SUMMARY OF SAFETY AND EFFECTIVENESS

I. General Information

Device Generic Name:	Dual Chamber Implantable Cardioverter Defibrillator System
Device Trade Name:	Medtronic® Jewel® AF 7250 Dual Chamber Implantable Cardioverter Defibrillator System
Applicant Name and Address:	Medtronic, Inc. 7000 Central Avenue, N.E. Minneapolis, MN 55432
PMA Number:	P980050
Date of Panel Recommendation:	June 24, 1999
Date of Notice of Approval to Applicant:	JUN 14 2000

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

II. Indications and Usage

The Medtronic® Jewel® AF 7250 Dual Chamber Implantable Cardioverter Defibrillator System is indicated for use in ICD patients either with atrial tachyarrhythmias or who are at significant risk of developing atrial tachyarrhythmias. Patients indicated for an ICD are those patients who are at risk of sudden death due to ventricular arrhythmias and who have experienced one of the following:

- Survival of at least one episode of cardiac arrest (manifested by loss of consciousness) due to a ventricular tachyarrhythmia
- Recurrent, poorly tolerated, sustained ventricular tachycardia (VT)

  Note: The clinical outcome for hemodynamically stable VT patients is not fully known. Safety and effectiveness studies have not been conducted.

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 (50Hz) Burst pacing therapy in terminating atrial fibrillation (AF) and atrial tachycardia (AT) was found to be 16.8 percent and 17.0 percent respectively in the patient population studied.

III. Device Description-

The Medtronic® Jewel® AF 7250 Dual Chamber Implantable Cardioverter Defibrillator System (hereafter referred to as the Jewel®AF) includes the Medtronic® Jewel® AF 7250 Dual Chamber Implantable Cardioverter Defibrillator (ICD), Model 9961 Application Software, and the Medtronic® Sprint™ Model 6943 Steroid Eluting, Screw-in, Atrial/Ventricular Lead. The Medtronic® Jewel® AF 7250 Dual Chamber Implantable Cardioverter Defibrillator 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 AF, AT, ventricular fibrillation (VF), (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® Sprint™ Model 6943 Steroid Eluting, Screw-in, Atrial/Ventricular Lead, or 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, and a telemetry programming head 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:
    - AntiTachycardia Pacing only
    - AntiTachycardia Pacing → 50 Hz Burst Pacing
    - AntiTachycardia 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 6943 Sprint Lead

The Medtronic® Sprint™ Model 6943 Lead was previously approved for bipolar sensing and cardioversion/defibrillation when positioned in the Right Ventricle. This application includes use of the Medtronic® Sprint™ Model 6943 Lead for bipolar pacing and cardioversion/defibrillation when positioned in the Right Atrium.

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

V. Warnings and Precautions

- **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.

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

- Program the first atrial defibrillation therapy to two times the atrial defibrillation threshold (aDFT), or the maximum output.
- Program ICD parameters such as sensitivity thresholds and detection intervals according to the recommendations in the technical manual.
- 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.

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 1. 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 1. 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 sold for clinical use in the following countries: United States; Austria, Belgium; Denmark; Finland; France; Germany; Greece; Ireland; Israel; Italy; Luxemburg; Netherlands; Norway; Poland; Portugal; Spain Sweden; Switzerland; Turkey; United Kingdom; and Yugoslavia. It has been sold commercially in Europe and Canada since July 1998. The Medtronic Model 6943 Lead has been sold in the United States, Europe and Canada for clinical use. It has also been sold for ventricular use in the United States since September, 1997. 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 is summarized below.

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

Patient enrollment (worldwide)	303 Patients
Patients implanted with Jewel ®AF	293 Patients
Cumulative patient follow-up	2393 patient-months
Average individual patient follow-up	7.9 months (range: 0 -20.0 months).

Patient Deaths: There were 26 deaths (8.6%) in the 303-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
Congestive Heart Failure	9	1 prior to implant, 18, 32, 122, 129, 171, 175, 209 and 421 days
Cardiac and/or Respiratory Arrest	6	49, 94, 109, 143, 272 and 307 days
Multiple Organ Failure	2	213 and 315 days
Ischemic Cerebrovascular Infarction	1	11 days
Ischemic Cardiomyopathy	1	29 days
Intracranial Hemorrhage	1	98 days
Intestinal Cancer	1	125 days
Acute Myocardial Ischemia	1	134 days
Sepsis Secondary to GI Abscess	1	188 days
Hypoxic Encephalopathy	1	231 days
Cerebral Hemorrhage	1	284 days
Low Cardiac Output Post-Valve Replacement Surgery	1	301 days

Table 5 summarizes adverse events experienced during the clinical investigation.

Table 5. Adverse Event Summary

Adverse Events Summary (N=303)[1]	Number	Patients	Percent
Adverse Events at Implant	23	23	7.6%
Complications	43	37	12.2%
Observations	144	101	33.3%
Non System-Related Adverse Events	56	39	12.9%
Total Adverse Events	266	155	51.2%
[1]Over a cumulative follow-up of 2393 patient months			

Table 6 reports system-related adverse events at implant. Table 7 reports system-related complications post-implant. Table 8 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. Lead-related adverse events are grouped together and listed first in each table.

Table 6. Adverse Events Related to ICD System at Implant (N=303)

Adverse Event	VT/AT # of events	VT/AT # of patients	VT-Only # of events	VT-Only # of patients	Total # of events	Total # of patients	Percent of Patients
Lead-Related	10	10	1	1	11	11	3.6%
Atrial lead dislodgement Model 6940*: (n=183); 2 pts, 1.0% Model 6943: (n=96); 3 pts, 3.1%	4	4	1	1	5	5	1.6%
Ventricular lead dislodgement Model 6942 (n=128); 1pt, 0.8%	1	1	0	0	1	1	0.3%
Failure to extend lead helix**	4	4	0	0	4	4	1.3%
Lead perforation	1	1	0	0	1	1	0.3%
Not Lead-Related	6	6	6	6	12	12	4.0%
Poor pin plug fit in header	0	0	2	2	2	2	0.7%
Software related	0	0	2	2	2	2	0.7%
Device failure	1	1	0	0	1	1	0.3%
Inappropriate AF/AT detection	1	1	0	0	1	1	0.3%
Inappropriate VT/VF detection	1	1	0	0	1	1	0.3%
Inappropriate atrial defibrillation synchronization	1	1	0	0	1	1	0.3%
Pneumothorax	0	0	1	1	1	1	0.3%
Spontaneous AF/AT episodes	1	1	0	0	1	1	0.3%
Subclavian vein thrombosis	1	1	0	0	1	1	0.3%
Unable to position lead	0	0	1	1	1	1	0.3%
Total	16	16	7	7	23	23	7.6%

*In one patient, VF was induced by atrial 50 Hz burst pacing via an atrial lead (Model 6940) that migrated into the ventricle. VF was detected and terminated with a shock, and atrial therapies were disabled as designed.

**Lead design modified.

Table 7. Complications Related to ICD System Post-implant (N=303)

Adverse event	VT/AT # of events	VT/AT # of patients	VT-Only # of events	VT-Only # of patients	Total # of events	Total #of patients	Percent Of Patients
Lead-Related*	12	10	2	2	14	12	4.0%
Atrial lead dislodgement Model 6940: (n=183); 2 pts, 1.0% Model 6943: (n=96); 5 pts, 5.2%	5	5	2	2	7	7	2.3%
Ventricular lead dislodgement Model 6942 (n=128); 2 pt, 1.6% Model 6932 (n=18): 1 pt, 5.5%	3	3	0	0	3	3	1%
CS lead dislodgement	1	1	0	0	1	1	0.3%
Pulm. Artery lead dislodgement	1	1	0	0	1	1	0.3%
Lead insulation breach	1	1	0	0	1	1	0.3%
Lead perforation	1	1	0	0	1	1	0.3%
Not Lead-Related*	20	18	9	9	29	27	8.9%
Device failure	5	4	1	1	6	5	1.7%
Increased ventricular defibrillation requirements	3	2	2	2	5	4	1.3%
Pocket infection	2	2	2	2	4	4	1.3%
Device migration	3	3	0	0	3	3	1%
Inappropriate VT/VF detection	1	1	1	1	2	2	0.7%
Diaphragmatic stimulation	1	1	0	0	1	1	0.3%
Failure to defibrillate AF/AT	1	1	0	0	1	1	0.3%
Incessant AT	1	1	0	0	1	1	0.3%
Pocket trauma	1	1	0	0	1	1	0.3%
Septicemia	0	0	1	1	1	1	0.3%
Seroma	1	1	0	0	1	1	0.3%
Spontaneous AF/AT episodes	0	0	1	1	1	1	0.3%
Spontaneous VT/VF episodes	0	0	1	1	1	1	0.3%
Subclavian vein thrombosis	1	1	0	0	1	1	0.3%
Total	32	26	11	11	43	37	12.2%

*These patients are not mutually exclusive.

Table 8. Observations Related to ICD System (N=303)

Adverse Event	Events (# at implant)	Patients	Percent of Patients
Lead-Related			4.3%
Atrial lead dislodgement Model 6940 (n=183): 3 events, 3 pts, 1.6% Model 6943 (n=96): 1 event, 1 pt, 1.0% Subcutan. Lead dislodgement (Model 6996)	4 2	4 2	1.3% 0.7%
Increased pacing threshold (#6936&42)	2	2	0.7%
Failure to capture (#6936, 43, 45)	3	3	1.0%
Undersensing (#6940)	2	2	0.7%
Not Lead-Related			
Inappropriate VT/VF detection	41	30	9.9%
Loss of atrial pacing (known software issue; since fixed)	11	11	3.6%
Spontaneous VT/VF episodes	12	10	3.3%
Inappropriate AF/AT detection	10	9	3.0%
Failure to defibrillate AF/AT	8	8	2.6%
Hematoma	5	5	1.7%
Oversensing	5	5	1.7%
Software related	4	4	1.3%
Spontaneous AF/AT episodes	4	4	1.3%
No ventricular pacing during atrial pacing therapy	3	3	1.0%
Pacemaker mediated tachycardia	2	2	0.3%
Pain, arm	2	1	0.3%
Stroke	2	2	0.7%
Syncope	2	2	0.7%
Total Observations (including single observations)[2]	144	101	33.3%

[1]Observations are adverse events that did not require invasive intervention.
[2]Observations that occurred in only one patient are listed following the table.
Some patients had more than one type of adverse event.

Single Observations – Each of the following was observed once in one patient:

- Ancillary Testing Equipment Failure
- Arm Swelling
- Atrial Exit Block (#6940)
- Atrial Standstill
- Atrial Therapies Disabled
- Congestive Heart Failure
- Device Migration
- Dizziness
- Fever
- Hypotension / Shortness Of Breath
- ↑ Atrial Defibrillation Requirements
- Loss Automatic Capacitor Formation
- Chest Pain
- Patient Fall
- Programmer Related
- Pulmonary Embolism
- Right Atrial Thrombus
- Seroma
- Shortness of Breath
- Twiddler's Syndrome

IX. Potential Adverse Events

Adverse events associated with ICD systems, in addition to those reported in the above table, include cardiac 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 9. 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 9. 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
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 10. The test results demonstrated that the Jewel® AF ICD will perform adequately in typical environments and is qualified for its intended use.

Table 10. 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 10 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 11. 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 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 (treatment of atrial tachyarrhythmias) of the Model 7250 Jewel® AF System in 303 patients.

Patient Population

The study specified that patients eligible for enrollment included those who met the standard ICD Indications for Use. In addition, these patients were further divided into two groups:

VT/AT - Patients with ≥ 2 documented episodes of atrial fibrillation (AF) or atrial tachycardia (AT) including atrial flutter within year prior to implant.

VT-Only - Patients with documented VT/VF but without documented AT or AF.

Crossover Study

The Jewel® AF clinical trial included a two-period, two-arm, cross-over design for the VT/AT subgroup. The study was designed with the intent to randomly assign patients in the VT/AT sub-group to have atrial 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 AT therapies to reduce the frequency and duration of atrial arrhythmias. From the sixth month onward, AT therapies were programmed or disabled at the discretion of the investigator.

Primary Objectives

- **System-Related Complications (complication-free survival):** assess the relative risk of system-related complications following implant of Jewel® AF ICD compared to Model 7271 GEM® DR system and Model 7219C system;
- **AF Therapy:** estimate effectiveness of atrial defibrillation shock therapy in terminating spontaneous AF episodes;
- **AT and Burst Therapy:** estimate effectiveness of atrial ATP and high-frequency (50Hz) burst therapies in terminating spontaneous AT episodes; and
- **Dual Chamber Algorithm:** estimate relative sensitivity of dual-chamber detection algorithm.

Secondary Objectives

- **Overall Mortality:** assess relative risk of death associated with Model 7250 vs. control Model 7219C (study later revised to use Model 7271 as control).

- **Change in Frequency and Duration of Atrial Tachyarrhythmias (AT/AF Burden):** assess the frequency and duration of atrial tachyarrhythmias.
- **Atrial Defibrillation Thresholds (aDFTs) at Implant and 3-month Post-Implant:** determine atrial DFT at implant and 3 months post implant.
- **Specificity of the Dual Chamber Detection Algorithm:** assess ability of supraventricular tachycardia (SVT) rules of dual chamber detection algorithm to prevent delivery of ventricular therapies for SVTs
- **Sensing, Pacing and Detection Analysis:** assess pacing and sensing functions (Atrial Rate Stabilization, Modeswitching and Far-Field Oversensing).
- **Pacing and Sensing Performance of the Model 6943 Lead for Atrial Use:** assess performance of Model 6943 Lead by obtaining lead measurements at implant and 3 months post implant.

Control Devices

Although the investigational plan prospectively specified the Model 7219C as the safety control, the study was later revsied to identify the Model 7271 GEM® DR as a safety comparison because the GEM® DR and Jewel® AF share the following characteristics: (1) both are dual chamber ICDs; (2) both share identical detection algorithms; and (3) both studies used a similar adverse event reporting classification.

Follow-up

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

Clinical Results

Patient Population

Table 12. Patient Population

Patient Cohort	Patients	Percent	Mean Follow-Up
VT/AT Group	230	76%	8.2 ± 4.8 months
VT Only Group	73	24%	7.0 ± 4.5 months
Total	303	100%	7.9 months[1]

[1]Cumulative follow-up = 2,393 patient-months

Demographics	Patient Population (N=303)	
Gender	243 (80%) Male ; 60 (20%) Female	
Age	63.6 years (18 - 84 years)	
LV Ejection Fraction	37.7% (10% – 86%)	
History of AT/AF	230 (76%)	
Primary Indication	Ventricular Arrhythmias	59%
	Sudden Cardiac Death (SCD)	27%
	Ventricular Arrhythmias & SCD	13%
Primary Cardiovascular History (non-exclusive)	Coronary Artery Disease and/or Myocardial Infarction	66%
	Cardiomyopathy	45%
	Congestive Heart Failure	25%

Table 13. Implant Experience

ICD and Lead Implant Success (N=303)	Patients
Patients in whom an implant was attempted	97%
Patients who received a two-lead system	89%
Reasons Not Implanted (10 pts, 3.3%)	
Failure to meet ventricular implant criteria	4
Inability to implant leads	2
Patient died after enrollment, but prior to implant	1
Need to minimize implant time due to patient condition	1
Clinical study was temporarily suspended by sponsor	1
No reason provided	1

Eighteen patients (5.9%) had the Jewel AF explanted for the following reasons:

Table 14. Device Explants (N=18)
(*Device/System Failure Suspected)

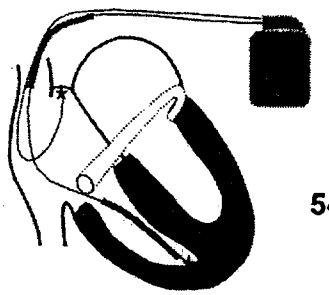
N	Reason	ICD Assessment
4	Patient Death	ICD operating within specification.
4	Needed ↑ Output	ICD operating within specification.
2	Heart Transplant	ICD operating within specification.
1	Pocket Infection	ICD operating within specification.
1	ICD Contamination	ICD operating within specification.
1	Patient Death*	Shorting and low resistance in transistor. Damage thought to have occurred after patient death and device explant.
2	Device Failure*	Shorting and low resistance in transistor. Most likely failure mode was long-lasting current enabled by can oxidation[1].
1	Device Failure*	Shorting and low resistance in transistor. Most likely failure mode was low impedance between can, SV coil, and introducer guidewires during implant testing.
1	Device Failure*	Most likely failure mode was high voltage delivery between can and ventricular lead insulation breach.
1	Device Failure*	Most likely failure mode was high voltage delivery into short circuit (cause unknown).

[1] This phenomenon was addressed by a circuit modification during the clinical study.

Lead Configurations

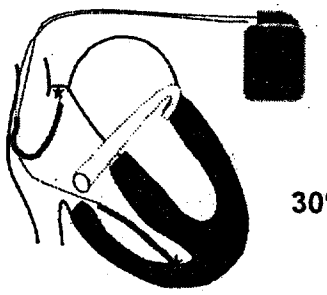
The figure below depicts the most common 2-lead and 3-lead configurations used in the clinical study, and identifies the percentage of the 293 patients implanted with each lead system.

Figure 1. Implanted Lead Configurations



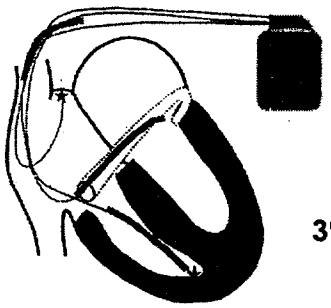
54%

2 Lead System
- Atrial P/S
- Ventricular P/S/HV (SVC and RV coils)
- Active device can



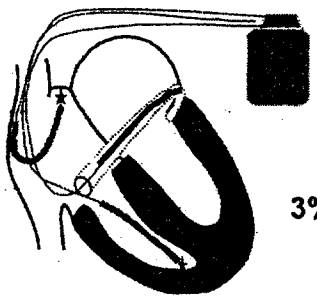
30%

2 Lead System
- Atrial P/S/HV (RA coil)
- Ventricular P/S/HV (RV coil)
- Active device can



3%

3 Lead System
- Atrial P/S
- Ventricular P/S/HV (SVC and RV coils)
- Coronary Sinus HV (CS coil)
- Active device can



3%

3 Lead System
- Atrial P/S/HV (RA coil)
- Ventricular P/S/HV (RV coil)
- Coronary Sinus HV (CS coil)
- Active device can

Other 2-lead systems:

Atrial P/S; Ventricular P/S/HV (RV coil) – 4%
Atrial P/S/HV (RA coil); Ventricular P/S/HV (SVC and RV coils) – 0.3%

Other 3-lead systems:

Atrial P/S; Ventricular P/S/HV (RV coil); Subcutaneous HV Patch – 1.7%
Atrial P/S; Ventricular P/S/HV (RV coil); SVC HV coil – 1%
Atrial P/S; Ventricular P/S/HV (RV coil); Subcutaneous HV Patch – 0.7%
Atrial P/S/HV (RA coil); Ventricular P/S/HV (RV coil); Subcutaneous HV Patch – 0.3%

Note: The Model 6937A Coronary Sinus lead remains investigational.

Tiered Therapy Programming Sequences

Programmed settings for atrial therapy parameters that occurred in the PMA patients at baseline, 3 months and the six-month follow-up (database cutoff December 31, 1998) are presented in the following tables.

VT/AT patients were randomized to atrial therapies ON or OFF at implant, with a cross-over to the opposite therapy setting at the 3 month follow-up; VT-Only patients were not required to have atrial therapies programmed ON. Randomization was competed as of the six-month follow-up, at which time the investigator could program the patient's device at his/her discretion.

Table 15. Device Programming at Baseline, 3 Months and 6 Months (VT/AT patients implanted with the 7250)

Parameter Settings	Baseline (n=221)	3 Months (n=161)	6 Months (n=139)
AT Treatment Therapies			
ATP+HFB	15.8%	16.8%	18.7%
HFB Only	5.4%	8.7%	10.1%
ATP Only	2.7%	3.7%	5.0%
ATP+HFB+Atrial Shock	2.7%	3.1%	2.2%
HFB+Atrial Shock	2.3%	1.9%	2.9%
ATP+Atrial Shock	1.4%	1.2%	2.2%
Atrial Shock Only	0.9%	0	0
All AT therapies OFF	68.8%	64.6%	59.0%
AF Treatment Therapies			
HFB Only	24.4%	30.4%	30.9%
HFB+Atrial Shock	11.3%	8.1%	10.8%
Atrial Shock Only	6.8%	5.0%	5.0%
All AF therapies OFF	57.5%	56.5%	53.2%

Table 16. Device Programming at PMA Data Cutoff Date (12/31/98) (VT/AT Patients)

Summary of Atrial Therapy Status	Baseline (n=221)	3 Months (n=161)	Last Interrogation (n=139)
All Atrial Therapies OFF	54.3%	52.8%	36.7%
At least 1 Atrial Therapy ON	45.7%	47.2%	63.3%

Clinical Results: Primary Study Objectives

System-Related Complications

Hypothesis: The objective is met when the ratio of the upper one-sided 95 percent confidence bound for the Crude Hazard Rate and the Cox Hazard Rate of the study group, Jewel® AF, versus the control, GEM® DR, is ≤3.

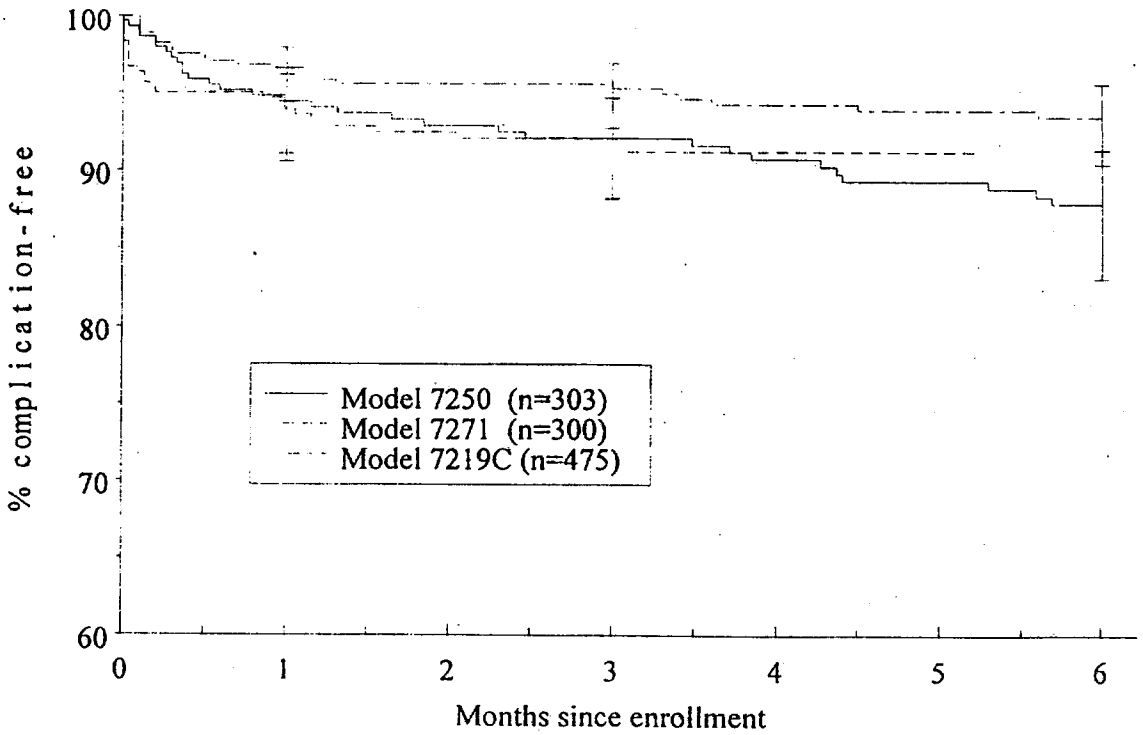
Results – The primary objective of complication-free survival was met. The results included the following:

Relative Risk of System-Related Complications	Relative Risk	CI
Model 7250 Jewel® AF vs. Model 7271 GEM® DR	0.97	0.60,1.55
Model 7250 Jewel® AF vs. Model 7219C	1.83	1.17,2.84

Table 17. Complication-Free Survival

Group	ICD Model	Complication-Free Survival	
		3 Months	6 Months
Study	Model 7250 Jewel® AF	92.1%	87.9%
Control	7219C	95.3%	93.5%
Control	Model 7271 GEM® DR	92.0%	91.2%

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



AT/AF Episode Summary

Utilizing data from the ICD's stored episode records and the investigators' classifications of the episodes, spontaneous treated AT/AF episodes were evaluated for performance of the atrial detection algorithm and effectiveness of the device's features for treating atrial tachyarrhythmias.

Parameter	Result
Total Spontaneous Non-Treated* AT/AF Episodes	8112
Total Spontaneous Treated AT/AF Episodes	1107
Number of Treated AT/AF Episodes Appropriately Detected	1052
Positive Predictive Value (PPV) [1052/1107]	95.0%

*61.0% of these non-treated AF/AT episodes were due to atrial therapies being programmed OFF; 39.0% of these non-treated AF/AT episodes were due to the atrial episode duration being less than the programmed time to deliver atrial therapy.

The clinical study did not evaluate the ability of the Jewel® AF to discriminate between AT vs. AF episodes since these classifications are considered device designations based on the way physicians programmed the Jewel AF, and may or may not correspond to specific atrial arrhythmias.

The number of treated AT and AF episodes as classified by the Jewel® AF are shown in the table below.

Parameter	Result
Treated Episodes Classified by Model 7250 as AT	695
Treated Episodes Classified by Model 7250 as AF	357

The Jewel® AF detected 1107 AT/AF episodes in 78 patients. 74 of the 78 patients experienced 1052 appropriately detected AT/AF episodes. 10 of the 78 patients experienced 55 inappropriately detected AT/AF episodes-all of them due to far-field R-wave sensing. Table 18 describes the programming changes made to resolve far-field R-wave sensing.

Table 18. Inappropriately Detected AT/AF Episodes

Patients	Inappropriately Detected AT/AF Episodes	Adverse Event Reported?	Resolution
1	23	Yes	Atrial sensitivity increased from 0.45 to 0.6mV.
2	1	Yes	Atrial sensitivity increased from 0.3 to 0.45mV.
3	20	Yes	Atrial sensitivity increased from 0.3 to 0.45mV.
4	3	Yes	Atrial sensitivity increased from 0.6 to 0.9mV.
5	1	Yes	Atrial sensitivity increased from 0.6 to 0.9mV.
6	1	No	Atrial sensitivity increased from 0.3 to 0.6mV.
7	1	No	Atrial sensitivity increased from 0.3 to 0.45mV.
8	1	No	Atrial sensitivity increased from 0.3 to 0.45mV.
9	3	No	Atrial therapies programmed OFF.
10	1	No	Atrial sensitivity increased from 0.3to 0.45mV.
Total	55	-	-

Table 19 provides a detailed breakdown of the 1052 appropriately detected AT/AF episodes by the sequence of therapies delivered.

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

#	Therapy Sequences	AT		AF	
		Episodes	Successes	Episodes	Successes
1	ATP	379	317	0	0
2	ATP, 50 Hz	115	31	93	10
3	ATP, 50 Hz, ATP	2	0	0	0
4	ATP, 50 Hz, ATP, 50 Hz	1	0	0	0
5	ATP, 50 Hz, A-Defib	12	11	5	3
6	ATP, 50 Hz, A-Defib, ATP, 50 Hz	1	0	0	0
7	ATP, A-Defib	2	2	3	3
8	50 Hz	84	21	146	39
9	50 Hz, ATP	53	17	0	0
10	50 Hz, ATP, 50 Hz	34	6	30	9
11	50 Hz, ATP, A-Defib	1	1	1	1
12	50 Hz, ATP, 50 Hz, A-Defib	0	0	3	2
13	50 Hz, A-Defib	0	0	33	26
14	A-Defib	10	5	42	32
15	A-Defib, 50 Hz	0	0	1	0
16	A-Defib, ATP, 50 Hz, A-Defib, 50 Hz	1	0	0	0
	TOTAL	695	411	357	125

AF Therapy

Hypothesis - The objective is met when the lower one-sided 95 percent confidence bound on atrial shock efficacy for termination of spontaneous AF episodes is >50%.

Results - A total of 2688 spontaneous AF episodes were observed in the clinical study. Of these, 357 (13.3%) were treated by the Jewel® AF (see Table 19). Of the 357 AF episodes from Table 19, 345 were treated with HFB therapy. Of the 345 episodes, 58 were successfully terminated (16.8%). Similarly, 88 of the 357 AF episodes were treated with atrial defibrillation shock therapy, and 67 of the 88 episodes were successfully terminated (76.1%).

Table 20. Spontaneous AF Episode Termination

Spontaneous AF Episode Termination	Patients	Result	95% CI
HFB Therapy Effectiveness	48*	17% (58/345*)	(11%, 26%)
Atrial Defibrillation Effectiveness	29*	76% (67/88*)	(61%, 85%)
AF Termination Effectiveness	54	35% (125/357)	(0.33, 0.53)

*Not mutually exclusive.

Note that these results provide the success rate for treated AF epsiodes and do not reflect the outcome of untreated AF episodes observed in the clinical study.

ATP and 50Hz Burst Therapy for Terminating AT

Hypothesis - The objective is met when lower one-sided 95 percent confidence bound for ATP and High Frequency Burst (HFB) Therapy efficacy for termination of spontaneous AT episodes is >50 percent.

Results - A total of 6476 spontaneous AT episodes were observed in the clinical study. Of these, 695 (10.7%) were treated by the Jewel® AF (see Table 19). Of the 695 AT episodes from Table 19, 605 were treated with ATP therapy with 334 being successfully terminated (55.2%). Of the 695 AT episodes, 341 were treated with HFB therapy with 58 being successfully terminated (17.0%). Similarly, 28 of the 695 AT episodes were treated with atrial defibrillation therapy and 19 were successfully terminated (67.9%). This device performance did not satisfy the study objective as stated.

Table 21. Spontaneous AT Episode Termination

Spontaneous AT Episode Termination	Patients	Result	95% CI
ATP Therapy Effectiveness	40*	55% (334/605*)	(31%, 51%)
HFB Therapy Effectiveness	35*	17% (58/341 *)	(7%, 23%)
Atrial Defibrillation Effectiveness	9*	68% (19/28 *)	(41%, 87%)
AT Termination Effectiveness	46	59.1% (411/695)	(0.55, 0.63)

*Not mutually exclusive.

Note that these results provide the success rate for treated AT epsiodes and do not reflect the outcome of untreated AT episodes observed in the clinical study.

Table 22 below summarizes the 1052 treated AT and AF episodes grouped by the episode type at the time of initial detection (i.e., detection at the time that first therapy was delivered) and their subsequent transitions.

Table 22. Atrial Tachyarrhythmia Transitions

Transition Sequence	Patients[2]	Episodes[1]	Percent
≤ 1 Transition			91.7%
AT → NSR	30	376	35.7%
AT → AT	21	149	14.2%
AF → NSR	30	78	7.4%
AF → AF	19	96	9.1%
AT → AF → NSR	12	25	2.4%
AT → AF	20	104	9.9%
AF → AT → NSR	7	24	2.3%
AF → AT	18	113	10.7%
> 1 Transition			8.3%
AT ⇒ NSR	2	4	0.4%
AT ⇒ AT	7	14	1.3%
AF ⇒ NSR	9	18	1.7%
AF ⇒ AF	10	24	2.3%
AT ⇒ AF ⇒ NSR	3	4	0.4%
AT ⇒ AF	6	8	0.8%
AF ⇒ AT ⇒ NSR	2	7	0.7%
AF ⇒ AT	4	8	0.8%
Total	74	1052	100.0%

[1] Mutually exclusive.
[2] Not mutually exclusive since the same pt. could experience > 1 set of transitions for different AT/AF episodes.

Note: From Table 22, the effectiveness of episode termination can be estimated as follows: Considering those episodes with ≤ 1 transition, there were 525 episodes (376+149 from the above table) that "stayed" in the AT zone throughout from the time the first therapy was delivered (initial detection) to the time the last therapy was delivered. Of those 525 AT episodes, 376 were successfully terminated by the Jewel® AF's AT/AF therapies (71.6% success rate).

The table below summarizes the number of treated and non-treated episodes that had transitions. Episodes are classified as non-treated when:

- The Jewel AF atrial therapies are programmed off (as required by the study protocol in one of the cross-over arms), or
- The episode terminates spontaneously before the programmed time to deliver atrial therapy.

AT → AF Transitions	
Treated AT Episodes	104/684 (15.2%)
Non-treated AT Episodes	338/5781 (5.8%)
AF → AT Transitions	
Treated AF Episodes	113/368 (30.7%)

Non-treated AF Episodes	311/2331 (13.1%)

Dual Chamber Detection Algorithm

Hypothesis - The objective is met when the lower one-sided 95 percent confidence bound for relative sensitivity of VT/VF detection is >95 percent.

Methods - Utilizing data from the ICD's stored episode records, 24 Holter recordings, and the investigators' classifications of the episodes, spontaneous VT/VF episodes were evaluated for performance of the dual-chamber detection algorithm. Overall, 67 Holter recordings from 49 patients with a combined total of 1153 hours ECG and telemetered markers/EGM were analyzed.

Results : 144 spontaneous VT/VF episodes were detected on the 24-hour Holter recordings. All 144 of these VT/VF episodes were appropriately detected by the device. No VT/VF episodes were missed. Based on the findings of the Holter analysis and review of adverse events, sensitivity of VT/VF detection was determined to be 100%.

Of the 1192 spontaneous ventricular episodes detected by the device, 1056 (88.6%) were classified by the investigator as appropriately detected yielding a positive predictive value (PPV) of 88.6%.

Table 23. Detection of Spontaneous VT/VF Episodes

Parameter	Result
Spontaneous Ventricular Episodes	1192
Number of VT/VF Episodes Appropriately Detected	1056
Number of VT/VF Episodes Inappropriately Detected	136
Positive Predictive Value (PPV) [1056/1192]	88.6%

Clinical Results: Secondary Study Objectives

There were no prospectively defined study hypotheses for the secondary study objectives. Instead, observational data were collected and compared to performance data from the control ICD(s).

Overall Mortality:

Methods - All patient deaths were reviewed by an Adverse Events Advisory Committee (AEAC) , an independent panel of physicians, and categorized as beleived to be Sudden Cardiac, Non Sudden Cardiac, Non Cardiac, or Unknown.

Results – The AEAC believes that 26/26 of the patient deaths were unrelated to use of the Jewel AF. The patient deaths were classified as follows:

Death Classification	VT/AT	VT-Only	Total
Sudden Cardiac	2	2	4
Non Sudden Cardiac	13	0	13
Non Cardiac	7	1	8
Unknown	0	1	1
Total	22	4	26

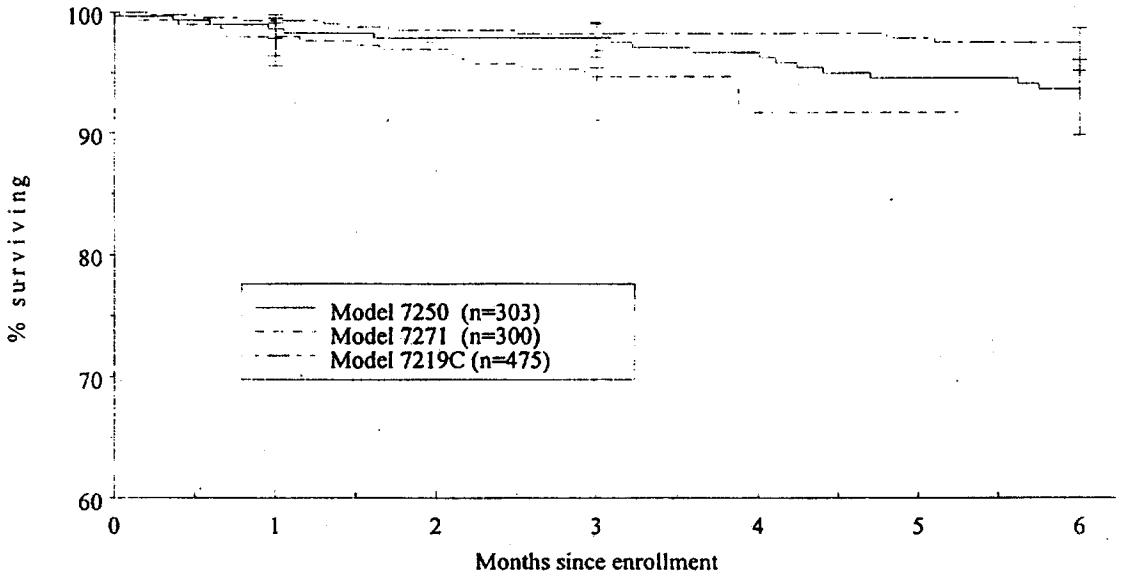
For the Model 7250, overall survival at 3 months was 97.9% and at 6 months was 93.6%. The table below compares these mortality results to the control ICD:

Table 24. Comparison of 3 and 6 Month Overall Survival Rates

	All-Cause Mortality		
ICD	Model 7250	Model 7219C	Model 7271
3 Months Survival	97.9%*	98.2%*	94.7%**
6 Months Survival	93.6%*	97.5%*	91.7%**

*7250 vs. 7219C (p=0.03).
**7250 vs. 7271 (p=0.12).

Figure 2. Survival (Kaplan-Meier Plot) For All Patients



Changes in Frequency and Duration of ATs:

Methods - A crossover substudy was performed with patients in the VT/AT group being randomized to atrial therapies ON vs. OFF for 3 months. Each patient acted as their own control to assess the safety and effectiveness of the atrial tachyarrhythmia therapies.

Results - Of the 221 VT/AT patients in the study, 109 were randomized to AT Therapies ON followed by OFF and 109 randomized to these therapies programmed OFF followed by ON. For a variety of reasons, the AT Therapies were not always programmed as prescribed in the investigational plan. In addititon, only 57 patients were crossed-over during the study and of these, 48 completed the assignment. According to Medtronic, this portion of the study was not completely followed because investigators chose to utilize those features that they perceived to be of value to the patient, and therefore, did not always program AT Therapies OFF, per the study protocol.

In assessing frequency and duration of atrial tachyarrhythmias, 48 patients were followed for 6 months and thereby completed the randomized assignment with AT Therapies programmed ON vs. OFF. The results showed that there was at least a 50% reduction in the frequency of AT/AF per day with the therapies ON versus OFF (p=0.18). The average paired difference demonstrated that patients with the therapies programmed ON had on average a 5 hour reduction per week in the total duration of spontaneous AT/AF episodes (p=0.088). However, these data were not considered statistically significant. In addititon, use of the ICD system has not been demonstrated to decrease the morbidity related to atrial tachyarrhythmias.

Atrial Defibrillation Thresholds at 3 Months Post-Implant

Methods - Atrial defibrillation thresholds (DFTs) were determined in VT/AT patients using the one-step and two-tiered protocols. The one-step protocol consisted of programming the atrial DFT at the first successful energy. The two-tiered method involved using the step-up method in determining DFTs and after the DFT was obtained, energy was stepped-up until a second success was attained.

Results - Atrial DFTs were measured in 72 VT/AT patients at implant (using the two-tiered protocol) and the mean aDFT was 6.6J +/- 4.9 J. Using the one-step protocol, atrial DFTs were measured in 126 patients at implant; the mean aDFT was 5.7 J+/-4.3J. Fifteen patients had aDFTs determined at 3 months using the two-step protocol. The mean was 5.6J+/- 3.3J at 3 months. Atrial DFTs remained stable over 3 months.

Based on the experience as described above, it is recommended that the first atrial defibrillation therapy be programmed to two times the atrial defibrillation threshold, or the maximum output.

Specificity of the Dual Chamber Detection Algorithm:

Methods - The purpose of this objective was to evaluate the ability of the Jewel® AF to withhold ventricular therapies in treating SVTs. However, specificity of the dual chamber algorithm was not assessed due to the inability of the Model 7250 to measure false or true negative VT /VF detections. Instead, the positive predictive value (PPV) of AT/AF was measured. PPV measures the accuracy of the dual chamber detection algorithm and is the ratio of true positive AT/AF detections to the sum of true positive and false positive AT/AF detections.

Results – Of the 1107 spontaneous atrial episodes, 1052 (94.8%) were classified as appropriately detected yielding a positive predictive value (PPV) of 94.8%.

Table 25. Detection of Spontaneous AT/AF Episodes

Parameter	Result
Spontaneous Atrial Episodes	1107
Number of AT/AF Episodes Appropriately Detected	1052
Number of AT/AF Episodes Inappropriately Detected	55
Positive Predictive Value (PPV) [1052/1107]	94.8%

Sensing, Pacing and Detection Analysis:

Methods - Pacing and sensing functions of the Jewel® AF were evaluated via ambulatory Holter monitoring of 49 patients to collect performance data reflecting the following study objectives: (1) verify appropriate sensing, pacing, and detection functions; (2) verify appropriate ARS performance; and (3) detect far-field R-wave sensing.

Results - On the average, 52.3% of the ventricular events and 26.4% of the atrial events were paced. 85.1% were programmed to DDD mode. 331 ventricular safety paces occurred during two of the recordings. ARS pulses occurred during 23 recordings. On the average, 4.7 percent of cardiac cycles involved an ARS pulse. Seventy-two percent of the recordings had no far-field R-wave oversensing. Far-field R-wave oversensing was one of the most common causes of ARS and modeswitching. The recordings demonstrated that the device functions performed as intended.

Table 26. Results of Holter Monitoring (N=49)

Functionality	Holter Monitoring Observation
Sensing	26.4% atrial and 52.3% ventricular events were paced
Pacing	85.1% of pacing was in DDD mode
Ventricular Safety Pacing	No ventricular crosstalk was observed. VSP most frequently triggered in response to PVCs.
Atrial Rate Stabilization	ARS occurred in 23 recordings (35%). No proarrhythmia was observed.
Mode Switching	Far-field R-wave sensing was one of the most common causes of ARS and mode switching.
Far-Field R-Wave Detection	28% of recordings showed some evidence of far-field R-wave oversensing.

Two hundred and fifty-six of 256 spontaneous VF episodes were terminated (100%) and 854/875 spontaneous VT episodes were terminated (97.6%). One thousand and seventy-two of 1072 (100%) atrial defibrillation shocks (induced and spontaneous) were appropriately synchronized to the R-wave, and did not result in proarrhythmia.

Table 27. Spontaneous Episodes During Monitoring

Functionality	Holter Monitoring Observation
VF Episode Termination	256/256 (100%)
VT Episode Termination	854/875 (97.6%)
Atrial Defib. Appropriately Synchronized	1072/1072 (100%)
Incidence of Ventricular Proarrhythmia	0/1072 (0%)

Pacing and Sensing Performance of the Model 6943 Lead:

Methods - Several pacing and sensing parameters were measured at implant, and at 1, 3 and 6 months post-implant. Pulse width threshold, pacing impedance, and P-wave amplitude were measured. For each pace/sense parameter, a test of null hypothesis that there is no change from implant to 1 month was tested using the Wilcoxon signed rank test.

Results - Ninety-six patients in the PMA population were implanted with the Model 6943 Lead. The measurements remained relatively stable throughout 6 months. The pacing and sensing performance is summarized in the table below:

Table 28. Pulse-Width Threshold (msec) Performed at 1.0V - Model 6943

Parameter	Implant	1 Month	3 Months	6 Months
N	61	57	47	44
Median	0.18	0.27	0.20	0.26
Range	0.03-0.82	0.03-0.76	0.06-0.64	0.03-1.07
95% Confidence Interval	0.15 - 0.24	0.20 - 0.30	0.18 - 0.30	0.18 - 0.37

Gender Bias Analysis

Differences between males and females with respect to complication-free survival, overall survival, spontaneous AF episode termination with atrial defibrillation therapy, and spontaneous AT episode termination with ATP followed by high frequency burst (HFB) were examined.

The Kaplan-Meier estimates of complication-free survival at 3 months are 90.6% for males and 97.9% for females. While females appear to be at a lower risk of experiencing a complication, the comparison of complication-free survival curves is not statistically significant at the 5% level (p=.082). With respect to overall mortality, the Kaplan-Meier estimates of survival at 3 months are 97.9% for males and 98.1% for females. There is no statistically significant difference between the survival curves for males and females (p=.471).

The percentages of males and females experiencing spontaneous AF episodes treated with atrial defibrillation therapy were 13% and 15%, respectively. The mean rate of successful spontaneous AF episode termination with atrial defibrillation therapy was 71% in males and 76% in females (p=.915). The percentages of males and females experiencing spontaneous AT episodes treated with ATP followed by HFB were 13% and 21%, respectively. The mean rate of successful spontaneous AT episode termination with ATP followed by HFB was 55% in males and 53% in females (p=.917).

In summary, based on univariate analyses, there are no statistically significant differences between males and females with respect to any of the primary outcomes.

Summary

This study of 303 patients implanted with the Jewel® AF and followed for 2,393 cumulative patient-months demonstrated acceptable safety and clinical performance of the device. A Model 7250 system was successfully implanted in 97% of patients in whom an implant was attempted; 89% of the patients implanted with the device received a two-lead system (i.e., no coronary sinus lead required). No unanticipated device-related adverse events occurred during the study, and the reported complications and observations were consistent with previous device studies and

current clinical experience. The device was effective in detecting and treating spontaneous atrial arrhythmias (55.2% of spontaneous AT episodes were terminated by ATP; 76% of spontaneous AF episodes were terminated by atrial defibrillation therapy. The device was also effective in the termination of spontaneous ventricular tachyarrhythmia episodes, and successfully withheld therapy for many SVT episodes (the positive predictive value of the dual chamber VT/VF detection algorithm was 88.6%). In assessing frequency and duration of atrial tachyarrhythmias, forty-eight patients were followed for 6 months and thereby completed the randomized assignment with AT Therapies ON or OFF. The results showed that there was at least a 50 percent reduction in the frequency of AT/AF per day with the therapies ON versus OFF ($p=0.18$). Also the average paired difference demonstrated that patients with the therapies ON had a reduction of on the average of 5 hours of AT/AF spontaneous episodes ($p=0.088$). There were no patient deaths attributed to the Jewel® AF System or procedure.

This clinical study has demonstrated that the Jewel® AF System is safe and effective for its intended use and performs as anticipated.

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 June 24, 1999 to review this PMA application. They voted for approval contingent upon the following:

- Revise the new paragraph of the Indications for Usage to remove the word "currently."
- Perform a post-approval study to assess the effectiveness of the High Frequency Burst feature in terminating atrial tachyarrhythmias.
- Perform a post-approval study to evaluate the incidence of lead-related complications of the Medtronic® Sprint™ Model 6943 Lead.

XII. FDA Decision

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

Based on the reviews of the PMA application for the Medtronic® Jewel® AF Implantable Cardioverter Defibrillator System, FDA recommended the following:

- labeling revisions;
- post approval study protocols (Burst and the Model 6943 lead) to provide additional data on the performance of the burst feature and to assess the incidence of lead-related complications;
- outline of the training program for the Jewel® AF;
- updated data on the atrial defibrillation efficacy of the Jewel® AF;
- recommendations/considerations for programming the energy of the first atrial shock; and
- Bioresearch monitoring requests, e.g., updated data on adverse events.

The manufacturer, Medtronic, Inc., responded to the above requests in the form of amendments to the PMA application. 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.