# Types of Endpoints of New Molecular Entities Approved by the FDA: The Increasing Importance of Patient-Reported Outcomes

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## BACKGROUND

- Clinical outcome assessments (COAs) measure aspects of a patient's health status and are used to evaluate the clinical and humanistic benefit of a therapy for a particular disease or condition
- Types of COAs include patient-reported outcomes (PROs), clinician-reported outcomes (ClinROs), and performance outcomes (PerfOs)
- A study looking at types of COAs of new molecular entities (NMEs) approved by the Food and Drug Administration (FDA) from 2011–2015 found that primary endpoints for the vast majority of studies were largely based on biomarkers alone (36.8%) and ClinROs alone (33.0%)[2]
  - Survival as a primary endpoint was the most prominent in pivotal studies related to cancer
  - The number of approvals based on PROs as primary endpoints was small
  - Primary endpoints related to PROs were common in diseases related to genitourinary, musculoskeletal, digestive, and nervous systems
- Given the increasing emphasis on patient-centered care, PROs have become especially important in recent years

**Table 1. COAs of Interest[a,1]**

| | |
|---|---|
| **Patient-reported outcomes (PROs)** | A measurement based on a report that comes directly from the patient (ie, study subject) about the status of a patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else |
| **Clinician-reported outcomes (ClinROs)** | A measurement based on a report that comes from a trained healthcare professional after observation of a patient's health condition. Most ClinRO measures involve a clinical judgment or interpretation of the observable signs, behaviors, or other manifestations related to a disease or condition |
| **Performance outcomes (PerfOs)** | A measurement based on a standardized task performed by a patient that is administered and evaluated by an appropriately trained individual or is independently completed. |

[a] This list of COAs is not exhaustive and there are other types of COAs, such as observer-reported outcomes (ObsROs), that are not included. ObsROs were not included in the current study, as they were not included as primary endpoints for any studies of interest.

## OBJECTIVES

- The objective of the current study was to assess the use of COAs as primary and secondary endpoints, particularly PROs, in confirmatory studies of NMEs approved by the FDA from 2016–2019

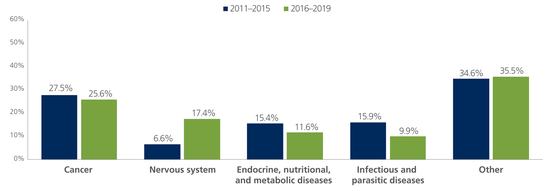
## METHODS

- NMEs approved by the FDA for treatment between January 1, 2016 and December 31, 2019 were identified using the FDA website
- FDA approval drug labels were reviewed to identify the drug indication and primary and secondary endpoints of confirmatory studies
- ICD-10 codes were used to classify the disease type, and the primary and secondary endpoints were classified based on the type of endpoint (survival, biomarker, ClinRO, PRO, PerfO)
- A descriptive analysis was conducted by analyzing the frequency of measured characteristics

## RESULTS

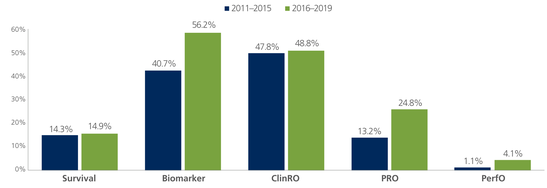
- A total of 122 NMEs were approved by the FDA for treatment during 2016–2019; however, approval of 1 of the NMEs[3] was based on limited clinical safety and efficacy data, and information on the pivotal trials for this NME was not provided in the FDA approval drug label. Therefore, there were 121 NMEs with sufficient data that were included in the final analysis
- The most common disease types of NMEs approved in 2016–2019 were: 1.) cancer; 2.) diseases of the nervous system; and 3.) endocrine, nutritional, and metabolic diseases; whereas in 2011-2015, the most common were: 1.) cancer; 2.) infectious and parasitic diseases; and 3.) endocrine, nutritional, and metabolic diseases (**Figure 1**)
- The proportions of NMEs approved in 2011–2015 compared to 2016–2019 for cancer were similar (27.5% vs 25.6%), but there was a much higher proportion of NMEs approved for diseases of the nervous system in 2016–2019 compared to 2011–2015 (17.4% vs 6.6%; **Figure 1**)
- **Figure 2** shows that use of all endpoints in pivotal studies for FDA-approved NMEs increased from 2011–2015 to 2016–2019, particularly for biomarkers (40.6%–56.2%) and PROs (13.2%–24.8%)
- Of the 182 approved NMEs in 2011–2015, 79.1% (n=144) used 1 type of endpoint by itself[2] compared to 61.2% (n=74) of approved NMEs in 2016–2019, indicating that there is increasing use of multiple endpoint types in pivotal studies
- **Table 2A** shows the types of primary endpoints (either alone or in conjunction with other endpoint types, allowing for summation of >100%) used in the pivotal studies for FDA-approved NMEs from 2011-2015[2]
- **Table 2B** shows the types of primary endpoints (either alone or in conjunction with other endpoint types, allowing for summation of >100%) used in the pivotal studies for FDA-approved NMEs from 2016–2019
  - Biomarkers were the most common primary endpoint, followed by ClinROs, PROs, survival, and PerfOs
  - Biomarkers and ClinROs were used for almost all NMEs for cancer
  - PROs were the most common primary endpoint for NMEs for diseases of the nervous system, followed by ClinROs and biomarkers
- When examining unique combinations of primary endpoints for FDA-approved NMEs from 2016–2019, biomarkers alone were the most common primary endpoint (24.0%), followed by biomarkers and ClinROs together (19.0%), PROs alone (18.2%), ClinROs alone (14.9%), and survival, biomarkers, and ClinROs together (9.9%)
- PROs were used in 100.0% of NMEs for mental, behavioral, and neurodevelopmental disorders; 66.7% of musculoskeletal system and connective tissue diseases; and 57.1% of diseases of the nervous system (**Figure 3**)
- 80 NMEs reported secondary endpoints used in their pivotal studies, and of these, 30.0% (n=24) used PROs as a secondary endpoint (either as the sole secondary endpoint or in conjunction with another type of COA)

**Figure 1. FDA-Approved NMEs From 2011–2015[2] and 2016–2019**



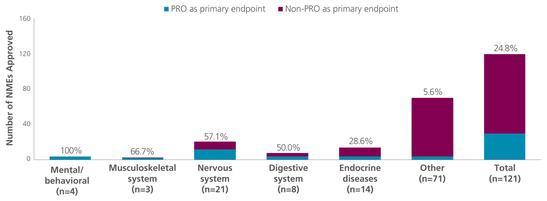

Key: FDA – Food and Drug Administration; NME – new molecular entity.

**Figure 2. Change in Primary Endpoint Use of FDA-Approved NMEs From 2011–2015[2] to 2016–2019**




Key: ClinRO – clinician-reported outcome; FDA – Food and Drug Administration; NME – new molecular entity; PerfO – performance outcome; PRO – patient-reported outcome.

**Figure 3. Percentage of PROs Used as Primary Endpoints in FDA-Approved NMEs From 2016–2019 by Disease Type**




Key: Endocrine diseases – endocrine, nutritional and metabolic diseases; FDA – Food and Drug Administration; Mental/behavioral – mental, behavioral, and neurodevelopmental disorders; Musculoskeletal system – diseases of the musculoskeletal system and connective tissue; NME – new molecular entity; PRO – patient-reported outcome.

**Table 2A. Types of Primary Endpoints of FDA-Approved NMEs From 2011–2015[2]**

| | Survival | Biomarker | ClinRO | PRO | PerfO | NMEs Approved |
|---|---|---|---|---|---|---|
| **Cancer** | 18 (36.0%) | 7 (14.0%) | 38 (77.0%) | 0 (0.0%) | 0 (0.0%) | 50 (27.5%) |
| **Nervous system** | NR | NR | NR | NR | NR | — |
| **Endocrine, nutritional, and metabolic diseases** | 2 (7.1%) | 24 (85.7%) | 2 (7.1%) | 1 (3.65) | 1 (3.6%) | 28 (15.4%) |
| **Infectious and parasitic diseases** | 1 (3.4%) | 16 (55.2%) | 11 (37.9%) | 3 (10.3%) | 0 (0.0%) | 29 (15.9%) |
| **Other** | 5 (6.7%) | 27 (36.0%) | 36 (48.0%) | 20 (26.7%) | 1 (1.3%) | 75 (41.2%) |
| **All** | **26 (14.3%)** | **74 (40.7%)** | **87 (47.8%)** | **24 (13.2%)** | **2 (1.1%)** | **182 (100.0%)** |

Key: ClinRO – clinician-reported outcome; FDA – Food and Drug Administration; NME – new molecular entity; NR – not reported; PerfO – performance outcome; PRO – patient-reported outcome.
Note: For many FDA-approved NMEs, there were multiple primary endpoints and, therefore, some NMEs utilized more than one endpoint type, allowing for summation of >100%.

**Table 2B. Types of Primary Endpoints of FDA-Approved NMEs From 2016–2019**

| | Survival | Biomarker | ClinRO | PRO | PerfO | NMEs Approved |
|---|---|---|---|---|---|---|
| **Cancer** | 14 (45.2%) | 29 (93.5%) | 29 (93.5%) | 0 (0.0%) | 0 (0.0%) | 31 (25.6%) |
| **Nervous system** | 0 (0.0%) | 3 (14.3%) | 7 (33.3%) | 12 (57.1%) | 2 (9.5%) | 21 (17.4%) |
| **Endocrine, nutritional, and metabolic diseases** | 1 (7.1%) | 7 (50.0%) | 5 (35.7%) | 4 (28.6%) | 1 (7.1%) | 14 (11.6%) |
| **Infectious and parasitic diseases** | 1 (8.3%) | 11 (91.7%) | 1 (8.3%) | 0 (0.0%) | 0 (0.0%) | 12 (9.9%) |
| **Other** | 2 (4.7%) | 18 (41.9%) | 17 (39.5%) | 14 (32.6%) | 2 (4.7%) | 43 (35.5%) |
| **All** | **18 (14.9%)** | **68 (56.2%)** | **59 (48.8%)** | **30 (24.8%)** | **5 (4.1%)** | **121 (100.0%)** |

Key: ClinRO – clinician-reported outcome; FDA – Food and Drug Administration; NME – new molecular entity; NR – not reported; PerfO – performance outcome; PRO – patient-reported outcome.
Note: For many FDA-approved NMEs, there were multiple primary endpoints and, therefore, some NMEs utilized more than one endpoint type, allowing for summation of >100%.

## DISCUSSION

- In 2011–2015, the most common disease types of NMEs in order were cancer; infectious and parasitic diseases; and endocrine, nutritional, and metabolic diseases; in 2016–2019, cancer remained the most common, but diseases of the nervous system were the second most common, and endocrine, nutritional, and metabolic diseases were the third most common, indicating that NMEs for diseases of the nervous system have increased relative to other disease types
- Use of all endpoints in pivotal studies for FDA-approved NMEs increased from 2011–2015 to 2016–2019, particularly for biomarkers and PROs
- In 2016–2019, biomarkers were the most common endpoint for cancer (along with ClinROs); endocrine, nutritional, and metabolic diseases; infectious diseases; and most other diseases; PROs were the most common endpoint for diseases of the nervous system
- The use of PROs as a primary endpoint in 2016–2019 (24.8%) almost doubled from what was previously reported in 2011–2015 (13.2%), and PROs were also used as a secondary endpoint in almost one-third of NMEs approved from 2016–2019
- Limitations of the current study include subjectivity of disease type classification and endpoint type classification, as well as the inability to determine interrater reliability for ratings of disease type classification and primary endpoint classification between FDA-approved NMEs from 2011–2015 and 2016–2019

## CONCLUSIONS

- There has been an increase in the proportion of NMEs related to diseases of the nervous system from 2011–2015 to 2016–2019; traditionally, diseases of the nervous system have been difficult to treat, but perhaps recent advances in science have allowed for more treatments of these diseases
- In the past, ClinROs were the most common primary endpoint in FDA-approved NMEs, but biomarkers have become more prominent in recent years, possibly an indication that improved technology and science have allowed for more objective markers of disease activity
- Although the majority of pivotal studies were largely based on biomarkers and ClinROs in the past 4 years, PROs have seen a sharp increase in use as the primary endpoint in pivotal studies, almost doubling from 2011–2015 to 2016–2019, indicating the rising importance of the patient perspective in pivotal trial outcomes

**References: 1.** Food and Drug Administration. Clinical outcome assessments (COA): frequency asked questions. https://www.fda.gov/about-fda/clinical-outcome-assessments-coa-frequently-asked-questions. Updated February 15, 2019. Accessed March 16, 2020. **2.** Gnanasakthy A, DeMuro C. Outcome assessments of primary endpoints of new drugs approved by the FDA (2011-2015). Poster presented at: 21st Annual International Meeting of the International Society for Pharmacoeconomics (ISPOR); May 21-25, 2016; Washington, DC. **3.** Recarbrio [package insert]. Whitehouse Station, NJ: Merck Sharp & Dohme Corp.; 2019.

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