atrial fibrillation	ICD operating within specification.
1	Anxiety about device therapy	ICD operating within specification.
1	Allergic reaction to manufacturing materials	ICD operating within specification.
1	Heart transplant	ICD operating within specification.
1	Inability to terminate atrial fibrillation	ICD operating within specification.

Lead Configurations

The table below indicates the lead configurations used in the clinical study, and identifies the percentage of the 144 patients receiving the Model 7250 who were implanted with each lead system.

Table 16. Implanted Lead Configurations

Final Lead System Configurations (ventricular/atrial/coronary sinus)	Total (N=144)	
6940 Atrial Lead	N	%
6945/6940	24	16.7
6942/6940	19	13.2
6942/6940/6937A	10	6.9
6945/6940/6937A	7	4.9
6945/6940/6937	1	0.7
Subtotal	**61**	**42.4**
6943 Atrial Lead		
6943/6943	6	4.2
6932/6943	3	2.1
6945/6943	1	0.7
6943/6943/6937A	49	34.0
6932/6943/6937A	6	4.2
6932/6943/6937	3	2.1
6943/6943/6937	2	1.4
6943/6943/6933	1	0.7
6943/6943/6940	1	0.7
Subtotal	**72**	**50.0**
Other Lead Configurations		
6945/4558	2	1.4
6942/5554	1	0.7
6942/5554/6937A	3	2.1
6942/1388T/6937A	1	0.7
6942/4269/6937A	1	0.7
6942/4592/6937A	1	0.7
6945/4068/6937A	1	0.7
6721L/5071/438/6721M	1	0.7
Subtotal	**11**	**7.6**

Therapy Programming

Programmed settings for atrial therapy parameters that occurred in the PMA patients at baseline, 3 months and the 6-month follow-up (database cutoff of May 31, 2000) are presented in the following table.

Table 17. Device Programming at Baseline, 3 Months and 6 Months (AF-Only patients implanted with the 7250)

Parameter Settings	Baseline (n=144)	3 Months (n=130)	6 Months (n=124)
AT Therapies			
None	64 (44.4%)	49 (37.7%)	44 (35.5%)
ATP only	18 (12.5%)	8 (6.2%)	3 (2.4%)
HFB only	--	3 (2.3%)	2 (1.6%)
Shock only	3 (2.1%)	3 (2.3%)	2 (1.6%)
ATP, HFB	27 (18.8%)	40 (30.8%)	48 (38.7%)
ATP, Shock	14 (9.7%)	9 (6.9%)	9 (7.3%)
HFB, Shock	2 (1.4%)	2 (1.5%)	2 (1.6%)
ATP, HFB, Shock	16 (11.1%)	16 (12.3%)	14 (11.3%)
AF Therapies			
None	44 (30.6%)	34 (26.2%)	30 (24.2%)
HFB only	30 (20.8%)	49 (37.7%)	53 (42.7%)
Shock only	32 (22.2%)	26 (20.0%)	21 (16.9%)
HFB, Shock	38 (26.4%)	21 (16.2%)	20 (16.1%)
Atrial Shock Therapies			
None	21 (14.6%)	15 (11.5%)	12 (9.7%)
AF shock only	27 (18.8%)	10 (7.7%)	10 (8.1%)
Patient activated shock only	52 (36.1%)	68 (52.3%)	70 (56.5%)
AT and AF shocks	19 (13.2%)	13 (10.0%)	11 (8.9%)
AT and patient activated shocks	1 (0.7%)	--	1 (0.8%)
AF and patient activated shocks	9 (6.3%)	7 (5.4%)	5 (4.0%)
AT, AF, and patient activated shocks	15 (10.4%)	17 (13.1%)	15 (12.1%)

Clinical Results: Primary Study Objectives

System-Related Complications

Hypothesis: The objective is met if the ratio of the upper one-sided 95 percent confidence bound for the relative risk of system-related complications comparing the Model 7250 to the Model 7219D is less than or equal to 3.

Results: The primary objective of complication-free survival was met. The results included the following:

Relative Risk of System-Related Complications	Relative Risk	Upper Bound
Model 7250 Jewel® AF vs. Model 7219D	1.31	2.25

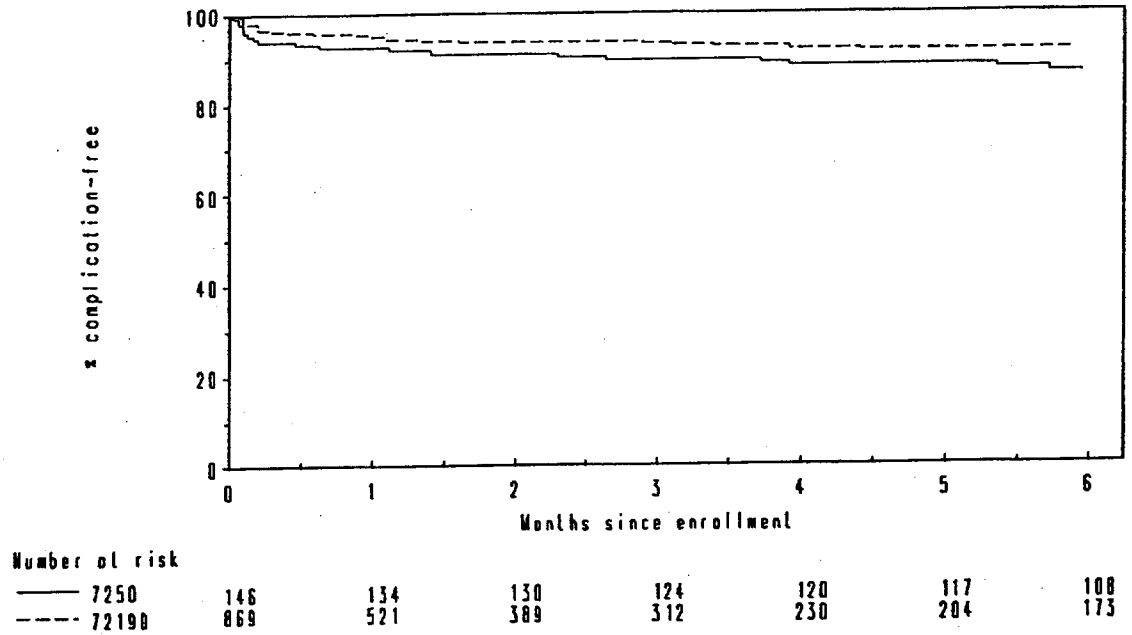

Figure 1. Complication-Free Survival (Kaplan-Meier Plot)

Termination of Spontaneous Atrial Arrhythmias

Hypothesis: The objective is met when the lower one-sided 95% confidence bound on the effectiveness of therapies in terminating spontaneous atrial episodes does not go below 75%. For this rate of effectiveness, the sequence of therapies delivered for the episode must include at least one atrial shock.

Results: Among 4859 total spontaneous, appropriately detected atrial episodes, one hundred and seven (107) patients experienced a total of 1200 spontaneous atrial episodes which were treated with a sequence of therapies which included at least one atrial shock. Of these episodes, 1092 (91.0%) were successfully terminated. Based

on the results from a generalized estimating equations (GEE) analysis of therapy effectiveness, the estimate of therapy effectiveness is 85.9% with a lower one-sided 95% confidence bound of 81.7%. Thus, this primary objective was met.

Table 18. Atrial Shock Efficacy for AT and AF Episodes

# Episodes Terminated/ # Episodes Treated	GE Estimate	Lower Confidence Bound
1092/1200 (91.0%)	85.9%	81.7%

Table 19 provides a detailed breakdown of the 4859 appropriately detected AT/AF episodes by the sequence of therapies delivered.

Table 19. Breakdown of Spontaneous AF/AT Episodes by Therapy Sequence

	AT		AF	
Therapy sequence	**Episodes**	**Successes**	**Episodes**	**Successes**
*aATP,50 Hz,aATP,A-Defib,aATP,A-Defib	1	1	0	0
*aATP,50 Hz,A-Defib,50 Hz,A-Defib,50 Hz,A-Defib	1	1	0	0
*aATP,50 Hz,aATP,50 Hz,A-Defib,50 Hz,A-Defib	1	1	0	0
*aATP,50 Hz,aATP,A-Defib,aATP,50 Hz	1	0	0	0
AATP	1406	1043	0	0
AATP,50 Hz	872	136	0	0
AATP,50 Hz,aATP	24	4	0	0
AATP,50 Hz,aATP,50 Hz	78	3	0	0
AATP,50 Hz,aATP,50 Hz,aATP	2	1	0	0
AATP,50 Hz,aATP,50 Hz,aATP,50 Hz	4	0	0	0
*aATP,50 Hz,aATP,50 Hz,A-Defib	18	17	0	0
*aATP,50 Hz,aATP,A-Defib	5	3	0	0
*aATP,50 Hz,aATP,A-Defib,aATP,50 Hz,A-Defib	2	1	0	0
*aATP,50 Hz,A-Defib	206	185	0	0
*aATP,50 Hz,A-Defib,aATP,50 Hz,A-Defib	2	2	0	0
*aATP,A-Defib	94	77	0	0
*aATP,A-Defib,aATP	1	1	0	0
*aATP,A-Defib,aATP,50 Hz	1	0	0	0
50 Hz	128	24	409	227
50 Hz,aATP	0	0	265	61
50 Hz,aATP,50 Hz	0	0	437	56
50 Hz,aATP,50 Hz,aATP	0	0	7	1
50 Hz,aATP,50 Hz,aATP,50 Hz	0	0	26	1
50 Hz,aATP,50 Hz,aATP,50 Hz,aATP,50 Hz	0	0	1	0
*50 Hz,aATP,50 Hz,aATP,50 Hz,A-Defib	0	0	5	5
*50 Hz,aATP,50 Hz,aATP,A-Defib	0	0	3	3
*50 Hz,aATP,50 Hz,A-Defib	0	0	160	145

Therapy sequence	AT		AF	
	Episodes	Successes	Episodes	Successes
*50 Hz,aATP,50 Hz,A-Defib,aATP	0	0	1	0
*50 Hz,aATP,A-Defib	0	0	33	31
*50 Hz,aATP,A-Defib,aATP,50 Hz,A-Defib	0	0	2	2
*50 Hz,aATP,A-Defib,aATP,A-Defib	0	0	2	1
*50 Hz,A-Defib	48	48	212	202
*50 Hz,A-Defib,aATP	0	0	1	0
*50 Hz,A-Defib,50 Hz,A-Defib	0	0	1	0
*A-Defib	95	88	298	278
*A-Defib,aATP	1	0	0	0
*A-Defib,50 Hz,A-Defib,50 Hz	0	0	1	1
*50 Hz,aATP,A-Defib,aATP,A-Defib,aATP,50 Hz	0	0	1	1
*50 Hz,A-Defib,aATP,50 Hz,A-Defib	0	0	1	1
*50 Hz,aATP,50 Hz,A-Defib,50 Hz	0	0	1	0
*50 Hz,aATP,A-Defib,50 Hz	0	0	1	0
Total	2991	1636	1868	1016

Indicates atrial shock is part of therapy sequence.

Clinical Results: Secondary Study Objectives

SF-36 and Symptom Checklist Assessment

Methods: Two instruments were used to assess improvement in health status. The first, the Health Status Questionnaire Short Form (SF-36), is a standardized generic health survey instrument. The second instrument used was the Symptom Checklist (SCL) developed by Bubien and Kay.

Results: Using repeated-measures analyses, a majority of the eight basic SF-36 scales showed significant improvement over time. The Role-Physical scale, which shows the greatest raw increase from baseline to 3 and 6 months among all the scales, has a significant MANOVA test of differences ($p<0.001$). Both contrasts, baseline to 3 months and baseline to 6 months, are significant ($p<0.001$ and $p<0.001$, respectively) as well. Also showing significant improvement over time are physical functioning (overall $p<0.001$, 3 and 6 month contrast p-values<0.001); vitality (overall $p<0.001$, 3-month $p<0.001$, 6-month $p=0.002$); social functioning (overall $p=0.024$, 3-month $p=0.010$, 6-month $p=0.022$); and mental health (overall $p=0.039$, 3-month $p=0.012$). Looking at the Symptom Checklist, the frequency of symptoms at 3 and 6 months decreases significantly from baseline. The overall test is significant ($p<0.001$) with the tests comparing baseline to 3 months and baseline to 6 months also significant ($p<0.001$ and $p<0.001$, respectively). Similarly, severity of symptoms decreases over time, with an overall $p=0.002$ and 3- and 6-month p-values less than 0.001 and equal to 0.006, respectively.

Table 20. Results of Repeated Measures MANOVA for SF-36 and SCL Scales

	Repeated Measures	Baseline to 3 months	Baseline to 6 months
Scale	MANOVA p-value	p-value	p-value
General Health	0.16	n/a	n/a
Physical Functioning	<0.001 **	<0.001 **	<0.001 **
Role Physical	<0.001 **	<0.001 **	<0.001 **
Role Emotional	0.16	n/a	n/a
Social Functioning	0.024 *	0.010 *	0.022 *
Mental Health	0.039 *	0.012 *	0.11
Bodily Pain	0.14	n/a	n/a
Vitality	<0.001 **	<0.001 **	0.002 **
Frequency of symptoms	<0.001 **	<0.001 **	<0.001 **
Severity of Symptoms	0.002 **	<0.001 **	0.006 **

Note: * indicates a significant result, without Bonferroni corrections

** indicates a highly significant result, without Bonferroni corrections n/a refers to not applicable since the overall test is not significant

Relative Risk of Death Compared to the Model 7219D:

Methods: Using a Cox proportional-hazards model, the risk of death for patients implanted with the Model 7250 system was compared to the risk of death reported in Medtronic's clinical study of its Model 7219D system.

Results: The estimated relative risk of death for the Model 7250 compared to the Model 7219D was 0.51 in a covariate adjusted Cox proportional hazards regression model. The upper one-sided 95% confidence bound on the relative risk was 2.17.

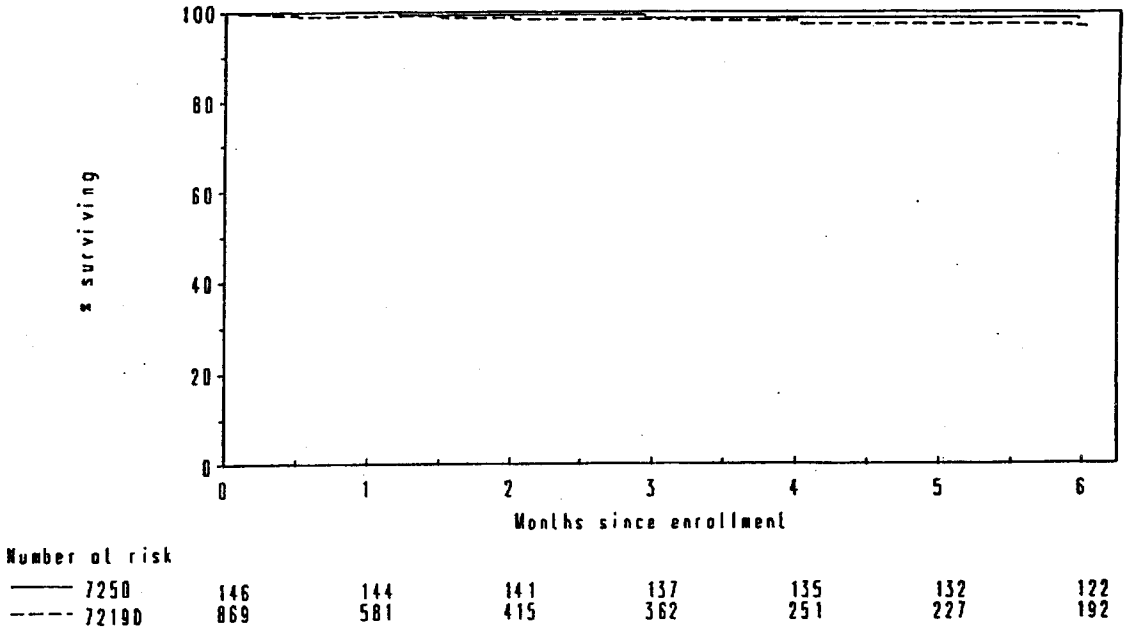

Figure 2. Mortality (Kaplan-Meier plot)

Positive Predictive Value of AT/AF Detection Algorithm:

Methods: The positive predictive value (PPV) measures the accuracy of the dual chamber detection algorithm. It is the ratio of true positive AT/AF detections to the sum of true positive and false positive AT/AF detections.

Results: Using a Generalized Estimating Equations model, the estimate of the PPV is 98.6% with a two-sided 95% confidence interval of (96.0%, 99.5%).

Table 21. PPV of Atrial Detection Algorithm

# Appropriate/ # Atrial Episodes Detected	GEE Estimate	Lower Confidence Bound
4859 / 4913 (98.8%)	98.6%	96.0%

Efficacy of atrial shock therapy for AF episodes:

Methods: Atrial shock was applied to terminate AF, and the efficacy of the treatment assessed.

Results: Of 1868 AF episodes, 723 were treated with atrial shock. These 723 episodes occurred in 85 patients. The GEE estimate of therapy efficacy is 88.4%, with a lower one-sided 95% confidence bound of 84.2%.

Table 22. Atrial Shock Efficacy for AF Episodes Only

# Episodes Terminated/ #	GEE	Lower Confidence

Episodes Treated	Estimate	Bound
668 / 723 (92.4%)	88.4%	84.2%

Efficacy of ATP and HFB in Terminating Atrial Tachyarrhythmias:

Methods: The Model 7250's atrial pacing therapies include antitachycardia pacing and high-frequency burst, the latter of which is employed to terminate both AT and AF episodes.

Results: Of 4859 spontaneous, appropriately detected atrial episodes, ATP and/or HFB were used in 4466 cases among 109 patients. The results are included below.

Table 23. ATP and HFB (pacing) Efficacy for Atrial Episodes

Therapy Delivered/ Type of Episodes	# Episodes Terminated/ # Episodes Treated	GEE estimate
Pacing / all atrial episodes	1560 / 4466 (34.9%)	28.0%
Pacing / AT episodes only	1212 / 2896 (41.9%)	35.5%
ATP / AT episodes only	1049 / 2720 (38.6%)	32.1%
HFB / AT episodes only	163 / 1394 (11.7%)	10.6%
HFB / AF episodes only	286 / 1570 (18.2%)	14.1%

Effect of Atrial Prevention Therapies on Frequency of AT/AF:

Methods: A subset of 75 patients completed both a 3-month period when atrial prevention therapies (atrial rate stabilization and switch back delay) were ON and another 3-month period when atrial prevention therapies were OFF. The order of therapies (ON/OFF or OFF/ON) was assigned at random; 38 patients (50.7%) were in the ON/OFF group and 37 patients (49.3%) were in the OFF/ON group. Frequency of atrial episodes was calculated for each period as the number of episodes in the period divided by the follow-up time in the period, normalized to 3 months. For each patient, the difference between the frequency of atrial episodes when atrial prevention therapies are OFF minus the frequency when therapies are ON was obtained. Positive differences indicated a reduction in frequency when therapies were ON.

Results: The difference in the frequency of atrial episodes when atrial prevention therapies are ON is not statistically significantly different from zero (Wilcoxon signed-rank test, p=0.72).

Table 24. Efficacy of Atrial Prevention Therapies

Difference, ON vs. OFF	p-value
0.0	0.72

Mean atrial defibrillation threshold at implant and 3-month follow-up:

Methods: Atrial DFT testing involved a two-tiered step-up protocol. Using this method, an atrial DFT (A-DFT+) was determined for 86 patients at implant and four patients at 3-month follow-up.

Results: The mean A-DFT+ at implant was 6.8 +/- 4.8 joules, and at 3 months was 2.5 +/- 1.0 joules. All four patients' A-DFT+ decreased from implant to 3-month follow-up.

Table 25. Mean Atrial DFTs at Implant and 3 Months

Time of Assessment	# Patients Assessed	Mean A-DFT+ (J)
Implant	86	6.8 +/- 4.8
3-Month Follow-up	4	2.5 +/- 1.0

Incidence of atrial shock-induced ventricular arrhythmia:

Methods: Post-atrial shock, episode records were inspected for evidence of shock-induced ventricular arrhythmia.

Results: Of the 1200 spontaneous atrial episodes treated with at least one atrial shock, no incidences of documented atrial shock induced ventricular arrhythmia occurred.

Table 26. Atrial Shock-Induced Ventricular Arrhythmias

# A-Shock-Induced VT/VF / # Atrial Episodes with Shock	Binomial Estimate	Upper Confidence Bound
0 / 1200	0.0%	0.3%

Model 9464 Patient Activator

The Model 9464 Patient Activator is a battery-powered, radio-frequency device used to self-activate atrial shock therapy in conjunction with the implanted Model 7250 device (Marketing approval is being sought for the downsized version, the Model 9465 InCheck™ Patient Assistant). For a patient to self-activate atrial shock therapy, the patient-activated therapy must be programmed ON in the implanted Model 7250 device. Pending patient-activated atrial shock therapy takes priority over automatic AF or AT therapies that may also be programmed ON.

Whenever a patient feels he/she may be in AF/AT and desires to receive therapy, the patient can send a request for atrial shock therapy to the implanted Model 7250 device by pressing the button on the Patient Activator. The Patient Activator is designed to provide information back to the patient after the button is pushed by way of audible tones and colored lights.

Although use of the Model 9464 Patient Activator was optional, the majority of the Model 7250 AF-Only patients decided to use it. Currently 70.8% of the AF-Only study patients have patient-activated shocks programmed ON.

Although the Model 9464 Patient Activator was used most heavily by the Model 7250 AF-Only patients, four patients from the AF+VT/VF Model 7250 study who suffered from symptomatic atrial arrhythmias also used the Patient Activator. Table 27 presents follow-up information for the patients from each study who used the Model 9464 Patient Activator through May 31, 2000.

Table 27. Follow-up Information: Model 9464 Users

Follow-up	AF-Only (N=67)	AF+VT/VF (N=4)	Total (N=71)
Mean +/- S.D. (months)	13.6 ± 6.4	22.3 ± 8.9	14.1
Range (months)	2.1 – 25.9	11.9 – 32.4	2.1 – 32.4

These 71 patients represent 1003 months of Model 9464 experience.

Table 27 shows the frequency of AF-Only patient population use of the Model 9464 for episodes lasting at least 30 minutes, i.e., those episodes of sufficient length to make spontaneous termination less likely. Use of the Model 9464 is divided into three-month intervals post-implant. The data indicates that patients consistently used the Model 9464 for treatment of atrial arrhythmias, with generalized estimating equations (GEE) estimates of frequency of use ranging from 40.9% to 52.1% for the 1551 episodes considered. The 459 episodes for which the patient activator was used below represent 82.1% of all uses of the activator, indicating that the 30-minute cutoff is successfully capturing actual use. After three months post-implant, for the GEE model no trend in time is evident (p=0.80), indicating that patient use of the Model 9464 was consistent over time.

Table 27. Model 9464 Frequency of Use for Episodes > 30 minutes

Time post-implant (months)	# of episodes lasting > 30 min	# episodes with Model 9464 use	# patients with episodes > 30 min	# patients with Model 9464 use	GEE estimate of frequency of use	% patients using Model 9464
0 – 3	685	176	57	46	52.1%	80.7%
3 – 6	192	57	39	25	42.3%	64.1%
6 – 9	203	76	34	23	40.9%	67.6%
9 – 12	188	64	23	12	41.9%	52.2%
12 – 15	176	65	25	10	42.1%	40.0%
15 – 18	107	21	14	8	42.5%	57.1%

Adverse Events

A summary of adverse events is shown in 27. There were 14 occasions in 11 patients when there was a failure to cardiovert or defibrillate an episode of AF/AT following the successful delivery of a patient activated shock. There were 13 adverse events related to the operation of the Model 9464 Patient Activator that occurred in 12 patients. Ten events were due to a patient's inability to activate a shock due to either too high of a ventricular rate, suspension of therapies, or the absence of an atrial arrhythmia (this last cause was categorized as a non-system/procedure related adverse event and occurred 1 time in 1 patient). The remaining three events were due to the Model 9464 reportedly not sounding warning tones prior to the shock, most likely because the activator was moved out of range of the device before receiving confirmation of therapy delivery.

Table 28. Summary of Model 9464 Patient Activator Adverse Events

Adverse Event	Number of Events	Number of patients (%)
Failure To Cardiovert/Defibrillate	14	11(7.6%)
Patient Activator – Inability To Activate Shock	10	9(6.2%)
Patient Activator – Shocks Without Prior Warning Tones	3	3 (0.7%)
Total	27	23(14.5%)

Database closure on 05/31/2000

Model 6937A CS/SVC Lead

Patients in both the AF-Only and the AF+VT/VF study were implanted with the Model 6937A coronary sinus lead. In the AF+VT/VF study, 35/530 patients (7%) were implanted with 36 Model 6937A leads at 10 investigative centers. In the AF-Only study, 79/146 patients (54%) were implanted with 79 Model 6937A leads at 17 investigative centers.

The Model 6937A follow-up experience by study appears in Table 29.

Table 29. Follow-up Information: Model 6937A CS/SVC Lead

Follow-up	AF+VT/VF (N=35)	AF-Only (N=79)	Total (N=114)
Mean +/- S.D. (months)	12.8 +/- 6.5	12.8 +/- 6.0	12.8 +/- 6.2
Range (months)	0.8 – 24.7	0.1 – 24.4	0.1 – 24.7

A-DFT+ testing was completed in 63 Model 6937A patients at implant. The mean A-DFT+ for all Model 6937A patients was 6.2 +/- 4.6 joules, and 6.6 +/- 4.8 joules for patients enrolled in the AF-Only study in particular.

Table 30 details adverse events (complications and observations) related to the Model 6937A in both the AF-Only and the AF+VT/VF studies.

Table 30. Model 6937A Lead-Related Adverse Events

Patient ID	Days Post Implant	Adverse Event Description / Outcome
AF+VT/VF		
010-109620-007	1	LEAD DISLODGMENT – Abnormal chest x-ray revealed CS lead was dislodged. The lead was successfully repositioned into the CS.
010-119510-003	4	LEAD DISLODGMENT – Inappropriate VF therapy due to noise / oversensing on ventricular channel associated with 6937A lead being dislodged into the outflow tract and interacting with the RV distal coil of 6945. 6937A lead was explanted after failed attempts to reposition it.
AF-Only		
022-410980-003	7	SUBCLAVIAN VEIN THROMBOSIS – The patient experienced swelling in his left arm. The patient's dose of Coumadin was increased.
022-313200-008	1	LEAD DISLODGMENT – Abnormal chest x-ray revealed CS lead was dislodged into the pulmonary artery, confirmed by angiogram two days later. 6937A lead was successfully repositioned into CS.

Gender Bias Analysis

Differences between males and females with respect to the primary clinical objectives of complication-free survival and effectiveness in terminating atrial arrhythmias were inspected. Based on univariate analyses, there were no statistically significant associations between gender and either of the primary outcomes. With respect to the primary objective associated with the safety of the Model 7250, a Cox proportional hazards regression model of the time to the first system/procedure related complication was used. The coefficient in the model representing differences between genders was not significant (p=0.74). A generalized estimating equations (GEE) model was used to examine the difference in the effectiveness of atrial shock therapy between males and females. The results show no statistically significant difference between genders (p=0.65).

Summary

This study of 146 patients with atrial tachyarrhythmias only, followed for 1838 cumulative months, demonstrated the acceptable safety and clinical performance of the Model 7250 Jewel AF system. A Model 7250 system was successfully implanted in 98.6% of patients for whom an implant was attempted. No unanticipated device-related adverse events occurred during the study, and the reported system/procedure related complications and observations were consistent with previous device studies and current clinical experience. The device was highly effective in detecting and treating spontaneous atrial arrhythmias. The use of the Patient Activator for terminating sustained episodes demonstrates the clinical utility of the Model 7250. There were no atrial shock induced ventricular arrhythmias. The trend for shock therapies (automatic and/or patient activated) to remain programmed ON during the course of the study and the willingness of patients to self-administer shock therapy support patient acceptability of the device.

XI. Conclusions Drawn from Studies

The results of the laboratory testing of the Jewel® AF System in combination with the results of the animal studies, clinical study, and product performance history of Medtronic devices containing the same components or features, demonstrated that the Jewel®AF System performs according to its design intent and is safe and effective when used according to device labeling.

XII. Panel Recommendation

FDA's advisory panel met on December 5, 2000 to review this PMA panel track supplement. They voted for approval contingent upon the following:

- Include a statement in the labeling that refers to an anticoagulation protocol to be used consistent with current guidelines.
- Include a warning about deactivating the device if there has been a transient ischemic attack (TIA) or cerebrovascular accident (CVA) to prevent a recurrent shock close to the neurologic event.

- Include a warning in the labeling that specifically states that there is no back-up bradycardia pacing during antitachycardia pacing.
- Include information in the labeling about the efficacy of the pacing algorithms.
- Include the lead dislodgement rates.
- Revise the wording of the Indications for Usage to read for treatment of patients with atrial fibrillation instead of for atrial tachyarrhythmias.
- Prepare a stratification of the deaths according to underlying heart disease,
- Submit a patient education program for use of the Patient Assistant.
- Include information that states that there should be adequate ventricular thresholds prior to leaving the device in the AF-only mode.
- Do a post approval study to assess the incidence of VT/VF, stroke, death and lead configurations versus dislodgement in AF-only patients with the device.

XIII. FDA Decision

FDA found Medtronic, Inc.'s facilities in compliance with the Device Good Manufacturing regulation (21 CFR PART 820).

Based on the reviews of the PMA panel track supplement for the Medtronic Jewel AF Implantable Cardioverter System (AF-only indication), FDA recommended the following:

- labeling revisions; and
- other information as stated above in XII based on the panel's review.

The manufacturer, Medtronic, Inc., responded to the above requests in the form of amendments to the PMA supplement. The data provided were considered by FDA to be acceptable.

XIV. Approval Specifications

Directions for use: See labeling

Hazards to Health from Use of the Device: See Indications, contraindications, Warnings, Precautions and adverse Events in the labeling.

Post-Approval Requirements and Restrictions: See approval order.

The Approval Order, Summary of Safety and Effectiveness Data, and labeling can be found on the Internet at http://www.fda.gov/cdrh/pmapage.html.