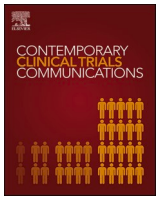
Contemporary Clinical Trials Communications 37 (2024) 101254

Contents lists available at ScienceDirect

Contemporary Clinical Trials Communications

journal homepage: www.elsevier.com/locate/conctc



Characteristics and use of patient-reported outcomes of clinical trials for high-risk neurological medical devices that received FDA premarket approval from 2001 to 2022

Morgan E. Ryan [a], Siddharth Srivastava [b], Lin Wan [c,d,e], Guang Yang [c,d,e,f,**], Bo Zhang [a,b,*]

[a] Biostatistics and Research Design Center, Institutional Centers for Clinical and Translational Research, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA
[b] Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA
[c] Department of Pediatrics, The First Medical Center of Chinese PLA General Hospital, Beijing, China
[d] Senior Department of Pediatrics, The Seventh Medical Center of Chinese PLA General Hospital, Beijing, China
[e] Medical School of Chinese PLA, Beijing, China
[f] Second School of Clinical Medicine, Southern Medical University, Guangzhou, China

ARTICLE INFO

Keywords:
Neurological disorders
High-risk medical devices
FDA regulation
Pivotal clinical trials
Patient-reported outcomes (PROs)

ABSTRACT

Neurological medical devices have revolutionized the management of neurological disorders, providing diagnostic, therapeutic, and monitoring solutions. High-risk neurological devices, such as deep brain stimulation and neurostimulators, offer groundbreaking treatments, emphasizing patient benefits while considering risks. To gain FDA approval, high-risk Class III devices necessitate premarket approval (PMA) applications with pivotal clinical trials, often assessing patient-reported outcomes (PROs). This article analyzes FDA-approved high-risk neurological devices from 2001 to 2022 via the PMA pathway. It explores device characteristics and pivotal clinical trials, and PRO incorporation. Of the 23 identified devices, pain neurology devices (30.4 %) predominated. All devices were therapeutic, with varying study designs. Pain neurology devices notably emphasized PRO endpoints as expected. This study underscores the significance of PROs in assessing device efficacy and safety, offering insights into regulatory processes and patient-centered care in neurological disorder management.

1. Introduction

Neurological medical devices have emerged as indispensable tools in modern clinical practice and treatment, revolutionizing the way neurological disorders are managed [1–3]. These cutting-edge devices play a critical role in diagnosing, monitoring, and providing therapeutic interventions for various neurological conditions. In particular, groundbreaking high-risk neurological medical devices are providing revolutionary treatment possibilities, all the while carefully weighing the advantages and potential risks for patients [1]. For instance, deep brain stimulation (DBS) devices, have revolutionized the management of Parkinson's disease and essential tremors by delivering electrical impulses to specific brain regions, alleviating motor symptoms and enhancing patients' quality of life [4]. Neurostimulators, on the other hand, are employed to manage chronic pain conditions like neuropathic pain and migraines, providing relief and reducing the dependence on medications [5].

To be legally marketed in the United States, medical devices must be reviewed and approved by the U.S. Food and Drug Administration (FDA) [6]. The FDA's Center for Devices and Radiological Health (CDRH) is primarily responsible for medical device review. High-risk medical devices refer to the Class III devices, which are life-supporting or life-sustaining and which present a high or potentially unreasonable risk of illness or injury to a patient. The assurance of the safety and effectiveness for an investigational Class III device is demonstrated by a thorough premarket approval (PMA) application that is submitted to the FDA [6]. During this process, pivotal clinical trials are reported to the FDA to demonstrate the safety and effectiveness through regulated clinical studies and their data. In these pivotal clinical trials in PMA applications, the endpoints are often patient-reported outcomes (PROs). A patient-reported outcome (PRO) is a subjective assessment reported directly from patients who received medical treatments in clinical trials

* Corresponding author. Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA, 02115, USA.
** Corresponding author. Senior Department of Pediatrics, the Seventh Medical Center of PLA General Hospital, Beijing, 100000, China.
E-mail addresses: yangg301@126.com (G. Yang), bo.zhang@childrens.harvard.edu (B. Zhang).

https://doi.org/10.1016/j.conctc.2024.101254
Received 28 August 2023; Received in revised form 27 December 2023; Accepted 1 January 2024
Available online 2 January 2024

and clinical practice [7–9]. PRO measures provide unique, direct assessment of health improvement and experiences from the patient's perspective, and such direct assessments are crucial in pivotal clinical trials [9]. In practice, use of PRO has been substantially extensive in evaluating neurological devices.

This short article aims to analyze the clinical studies conducted on high-risk neurological medical devices that received FDA approval through the PMA pathway from 2001 to 2022. The primary objectives are threefold: (i) enhance comprehension of the quantity and caliber of high-risk neurological medical devices approved by the FDA, (ii) gain deeper insight into the evidence established within the pivotal clinical trials regulated by the FDA for these devices, and (iii) evaluate the incorporation of PROs in these trials.

2. Methods

In the United States, most high-risk Class III medical devices are approved for marketing through the PMA applications that are reviewed by the FDA. When a Class III device is approved, the FDA publishes a "Summary of Safety and Effectiveness Data" (SSED) to report the details of its PMA application, including the details in pivotal clinical trials for demonstrating safety and effectiveness of the new device [6]. The CDRH's public database of PMAs (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm) was searched for the SSEDs of FDA-approved high-risk Class III neurological devices. The search criteria are (i) a period between from January 2001 to June 2022 in "Decision Date", (ii) "Neurology" in "Advisory Committee" (parts 862–892 of Title 21 of the Code of Federal Regulations classifies and organizes distinct types of devices into 16 medical specialties, each of which has its advisory committee), (iii) "Original Only" for "Supplement Type". Fig. 1 displays a flow diagram of the search for SSEDs presented in this study.

Each SSED for a PMA that met these selection criteria was thoroughly reviewed to identify the details regarding the approved medical device and the reported pivotal clinical studies. Missing information was supplemented with documentation from ClinicalTrials.gov, if available. A database was then created from the findings from all examined SSEDs (supplementary materials, Table S1). Information for each high-risk neurological medical device SSED into a database which included, but not limited to, approval date, neurological specialty area, therapeutic or diagnostic device, number of subjects enrolled in the pivotal study, number of centers and the locations of the centers, and study design details. Information was also collected on whether primary, secondary, or tertiary endpoints included PROs and the type of PROs in safety endpoints. Details of statistical analysis are elaborated in Table 1.

3. Results

Twenty-three high-risk neurological medical devices approved via the PMA pathway between January 2001 and June 2022 were identified. Characteristics of device premarket approval SSEDs are presented in Table 1. Of the 23 devices, 5 (21.7 %) were approved between 2001 and 2007, 8 (34.8 %) between 2008 and 2015, and 10 (43.5 %) between 2016 and 2022. All devices were therapeutic devices, mainly because most of the diagnostic devices were Class II devices and approved through 510(k) or De Novo pathways. The majority of these 23 devices were either for cerebrovascular disorders (N = 7, 30.4 %) or pain neurology (N = 7, 30.4 %). Other neurological specialty areas included

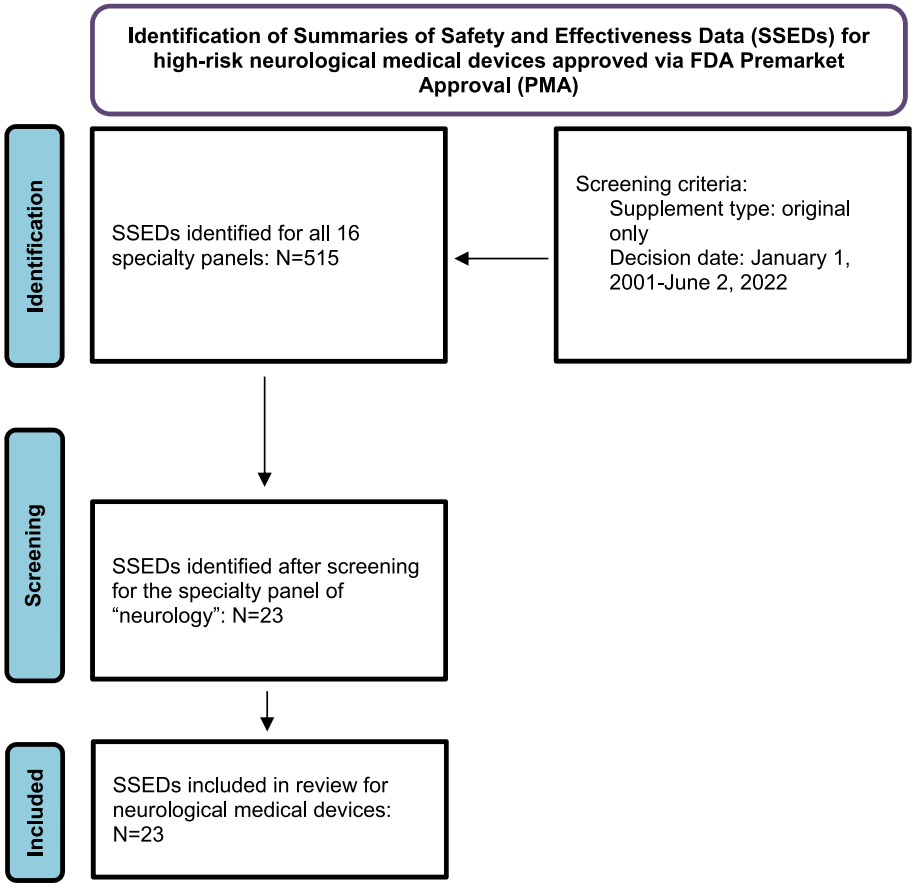


Fig. 1. A flow diagram for the Summary of Safety and Effectiveness Data (SSED) reviews of high-risk neurological medical devices receiving initial marketing approval via the FDA Premarket Approval (PMA) database from January 2001 to June 2022. The database was accessed and the SSEDs were searched on June 2, 2022 in the Center for Devices and Radiological Health's public database of PMAs (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm).

Table 1
Characteristics and use of patient-reported outcomes (PROs) of clinical trials for high-risk neurological medical devices receiving marketing approval via the Premarket Approval (PMA) pathway from January 2001 to June 2022. Statistical analysis: descriptive statistics including counts (percentages) for categorical variables and median (interquartile range [IQR]) for continuous variables were used to characterize the neurological devices; Fisher's exact test for categorical variables and Wilcoxon rank sum test for continuous variables were then used to evaluate differences between the two device groups; nominal p-values are presented without correcting for multiplicity. *Three PMAs did not report any pivotal clinical trials but were approved based upon meta-analyses or literature reviews. Therefore, there was missing information from these PMAs. The NA categories were excluded, when two-group comparison was performed.

Characteristics	N (%) or median (Q1, Q3)			
	Overall (N = 23)	**Pain neurology devices (N = 7)**	**Other neurological devices (N = 16)**	**p-value**
Neurological devices and their PMAsl				
Year of PMA approva				1.000
2001–2007	5 (21.74 %)	2 (28.57 %)	3 (18.75 %)	
2008–2015	8 (34.78 %)	2 (28.57 %)	6 (37.50 %)	
2016–2022	10 (43.48 %)	3 (42.86 %)	7 (43.75 %)	
Neurological specialty area				<0.001
Cerebrovascular disorders	7 (30.43 %)	-	7 (43.75 %)	
Epilepsy	1 (4.35 %)	-	1 (6.25 %)	
Movement disorders	3 (13.04 %)	-	3 (18.75 %)	
Neonatal neurology	1 (4.35 %)	-	1 (6.25 %)	
Neuro-oncology	1 (4.35 %)	-	1 (6.25 %)	
Pain neurology	7 (30.43 %)	7 (100.00 %)	-	
Surgical repair/aide	3 (13.04 %)	-	3 (18.75 %)	
Therapeutic/diagnostic devicel				
Therapeutic device	23 (100.00 %)	7 (100.00 %)	16 (100.00 %)	-
Diagnostic device	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	
Expedited review				0.526
Yes	3 (12.04 %)	0 (0.00 %)	3 (18.75 %)	
No	20 (86.96 %)	7 (100.00 %)	13 (81.25 %)	
Implantable device				0.272
Yes	18 (78.26 %)	7 (100.00 %)	11 (68.75 %)	
No	5 (21.74 %)	0 (0.00 %)	5 (31.25 %)	
Pivotal clinical trials in PMA				
No. of subjects enrolled				0.483
	191.00 (152.00, 250.00)	191.00 (152.00, 1056.00)	190 (139.50, 239.00)	
Single/multiple centersl				
Multiple centers	23 (100.00 %)	7 (100.00 %)	16 (100.00 %)	-
Single	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	
Locations				0.603
All United States	12 (52.17 %)	4 (57.14 %)	8 (50.00 %)	
Partial United States	8 (34.78 %)	1 (14.29 %)	7 (43.75 %)	
Outside United States	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	
NA*	3 (13.04 %)	2 (28.57 %)	1 (6.25 %)	
Blinding				0.125
Open-labe	13 (56.52 %)	2 (28.57 %)	11 (68.75 %)	
Double-blind	5 (21.74 %)	3 (42.86 %)	2 (12.50 %)	
Single-blind	2 (8.70 %)	0 (0.00 %)	2 (12.50 %)	
NA*	3 (13.04 %)	2 (28.57 %)	1 (6.25 %)	
Number of study groups				0.114
One	7 (30.43 %)	0 (0.00 %)	7 (43.75 %)	
Two	13 (56.52 %)	5 (71.43 %)	8 (50.00 %)	
NA*	3 (13.04 %)	2 (28.57 %)	1 (6.25 %)	
Comparator				0.149
Active contro	9 (39.13 %)	3 (42.86 %)	6 (37.50 %)	
Placebo/sham contro	4 (17.39 %)	2 (28.57 %)	2 (12.50 %)	
No contro	7 (30.43 %)	0 (0.00 %)	7 (43.75 %)	
NA*	3 (13.04 %)	2 (28.57 %)	1 (6.25 %)	
Randomized tria				0.114
Yes	13 (56.52 %)	5 (71.43 %)	8 (50.00 %)	
No	7 (30.43 %)	0 (0.00 %)	7 (43.75 %)	
NA*	3 (13.04 %)	2 (28.57 %)	1 (6.25 %)	
Analysis population				0.607
Only intention-to-treat (ITT)	4 (17.39 %)	2 (28.57 %)	2 (12.50 %)	
Only modified ITT	2 (8.70 %)	0 (0.00 %)	2 (12.50 %)	
ITT/modified ITT with other populations (per-protocol and/or safety populations)	16 (69.57 %)	5 (71.43 %)	11 (68.75 %)	
NA*	1 (4.35 %)	0 (0.00 %)	1 (6.25 %)	
PRO measure in at least one efficacy endpoint				0.005

(*continued on next page*)

Table 1 (*continued*)

Characteristics	N (%) or median (Q1, Q3)			
	Overall (N = 23)	**Pain neurology devices (N = 7)**	**Other neurological devices (N = 16)**	**p-value**
Yes	12 (52.17 %)	7 (100.00 %)	5 (31.25 %)	
No	11 (47.83 %)	0 (0.00 %)	11 (68.75 %)	
PRO measure in primary efficacy endpoints				0.005
Yes	9 (39.13 %)	6 (85.71 %)	3 (18.75 %)	
No	14 (60.87 %)	1 (14.29 %)	13 (81.25 %)	
PRO measure in secondary efficacy endpoints				0.182
Yes	8 (34.78 %)	4 (57.14 %)	4 (25.00 %)	
No	15 (65.22 %)	3 (42.86 %)	12 (75.00 %)	
PRO measure in tertiary or other efficacy endpoints				0.020
Yes	3 (13.04 %)	3 (42.86 %)	0 (0.00 %)	
No	20 (86.96 %)	4 (57.14 %)	16 (100.00 %)	
Any pain-related PROs in safety endpoints				0.005
Yes	12 (52.17 %)	7 (100.00 %)	5 (31.25 %)	
No	11 (47.83 %)	0 (0.00 %)	11 (68.75 %)	
Any pain-related PROs in safety endpoints through the visual analog scale				0.304
Yes	1 (4.35 %)	1 (14.29 %)	0 (0.00 %)	
No	22 (95.65 %)	6 (85.71 %)	16 (100.00 %)	
Any PROs adverse events other than pain in safety endpoints				1.000
Yes	9 (39.13 %)	3 (42.86 %)	6 (37.50 %)	
No	14 (60.87 %)	4 (57.14 %)	10 (62.50 %)	

movement disorders (N = 3, 13.0 %), surgical repair/aide (N = 3, 13 %), epilepsy (N = 1, 4.4 %), neonatal neurology (N = 1, 4.4 %), and neuro-oncology (N = 1, 4.4 %). Only 3 devices (12.0 %) had an expedited review and 5 (21.7 %) were not implantable. When the devices were separated to two groups of pain neurology devices versus other devices, there were no statistically significant differences in approval year (p = 1.000), whether the review was expedited (p = 0.526), or whether the device was implantable (p = 0.272).

Among the pivotal clinical trials designed and conducted for the 23 devices, all trials were multicenter with approximately half (N = 12, 52.2 %) conducted entirely in the United States. The median number of subjects enrolled was 191.0 (IQR: 152.0–250.0). Regarding study design, 13 (56.5 %) were open-label, 5 (21.7 %) were double-blind, and 2 (8.7 %) were single-blind. Seven (30.4 %) had only one study group while 13 (56.5 %) had two study groups. All 13 (56.5 %) of studies with two study groups were randomized, while the other 7 (30.4 %) studies were not randomized. Nine (39.1 %) had an active control group, 4 (17.4 %) had a placebo/sham group, and 7 (30.4 %) had no control. Noticeably, 2 of the neurological devices were approved only based upon literature reviews [10,11], and one was approved based upon meta-analysis combined with literature review [12]. Therefore, information on their pivotal trials reported in SSEDs was missing. Upon comparing pain neurology devices with other devices, there were no statistically significant differences in number of subjects enrolled (p = 0.483), location of studies (p = 0.603), blinding (p = 0.125), number of study groups (p = 0.114), comparator group type (p = 0.149), whether the studies were randomized (p = 0.114), or analysis population (p = 0.607).

Additionally, there was no statistically significant differences in whether secondary efficacy endpoints included a PRO measurement (p = 0.182), whether there were any pain related PROs in safety endpoints through the visual analog scale for safety endpoints (p = 0.304), or whether there were any PRO adverse events other than pain in safety endpoints (p = 1.000). However, all pain neurology devices had a PRO measure as at least one of the efficacy endpoints compared to only 5 (31.3 %) devices from other neurological devices (p = 0.005). There was also a significant difference in the studies that had a PRO measure as a primary efficacy endpoint (85.7 % vs. 18.8 %, p = 0.005), as well as tertiary or other efficacy endpoints (42.9 % vs. 0 %, p = 0.020) between pain neurology devices and other neurological devices. All pain neurology devices had pain related PROs as a safety endpoint compared to only 5 (31.3 %) devices from other neurological specialty areas (p = 0.005).

4. Discussion and conclusions

The scope of this short article encompasses an exhaustive analysis of the clinical studies underpinning high-risk Class III neurological medical devices granted CDRH approval via the PMA pathway between 2001 and 2022. The methodology employed in this study involves a comprehensive review of SSED documents published by the CDRH for each approved neurological device (supplementary materials, Table S1). By focusing on this two-decade span, the study aims to distill key insights into the characteristics and use of PROs of the pivotal clinical trials designed for these devices. Concurrently, it delves into the evidentiary foundation established within the regulatory framework of pivotal clinical trials, elucidating the extent of evidence generated to support these innovative devices.

Moreover, the article scrutinizes the extent to which PROs are harnessed in these pivotal trials, highlighting the role of patient-centric outcomes in evaluating device efficacy and impact. A distinctive facet of these pivotal clinical trials is the prominent role of PROs as endpoints. Significantly, the study unveils the pivotal role of PROs in assessing neurological device efficacy and safety. While the use of PROs is extensive in evaluating neurological devices, the study reveals that pain neurology devices exhibit a notable emphasis on PRO endpoints, both as primary and secondary measures. This divergence from other neurological devices highlights the distinct priorities within pain management and the value attributed to PROs in this context.

Despite the comprehensive analysis conducted in this study, it is crucial to acknowledge certain limitations that may impact the generalizability and interpretation of the findings. Firstly, the scope of the research is constrained to high-risk Class III neurological medical devices approved by the FDA through the PMA. It does not include those devices or those approved through alternative pathways (e.g., 510(k), De Novo, and Humanitarian Device Exemption), potentially limiting the overall representativeness of the broader landscape of neurological

medical devices. Additionally, the reliance on FDA's publicly available data may introduce a source of bias. The completeness and accuracy of the data within these documents depend on the thoroughness of reporting by the FDA scientific reviewers. In cases where information was unavailable or incomplete, supplementary data from ClinicalTrials.gov was utilized, introducing an additional layer of potential variability in data quality. Lastly, the study's analysis is retrospective, relying on historical data, and does not account for potential changes in regulatory processes, technological advancements, or shifts in medical practices that may have occurred after the study's endpoint in June 2022. Therefore, the findings should be interpreted in the context of the regulatory landscape and clinical practices prevalent during the studied period.

In conclusion, this article contributes valuable insights into the realm of high-risk neurological medical devices, their regulatory journey, and the pivotal role of PROs. The interplay between revolutionary device innovation, regulatory scrutiny, and patient-centered assessments underscores the holistic approach required in advancing neurological disorder management.

Ethics approval and consent to participate

This study was conducted by analyzing de-identified, publicly available data, and therefore does not constitute human subjects research; its ethics review was waived because there was no interaction with any individual and no identifiable private information was used.

Consent for publication

Not applicable.

Availability of data and materials

All original Summary of Safety and Effectiveness Data are publicly available in the CDRH's public database of PMAs (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm).

Funding

None.

CRediT authorship contribution statement

Morgan E. Ryan: Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Siddharth Srivastava:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Investigation, Data curation, Conceptualization. **Lin Wan:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Investigation, Data curation, Conceptualization. **Guang Yang:** Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Bo Zhang:** Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data are publicly available

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.conctc.2024.101254.

References

[1] C. Peña, K. Bowsher, J. Samuels-Reid, FDA-approved neurologic devices intended for use in infants, children, and adolescents, Neurology 63 (7) (2004 Oct 12) 1163–1167.
[2] N.T. Phi, T. Oikonomidi, P. Ravaud, V.T. Tran, Assessment of US Food and Drug administration–approved digital medical devices for just-in-time interventions: a systematic review, JAMA Intern. Med. 183 (8) (2023 Jul 17) 858–869.
[3] C.M. Loftus, M. Hoffmann, W. Heetderks, X. Zheng, C. Peña, Regulation of neurological devices and neurointerventional endovascular approaches for acute ischemic stroke, Front. Neurol. 9 (2018 Jun 11) 320.
[4] Food and Drug Administration. Summary of Safety and Effectiveness Data: Vercise™ Deep Brain Stimulation (DBS) System (P150031B). https://www.accessdata.fda.gov/cdrh_docs/pdf15/P150031B.pdf.pdf. Accessed June 2, 2022.
[5] Food and Drug Administration. Summary of Safety and Effectiveness Data: Saluda Medical Evoke® SCS System (P190002B). https://www.accessdata.fda.gov/cdrh_docs/pdf19/P190002B.pdf. Accessed June 2, 2022.
[6] P.B. Hutt, R.A. Merrill, A.M. Kirschenbaum, The standard of evidence required for premarket approval under the medical device amendments of 1976, Food Drug Law J. 47 (6) (1992 Jan 1) 605–628.
[7] K.N. Lohr, B.J. Zebrack, Using patient-reported outcomes in clinical practice: challenges and opportunities, Qual. Life Res. 18 (1) (2009 Feb) 99–107.
[8] N.K. Leidy, M. Vernon, Perspectives on patient-reported outcomes, Pharmacoeconomics 26 (5) (2008 May) 363–370.
[9] U.S. Food and Drug Administration, Guidance for industry, patient-reported outcome measures: use in medical product development to support labeling claims, Document issued in December (2009).
[10] Food and Drug Administration. Summary of Safety and Effectiveness Data: PRECISION™ Spinal Cord Stimulator (SCS) System (P030017B). https://www.accessdata.fda.gov/cdrh_docs/pdf3/P030017B.pdf.pdf.pdf. Accessed June 2, 2022.
[11] Food and Drug Administration. Summary of Safety and Effectiveness Data: Genesis Neurostimulation (IPG) System (P010032B). https://www.accessdata.fda.gov/cdrh_docs/pdf/P010032b.pdf. Accessed June 2, 2022.
[12] Food and Drug Administration. Summary of Safety and Effectiveness Data: Algovita™ Spinal Cord Stimulation (SCS) System (P130028B). https://www.accessdata.fda.gov/cdrh_docs/pdf13/P130028b.pdf. Accessed June 2, 2022.