# Use of External Control Arms in Novel Drug Approvals by the U.S. Food and Drug Administration: A Targeted Review

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## INTRODUCTION

- Randomized clinical trials (RCTs) have long been considered the gold standard in clinical research. However, challenges such as limited patient population size, patient heterogeneity, and ethical concerns have prompted the exploration of real-world evidence (RWE) to complement or even replace RCTs.
- External control arms (ECAs) have emerged as a promising realm of RWE, allowing for comparison of treatment effects with historical or concurrent controls, thereby potentially reducing the need for placebo-controlled trials.
- The U.S. Food and Drug administration (FDA) has increasingly embraced the integration of ECAs into the regulatory decision-making process.

## OBJECTIVE

- This study aims to assess the frequency with which ECAs are being utilized in novel drug approvals by the FDA, from 2017–2023, and examine the methodological considerations, methods to derive ECAs, and challenges associated.

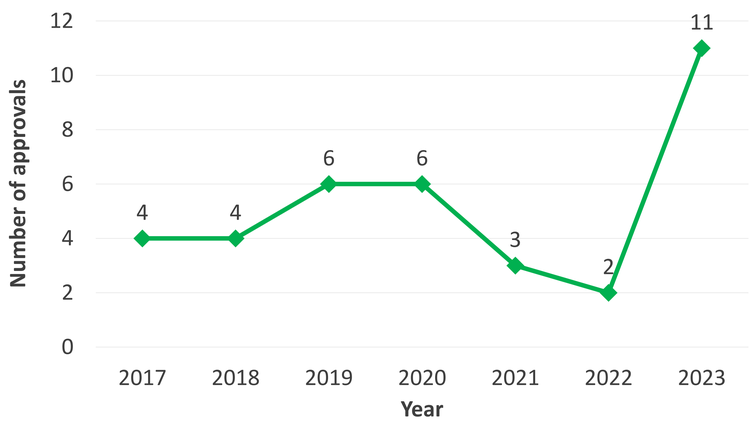
## METHODS

- NDAs between 2017 and 2023 were identified from the FDA database.
- FDA labels, approval letters, and NDA review documents were searched using keywords to identify approvals where ECAs were used in pivotal trials.
- Details pertaining to approval year, disease area, and sources of ECA were analysed and categorized.

## RESULTS

- Between 2017 and 2023, 349 novel drugs were approved by the FDA; of which ECAs were utilized in 10.3% of the approvals, increasing from four in 2017 to 11 in 2023 **(Figure 1)**.

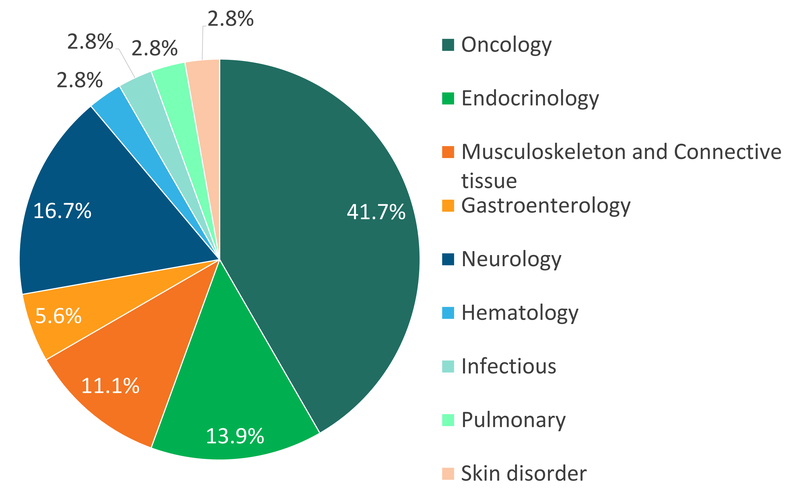
**Figure 1. Number of ECA-based approvals by FDA between 2017-2023**




## RESULTS (CONTINUED)

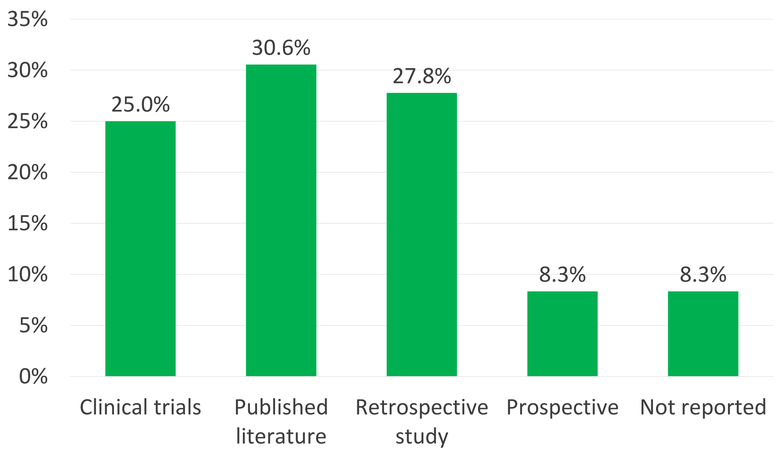
- Due to a limited patient cohort, ECAs were most commonly utilized in submission for oncology indications (41.7%), neurology (16.7%) and endocrinology (13.9%) **(Figure 2)**.
  - Most ECA-based approvals (86.1%) were for rare diseases, including NSCLC (9.7%), Mekel cell carcinoma (6.5%), multiple myeloma (6.5%), Fabry's diseases (6.5%), and Duchenne muscular dystrophy (6.5%).

**Figure 2. Proportion of approvals by indication type**




- ECAs were derived from retrospective studies (28.6%), previously published data (28.6%), clinical trials (25.7%), prospective studies (8.57%) and others (8.57%) **(Figure 3)**.

**Figure 3. Type of evidence used to derive ECA**




## RESULTS (CONTINUED)

- Due to the high unmet need for several diseases, the FDA has steadily increased the acceptance of ECA-based submissions. However, there are certain limitations highlighted by the FDA in its feedback **(Table 1)**.

**Table 1. Sample feedback underlying ECAs in FDA-based novel drug approvals**

| Brand name | ECA | FDA feedback |
|---|---|---|
| **Elfabrio** | Observational study | • Use of ECA provided informative and supportive evidence to evaluate primary endpoints<br>• There are limitations to use of external control arms |
| **Skyclarys** | Clinical trials | • Confounding and numerous known and unknown factors can lead to bias<br>• Results should be interpreted carefully |
| **Sohonos** | Clinical trials | • Residual uncertainty on the impact of unknown confounding factors and potential bias<br>• Differential loss to follow-up |
| **Amvuttra** | Clinical trials | • Unethical to use concurrent placebo due to life-threatening nature of disease<br>• Reasonable to consider the use of external control |
| **Koselugo** | Prospective study | • ECA provided supportive evidence for efficacy<br>• ECA inadequate for any comparative analysis |
| **Tazverik** | Retrospective study | • Natural history study was not adequately designed to serve as an external control arm<br>• Methodology inadequate to perform comparative analysis |

## CONCLUSIONS

- The increased acceptance of ECAs by regulatory agencies signifies their transformative role in improving clinical trials in conditions with limited patient cohorts.
- Although approvals have increased, the FDA's Center for Drug Evaluation and Research has suggested pharmaceutical companies to carefully consider the selection bias, heterogeneity, and confounding factors associated with the use of ECAs.
- Considerations must be taken to address potential biases associated with ECAs and to ensure the validity of comparisons.

**REFERENCES**

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