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Intrathecal Drug Delivery Systems (IDDS): The Implantable Systems Performance Registry (ISPR)

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Objectives: The ISPR was initially created to monitor the product performance of Medtronic implanted intrathecal drug infusion and spinal cord systems available in the United States.

Materials and Methods: Data were collected from 50 representative sites implanting and following patients with intrathecal drug delivery systems across the United States between August 7, 2003 and January 31, 2014. Device performance over time was estimated using life table survival methods.

Results: Of the 6093 patients enrolled in the ISPR, 3405 (55.9%) were female and 2675 (43.9%) were male, and 13 (0.2%) did not provide gender data. The average age at enrollment was 52.9 years (SD =17.6 years) and average follow-up time was 29.6 months. Currently, the estimates of device survival from pump-related events exceed 90% for all pump models across the applicable follow-up time points. The majority of product performance events were catheter-related. At 5 years of follow-up, all applicable catheter models, with the exception of revised not as designed or grafted not as designed catheters, had greater than 81% survival from catheter-related events.

Conclusions: The ISPR is designed to serve as an ongoing source of system and device-related information with a focus on "real-world" safety and product performance. ISPR data continue to be used to guide future product development efforts aimed at improving product reliability and quality.

Keywords: intrathecal drug delivery, neuromodulation, pain, registry, spasticity

Conflict of Interest: Drs. Konrad, Huffman, Stearns, and Grigsby are paid consultants of Medtronic. Dr. Konrad also receives grant support from Medtronic. Katherine Stromberg, Mollie Roediger, Michelle Wells, and Todd Weaver are all employees of Medtronic, plc.

INTRODUCTION

The development of registries has gained momentum and has become increasingly important in recent years. The United States Food and Drug Administration (FDA) announced a risk minimization plan in March 2005, listing registries as an important risk minimization tool (1). The FDA has also begun requiring some pharmaceutical manufacturers to conduct registries in areas such as pregnancy exposures (2). With growing interest in registries, the Agency for Healthcare Research and Quality (AHRQ) initially released a document in April 2007 entitled, Registries for Evaluating Patient Outcomes: A User's Guide (3). The document was subsequently updated in 2010 and 2014 (4,5). These documents are intended as a guide to the design, implementation, analysis, interpretation, and evaluation of the quality of a registry for understanding patient outcomes.

In September 2012, the FDA's Center for Device and Radiologic Health (CDRH) issued a report entitled, Strengthening Our National System for Medical Device Postmarket Surveillance (6). As part of this report, which outlined CDRH's vision to improve the current postmarket surveillance system, CDRH indicated its willingness to consider new methods to generate, synthesize, and appraise data,

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such as utilizing and pooling data from various registries. The authors indicated that registries can fulfill a unique role in medical device surveillance because of the ability to provide detailed information about patients, procedures, and devices not routinely collected in electronic health records or claims data.

Concurrently, the promulgation of patient registries across various medical therapies has grown over the last decade. In a survey conducted by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), 44% of respondents indicated that their organization (e.g., pharmaceutical industry, medical device industry, contract research organization, or academia) is currently involved in one or more patient registries (7). In fact, many different types of patient registries have already been developed. One of the best-known registries in the United States is the Surveillance Epidemiology and End Results (SEER) Program, which publishes data on cancer statistics in the United States and is managed by the National Cancer Institute (8). Several other well-established registries are analyzing treatment outcomes for conditions such as emphysema, heart disease, depression, and Parkinson's disease.

Subsequently, the use of data from patient registries is becoming a more accepted practice in clinical research to gain regulatory approval or meet high publication standards. In September 2013, the FDA agreed to expand the labeling for Edwards Lifesciences's Sapien transcatheter aortic valve replacement, based largely on data from a post-market registry (9). Also in September 2013, the *New England Journal of Medicine* published results from the Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia (TASTE) study, a registry-based randomized clinical trial, along with an editorial supporting the use of this type of study design in appropriate instances (10,11).

Specifically, a patient registry is defined as "organized systems that use observational study methods to collect uniform data to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure and to serve a predetermined scientific, clinical, or policy purpose(s)" (5). With this type of study design, the authors emphasized that patient registries have the ability to conduct surveillance; assess natural history of the disease; determine the underlying incidence or prevalence rate; assess service delivery and identify groups at high risk for service delivery; document the types of patients served by a health provider; and describe and estimate survival.

Thus, registries can serve as an effective tool in gathering information in the growing field of Neuromodulation, specifically, evaluating product performance and assessing safety or other medical sequelae related to the treatment of pain and spasticity that have not been fully elucidated. In general, ongoing health care utilization for patients suffering from intractable pain and severe spasticity can be lengthy, costly, and may result in variation in patient outcomes. Unresolved pain and spasticity may diminish quality of life and decrease performance scores which ultimately impacts health care and societal costs. Therapies offered by interventional pain management and spasticity specialists including implanted drug delivery systems have been shown to improve both performance scores and quality of life, increase function, and reduce costs of care (12–19). However, these treatment strategies require careful patient management and continuous monitoring of product performance and safety (20).

The Implantable Systems Performance Registry (ISPR) created by Medtronic is the first registry voluntarily developed to monitor the product performance of Medtronic implanted intrathecal drug infusion and spinal cord systems available in the United States (21–23). Medtronic created the ISPR to provide valuable real world information for populations treated with these therapies and the objectives are in alignment with both the AHRQ and the FDA initiatives. Specifically, the registry collects longitudinal data on medical devices that can be used to better understand product performance and how that performance can be improved. This information can be utilized by physicians to direct current practice and ultimately positively impact patient outcomes.

The objective of this manuscript is to provide an overview of the ISPR study design and summarize real world product performance results for intrathecal drug delivery systems.

MATERIALS AND METHODS

The ISPR was created by Medtronic to monitor the performance of intrathecal drug delivery systems, spinal cord stimulation systems, deep brain stimulation systems, and sacral neuromodulation systems commercially available in the United States. The year of initiation into the ISPR for these therapies was 2003, 2004, 2009, and 2010, respectively. Prior to the development of this registry, patient and product outcomes were typically measured by retrospectively analyzing data obtained from other Medtronic data systems, including Returned Product Analysis (RPA) and Complaints data. The ISPR allows for active surveillance of products through ongoing data collection. This information is used to guide future product development efforts aimed at improving product reliability and quality. The data are also used to measure progress toward improving product performance to fulfill regulatory requirements. In addition, data from the ISPR provide information about the treatment practices or use patterns of physicians implanting and managing these therapies. The ISPR is registered on clinicaltrials.gov.

Objectives

The objectives of the ISPR are to:

- Quantify and compare the rates of device-related events for market-released Medtronic Neuromodulation intrathecal drug delivery and stimulation devices;
- Provide a repository for standard data on patient demographics, product use, and device-related events that can be used to investigate future questions related to product design and use and their associations with adverse events;
- Characterize adverse events related to the device, implant procedure, and/or delivery of therapy (e.g., intrathecal medication);
- Characterize implant technique and device/feature utilization (e.g., to potentially understand if risk profiles differ by technique).

Site Selection

The ISPR has collected data from 50 sites for intrathecal drug delivery systems across the United States. Sites were selected using a stratified randomized sampling technique to ensure results could be generalizable, and that inferences could be made regarding the patient population as a whole. A sampling of diverse sites provides estimates reflective of real world product use, technique, and risks and benefit, as it is not feasible to enroll all patients with a commercially available implanted product. Selection and stratification criteria included implanter specialty, geography, academic or non-academic practice setting, implant volume, and patient indication for implant.

Appropriate institutional review board approval was granted before the study began and all institutional guidelines were followed. Informed consent forms were collected for all patients.

Data Collection

Patient history and device information was collected retrospectively for patients who were implanted prior to enrollment into the ISPR and prospectively for patients who were enrolled prior to implant. Patient status updates were obtained every six months or until discontinuation from the registry. In early versions of the protocol, an event was reportable in the registry only if a device required a surgical intervention, led to therapy abandonment, or resulted in death. In April 2010, event data collection was expanded to capture any event associated with the device, therapy, or implant procedure, as well as any event that resulted in death (regardless of relatedness to the device). Sites are required to report events as a condition of their contractual agreement and the sponsor monitors event reporting.

Event Classification

For analysis purposes, events collected through the ISPR were collapsed into two categories: product performance events and non-product performance events. Product performance events were considered the primary endpoint of interest because reliability of the therapy delivery system is tantamount for patient safety and should be independent of approved intended uses. The differences between product and non-product performance events were the following:

- Product performance events were defined as events that were possibly due to a device-related issue as assigned by the physician reporting the event. In order for an event to be considered a product performance event, the system or component (device) had to perform outside of specifications (e.g., technical manual).
- Non-product performance events were defined as any undesirable experience (associated with signs, symptoms, illnesses, or other medical events) occurring to the patient that appeared or worsened during the clinical study, that possibly resulted from or was related to the implant procedure, therapy, or delivery of therapy, and could not be classified as product performance-related. Examples include pump pocket infection or pain at the pump pocket site. Although these types of events are related to the device implant procedure or therapy, they are not considered device performance issues or malfunctions.

All events reported in the ISPR were coded using version 8.0 of the Medical Dictionary for Regulatory Activities (MedDRA). Medtronic's own coding system for events related to implanted neuromodulation systems was integrated with the MedDRA dictionary.

Statistical Methods

Device performance over time was estimated using life table survival methods (24). The survival estimates were calculated over three-month intervals and include experience for each device up until a product performance-related event occurred (considered a failure event), or until the device was removed or therapy was abandoned for non-product performance reasons (including normal battery depletion, patient death, patient lost to follow-up), or for as long as the device has been followed in the study, whichever occurred first. Linear 95% confidence intervals were constructed around the product performance survival estimates for each year post-implant.

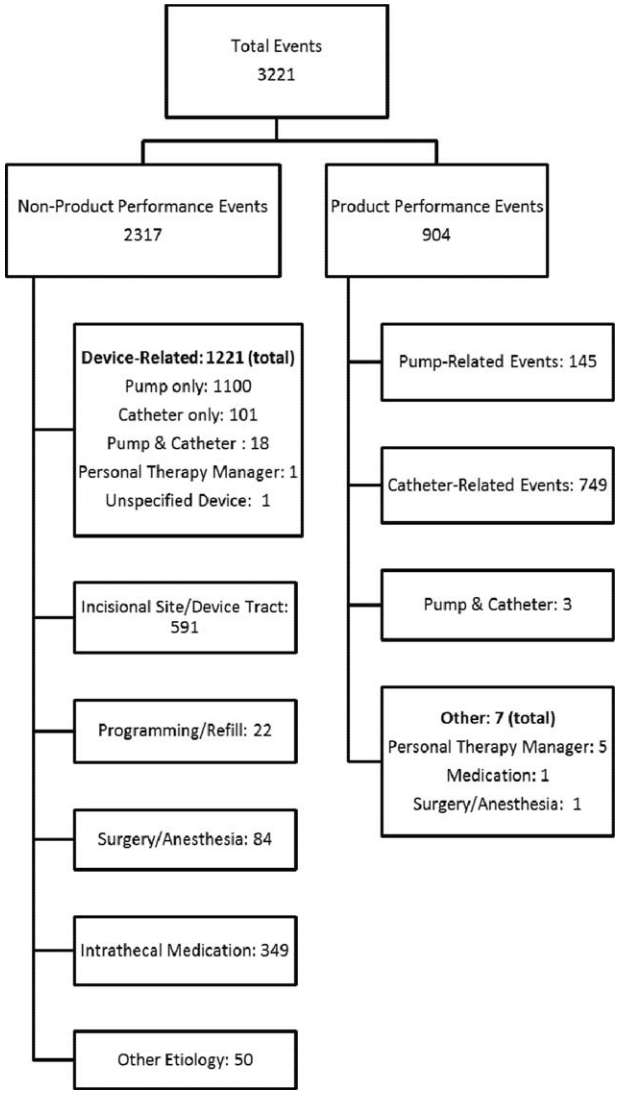

Figure 1. Events by category.

Cumulative device survival plots were used to show the percentage of implanted devices that remain free from product performance-related events at various time points. For example, a device survival probability of 90% indicates that through the stated follow-up time, the device had a 10% risk of incurring a product performance event since the time of implant. The device survival curves shown are only presented where at least 20 total devices were still being followed in any given interval. Device survival estimates are presented at the device level, not at the system level which involves the combination of two or more devices (e.g., pump, catheter, revised catheter).

RESULTS

There were 6093 patients implanted with an intrathecal drug delivery system and enrolled at a total of 50 sites in the ISPR during the reporting period between August 7, 2003 and January 31, 2014. These patients represent approximately 5% of all pumps commercially implanted in the United States during this timeframe. Of the 6093 patients, 3405 (55.9%) were female and 2675 (43.9%) were

Table 1. Intrathecal Drug Delivery System Product Performance Events.

Event*	Number of Product Performance Events	Number of Patients With Event†	Percent of Patients With Event ($n = 6093$)
Catheter kink/occlusion	240	213	3.50%
Catheter dislodgment from intrathecal space	207	185	3.04%
Catheter break/cut	153	141	2.31%
Motor stall‡	56	56	0.92%
Catheter related complication§	50	46	0.75%
Medical device complication¶	49	47	0.77%
Corrosion and/or gear wear	24	24	0.39%
Catheter disconnection at pump	23	23	0.38%
Unable to enter/withdraw from catheter access port	21	21	0.34%
Catheter leakage	18	18	0.30%
Catheter disconnection at distal connection	13	13	0.21%
Pump underinfusion	11	11	0.18%
Device malfunction**	6	6	0.10%
Catheter blockage	4	3	0.05%
Overinfusion††	4	4	0.07%
Reduced battery performance	4	4	0.07%
Pump no infusion	3	3	0.05%
Deformed pump tube	2	2	0.03%
Motor feedthrough anomaly	2	2	0.03%
Pump inversion	2	2	0.03%
Reservoir access issues due to residue	2	2	0.03%
Alarm and/or resonator anomaly	1	1	0.02%
CSF abnormal	1	1	0.02%
Coil shorted to case	1	1	0.02%
Concave pump shield	1	1	0.02%
Cracked rotor magnet holder	1	1	0.02%
Device breakage	1	1	0.02%
Hole in pump tube	1	1	0.02%
Leaky capacitor	1	1	0.02%
Roller arm seized to ball bearing	1	1	0.02%
Not coded	1	1	0.02%
Total	904	704	11.55%

*Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term/Lower Level Term or Medtronic's coding system term for events that do not exist in the MedDRA dictionary.
†The total number of patients with events may not represent the sum of all rows, as a patient may have experienced more than one type of event.
‡Physician reported motor stall or device returned and confirmed by return product analysis (with or without documented motor corrosion).
§Includes 17 events reported as catheter malfunction, 17 difficulty aspirating catheter, 4 coiled or looped catheters, 2 catheter failures, 1 catheter wear, 1 patency issue with catheter, 1 catheter aneurysm, 1 torsion of the catheter preventing side port aspiration, 1 unraveling catheter, 1 catheter connector housing issue, 1 suspected catheter issue, 1 catheter wrapped around pump, 1 sediment in catheter, and 1 compression on catheter.
¶Includes 15 events reported as inconsistency in pump reservoir volume, 13 events reported as pump connector break or cut, 5 events reported as pump malfunction, 1 broken catheter anchor, 1 catheter damage, 1 bent sutureless connector clips, 1 non-functioning catheter, 1 possible corrosion of pump, 1 pump unable to interrogate/program, 1 sutureless connector failure, 1 telemetry stopped secondary to error code, 1 temporary Patient Therapy Manager (PTM) malfunction, 1 unable to aspirate CSF, 1 under medicated event attributed to the pump, 1 worn catheter connector, 1 erroneous empty reservoir alarm, 1 leak at pump connector, 1 worn pump connector, and 1 pump in safe state.
**Includes four events reported as PTM malfunctions, 1 fluctuating medication distribution, and 1 pump beeped.
††Physician reported overinfusion or device returned and confirmed by return product analysis.

male (data missing for $n = 13$ patients). The average age at enrollment was 52.9 years (standard deviation, 17.6 years) and average follow-up time was 29.6 months. Primary indications reported by the physician at implant included 56.0% of patients implanted for treatment of non-malignant pain, 23.7% for treatment of intractable spasticity, and 19.4% for treatment of malignant pain (pain associated with a known malignancy). The remaining patients either had a combination of intractable spasticity and non-malignant pain (0.6%), or had no primary indication specified (0.2%).

There were 3221 events reported between August 7, 2003 and January 31, 2014. Twenty-eight percent of the events (904/3221) were categorized as product performance-related events (Fig. 1). The 904 product performance events occurred in 704 patients or 11.6% of the total patient population (Table 1).

Seventy-two percent of the events (2317/3221) were categorized as non-product performance-related events (Fig. 1). The 2317 non-product performance events occurred in 1596 patients (26.2% of the total patient population).

During the reporting period, there were 1439 patient deaths reported in the ISPR for patients with implanted intrathecal drug delivery systems, none of which were reported by the participating physician as a direct result of a device-related event or due to

Table 2. Device Survival From Pump Events Summary Table.

Intrathecal Drug Delivery Pump Characteristics				Device Survival Probability (95% Confidence Intervals)				
Model Name	Pumps Enrolled in Study (Currently Active at Time of Data Cut-off)	Device Events*	Follow-up Time (Months) Mean ± SD	One Year	Two Years	Four Years	Six Years	Eight Years
SynchroMed EL 18 mL	1151 (2)	34	31.5 ± 20.6	99.0% (97.7%, 100.0%) $n = 219$	97.9% (96.2%, 99.7%) $n = 448$	95.8% (93.8%, 97.8%) $n = 663$	93.3% (90.8%, 95.8%) $n = 286$	92.3% (89.4%, 95.1%) $n = 41$
SynchroMed II 20 mL	2374 (1,073)	38	29.1 ± 24.6	99.9% (99.7%, 100.0%) $n = 1693$	99.4% (98.9%, 99.8%) $n = 1193$	97.6% (96.5%, 98.6%) $n = 632$	94.9% (93.0%, 96.9%) $n = 269$	-
SynchroMed II 40 mL	3703 (1,121)	61	22.3 ± 22.6	99.6% (99.4%, 99.9%) $n = 2079$	99.2% (98.8%, 99.6%) $n = 1435$	96.7% (95.6%, 97.9%) $n = 664$	91.4% (88.8%, 94.0%) $n = 222$	-

*There were a total of 148 pump-related events reported to the ISPR, but only 133 events included in this summary table. The remaining events either occurred in pump models for which no device survival curves are presented due to an insufficient number of enrolled devices (i.e., SynchroMed EL 10 mL, $n = 1$), were subsequent events that did not affect the device survival estimates ($n = 4$), or were events that were not able to be associated with a specific pump (e.g., the event had a pump etiology, but no pump serial number was specified, $n = 10$).

intrathecal drug delivery therapy. Sixty-six percent of patient deaths occurred in patients receiving therapy for malignant pain, 26% for non-malignant pain, and 8% for intractable spasticity.

Pumps

During the reporting period, 7266 pumps were followed in the ISPR. Differences between the total number of patients ($n = 6093$) vs. pumps were due to the fact that some patients were subsequently re-implanted with a pump one or more times.

Most of the pumps enrolled were SynchroMed II (83.6%) or SynchroMed EL (16.3%), and a small number of pumps were SynchroMed (0.1%). There were 148 product performance-related events with an underlying reported etiology related to pump function. Of these, 134 were the first event attributable to an enrolled pump. Table 2 and Figure 2 illustrate pump survival from pump-related product performance events and 95% confidence intervals for models where at least 20 pumps contributed to each time interval.

Currently, estimates of device survival from pump-related events exceed 90% for all pump models (lower confidence intervals exceed 88%) at the applicable follow-up time points.

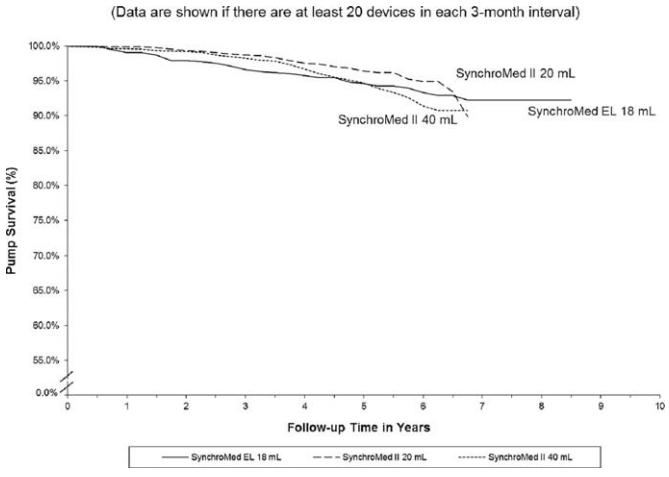

Figure 2. Pump survival from pump events.

Catheters

During the reporting period, 6816 catheters were followed in the ISPR. The total number of catheters is not equal to the total number of pumps ($n = 7266$) because a patient may have undergone a

Table 3. Catheters by Model.

Model Number	Number of Catheters (%)
8709	2775 (40.7%)
8709SC	996 (14.6%)
8711	624 (9.2%)
8731	493 (7.2%)
Ascenda (8780 and 8781 combined)	373 (5.5%)
8703W	188 (2.8%)
8731SC	176 (2.6%)
Other/unspecified	40 (0.6%)
Revised not as designed*	508 (7.5%)
Grafted not as designed†	376 (5.5%)
Revised as designed‡	213 (3.1%)
Ascenda RAD§	54 (0.8%)
Total	6816

*Medtronic non-8731 catheters that had been repaired with an 8596 proximal or 8598 distal revision kit.
†Catheters that involve the ad-hoc assembly of components other than a Medtronic repair kit or brand new catheter.
‡8731 catheters that had been repaired with an 8596 proximal or 8598 distal revision kit.
§8780 or 8781 catheters repaired with the 8782 or 8784 revision kit.

Table 4. Device Survival From Catheter Events Summary Table.

Catheter Characteristics				Device Survival Probability (95% Confidence Intervals)					
Model Number	Catheters Enrolled in Study (Currently Active at Time of Data Cut-off)	Device Events*	Follow-up Time (Months) Mean ± SD	One Year	Three Years	Five Years	Seven Years	Nine Years	Eleven Years
8709[†]	2775 (417)	262	29.3 ± 29.6	93.5% (92.1%, 94.8%) $n = 1097$	88.3% (86.5%, 90.2%) $n = 917$	84.5% (82.3%, 86.7%) $n = 667$	76.8% (73.9%, 79.7%) $n = 417$	71.9% (68.3%, 75.4%) $n = 189$	67.1% (62.5%, 71.6%) $n = 87$
8709SC (Sutureless Connector)	996 (453)	94	22.3 ± 19.1	94.0% (92.4%, 95.7%) $n = 671$	85.7% (82.5%, 88.8%) $n = 238$	82.7% (78.7%, 86.6%) $n = 76$	-	-	-
8711	624 (176)	76	37.2 ± 29.5	94.2% (91.9%, 96.6%) $n = 350$	86.7% (83.0%, 90.4%) $n = 260$	83.4% (79.3%, 87.5%) $n = 207$	78.1% (72.9%, 83.3%) $n = 96$	71.6% (64.5%, 78.6%) $n = 52$	64.4% (54.9%, 73.8%) $n = 23$
8731	493 (85)	44	40.2 ± 31.0	95.0% (92.2%, 97.9%) $n = 293$	92.6% (89.4%, 95.8%) $n = 276$	89.2% (85.2%, 93.1%) $n = 157$	80.2% (74.4%, 86.0%) $n = 95$	78.1% (71.7%, 84.4%) $n = 27$	-
8731SC (Sutureless Connector)	176 (94)	11	22.1 ± 20.3	95.4% (91.6%, 99.1%) $n = 110$	90.8% (85.1%, 96.5%) $n = 46$	-	-	-	-
Ascenda (8780 and 8781 combined)	373 (284)	15	3.6 ± 3.9	89.2% (82.6%, 95.9%) $n = 38$	-	-	-	-	-
Revisedas designed	213 (101)	23	25.1 ± 29.6	93.0% (88.5%, 97.6%) $n = 101$	86.2% (79.3%, 93.1%) $n = 56$	81.1% (72.5%, 89.8%) $n = 39$	69.3% (56.1%, 82.5%) $n = 21$	-	-
Revised not as designed	508 (281)	63	25.0 ± 22.7	91.3% (88.5%, 94.1%) $n = 346$	86.8% (82.9%, 90.6%) $n = 134$	79.2% (72.8%, 85.5%) $n = 59$	-	-	-
Grafted not as designed	376 (181)	58	23.4 ± 25.2	88.6% (84.9%, 92.3%) $n = 219$	78.6% (72.7%, 84.5%) $n = 77$	74.4% (67.0%, 81.8%) $n = 39$	66.3% (55.1%, 77.5%) $n = 21$	-	-

*There were a total of 752 catheter-related events reported to the ISPR, but only 646 events included in this summary table. The remaining catheter-related events either occurred in catheter models for which no device survival curves are presented due to an insufficient number of enrolled devices ($n = 24$) or were subsequent events that did not affect the device survival estimates.
[†]Includes 8709 and 8709AA Models.

pump replacement but used the same catheter, or patients may have been implanted with Medtronic pumps and non-Medtronic catheters which are not included in the analysis. Table 3 provides the number and percentage of catheters by model.

There were 752 product performance events reported related to the catheter; of these, 670 were the first event attributable to an enrolled catheter. Table 4 and Figure 3 represent catheter survival from catheter-related product performance events and 95% confidence intervals where at least 20 catheters contributed to each interval.

Currently, the estimates of survival from catheter-related events exceed 81% (confidence intervals are equal to, or exceed 72%) through five years of follow-up for catheters with follow-up through that time point with the exception of revised not as designed and grafted not as designed catheters.

The survival estimates suggest that the survival of catheters grafted not as designed (those catheters repaired or spliced using non-Medtronic components, or Medtronic components other than the Model 8596 or 8598 revision kits) have a lower probability of survival than other catheter models. Medtronic catheter repair kits and two-piece catheters include specially designed connector pins and strain relief sleeves to splice the catheter segments together. Catheters grafted not as designed, by definition, involve the ad-hoc assembly of components other than those from a Medtronic repair kit with results indicating poorer product performance.

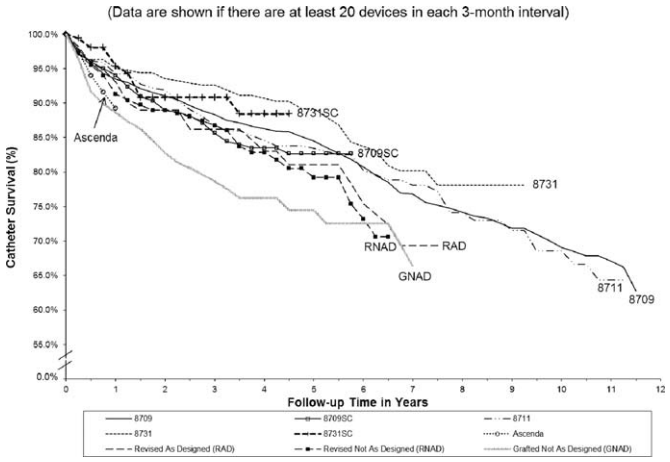

Figure 3. Catheter survival from catheter events.

DISCUSSION

At five years of follow-up time, catheters were two to three times more likely to have a product performance event than a pump. The most common reasons for pump-related product performance events were motor stalls or corrosion and/or gear wear (80 of 148 total pump-related events). As previously reported in the Medtronic Neuromodulation Product Performance Report, more than half of the gear corrosion cases confirmed by Medtronic RPA had at least one exposure to off-label drug admixtures (25). Although the causality for this observation may not be fully elucidated, it is important to examine the overall risk of pump failure when prescribing off-label drugs for patients (26).

The catheter complication rate at three and five years was consistent with previous reports of catheter complications of approximately 20%, with catheter dislodgments, break or fractures, and kinks and occlusions being the most common type of complication (27). Catheters revised or grafted not as designed demonstrated the lowest probability of survival at five years of follow-up. This observation underscores the importance of following the labeling when using catheter revision kits.

At one year of follow-up, the Ascenda catheter demonstrated a survival rate of approximately 90%, which was lower than previous commercially available catheter models at that time point. Although the sample size for Ascenda was fewer than 400 and the confidence intervals for the survival estimates of the various catheter models overlapped, this result warrants further evaluation of either the new structural design or implanting technique since deployment of the catheter and anchor are uniquely different than previous models. Whether these events represented an early adoption effect as a result of these factors or a safety signal will require further vigilance. Thus, additional analyses by Ascenda model, patient indication, patient conditions, and surgical technique, will be conducted and shared in subsequent reports.

CONCLUSION

Registries allow for the systematic collection of prospectively defined longitudinal clinical data that can provide insight into current medical practices. Although registries are not designed to test cause and effect relationships, they facilitate hypothesis generation, provide descriptive information that further characterizes risk, and can provide ongoing monitoring of performance. In addition, registry information makes it possible to track therapy and device performance over extended follow-up intervals, providing long-term data not available in typical clinical studies. Furthermore, post-market surveillance registries provide more complete ascertainment of adverse events beyond that possible with passive surveillance methods. Product and outcome registries are increasing in acceptance within the FDA and medical community. The multi-site sampling approach increases the generalizability, or external validity, of the results.

The concern for possible selection bias has been minimized in the ISPR through the enrollment of consecutive patients at each participating site. For the minority of patients who did not consent at the time of enrollment, refusal to participate should not create a selection bias in that future device performance cannot be predicted in advance (28). In addition, data quality is evaluated and resolved through a risk based monitoring of a sampling of subject data and assessing protocol adherence at each participating site, which has occurred at most sites and is continuing on a periodic basis.

This report reflects a snapshot of information restricted to 6093 patients receiving intrathecal drug delivery therapy collected from 50 sites voluntarily participating in the registry. Thus, conclusions should be limited with the understanding that the information will continue to grow, be reviewed and clarified, and results will change as more sites are activated and new patients are enrolled and followed for longer periods of time. Medtronic regularly releases updates of this product performance information on the Internet in the form of the Medtronic Neuromodulation Product Performance Report (25).

Associations between product performance and implant techniques may exist. The data contained in this registry provide information about the clinical use of the implanted systems, which may be helpful in the future for elucidating commonalities of patients, conditions, or environments that may result in events. This eventually may also provide insight into the etiology of events and possible generation or refinement of best practices for the implant and management of intrathecal drug delivery systems (29).

Future Publications

It is important to not only understand product performance issues and investigate adverse and device events to determine etiology, but also determine overall patient risks of therapy, especially as it relates to unexpected events outside of current labeling. Thus, future reports will contain detailed information regarding non-product performance events, such as infections and inflammatory mass (granulomas). In addition, covariate adjusted device survival analyses or stratification on implant technique will also be employed to further elucidate contributing factors for device performance.

Furthermore, future versions of the registry will include the collection of key patient reported outcomes for each therapy (e.g., pain, spasticity) in order to better understand the long-term clinical benefit of intrathecal drug delivery therapy. Ultimately, it is critical that manufacturers work with practitioners, societies, and regulators to openly disclose this information so clinicians can make the best clinical recommendations to improve patient health (30,31).

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Drs. Konrad, Huffman, Stearns, Plunkett, and Grigsby were all primary investigators in the registry and critically reviewed and edited the manuscript. Katherine Stromberg and Mollie Roediger analyzed the data and prepared/edited the manuscript. Michelle Wells and Todd Weaver managed the conduct of the registry and prepared the draft manuscript. All authors approved the final manuscript.

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COMMENTS

For neuromodulation to progress, quality implant registries are imperative to monitor device performance and survival. This article represents an excellent example of data collection and analysis that can be used to guide development of future products and to refine current offerings. Readers may find it instructive that one newly designed product, the Ascenda catheter demonstrated less than 90% one year survival (less than all other earlier catheter systems with the exception of catheters combining various elements that were not designed to be integrated). The authors note that this could be an early signal of product flaw and that further vigilance is necessary in this regard. These data are precisely the type of information that registries can provide enhance progress in the field of neuromodulation.

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This is a valuable paper analyzing hardware complications of intrathecal drug delivery systems (Medtronic). The only thing I would recommend is to mention the acceptance, if needed in the US, from all the ethical committees of the various institutions merged in this study to share data on patients.

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This paper is an important contribution to the literature on Intrathecal Drug Delivery Systems (IDDS). The implantation of programmable pumps for intrathecal drug application is a well-established procedure for the treatment of severe cancer pain as well as non-cancer chronic pain an in severe spasticity (1–3).

So far there is no practical data available to evaluate the quality of the devices in long-term use, the results of medical treatment as well as the number of revision procedures especially in a significant volume of patients nationally and internationally.

In addition there is also no reliable data available on malfunctions and complete technical failure of the devices, which could be accounted for by the nature of the disease itself, the operation technique or the chosen device. There are a high number of reasons, which have influence on therapeutic outcome. To close the lack of knowledge profoundly a comprehensive database is needed. In the long term those data will contribute to decrease the number of revision procedures.

Therefore the lifetime of the implants is of major interest. The knowledge of the standard lifetime of an implant can help to recognize very early a sudden change in quality of a product or the reliability an operational technique as well as an obvious reflection of unanticipated events. Such a registry could serve as an early warning system and help to improve the quality of care as well as patient safety.

Furthermore comprehensive data on health service research will be gathered, such as:

- Information about the quality of care the patient received
- Transparency of the cost effectiveness and the treatment quality
- Evaluation tool for the physicians to monitor their performance
- Establish a database to help the scientific societies to evaluate the efficacy of new techniques and implants
- Provide a register of long term results for health care officials
- Create an early warning system to provide feedback to the manufacturers regarding product failure and potential risk of unanticipated events.

There are many reasons to talk about national and international registries.

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An important and well-needed post marketing surveillance of a device that is likely to gain more popularity as a tool in alleviation of chronic painful conditions.

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Comments not included in the Early View version of this paper.

