Evidence of RWE in Oncology Accelerated Approvals: Analysis of Existing Evidence and Way Forward

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Listen. Devise. **Breakthrough**

Contents

Rationale

Real-world evidence (RWE) is gaining recognition in regulatory approvals by leveraging real-life patient data and outcomes.

Despite its promise, RWE is underutilized in oncology, with traditional clinical trials as the dominant evidence source.

An evidence gap exists in understanding RWE, clinical trial, and hybrid data use in oncology AAs, especially with AI/ML's impact.

This scoping review aims to evaluate RWE's current role in oncology AAs and the extent of AI/ML integration to guide regulatory advancements.

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RWE Benefits

CONTEXTUALIZATION:

RWE shows how treatments perform in everyday clinical settings, factoring in real-world variables like demographics and comorbidities.

COMPARISON:

RWE enables comparison of treatment options, assessing their effectiveness across diverse patient populations.

BOTH:

RWE often serves both purposes, contextualizing outcomes while enabling meaningful comparisons across therapies and patient groups.

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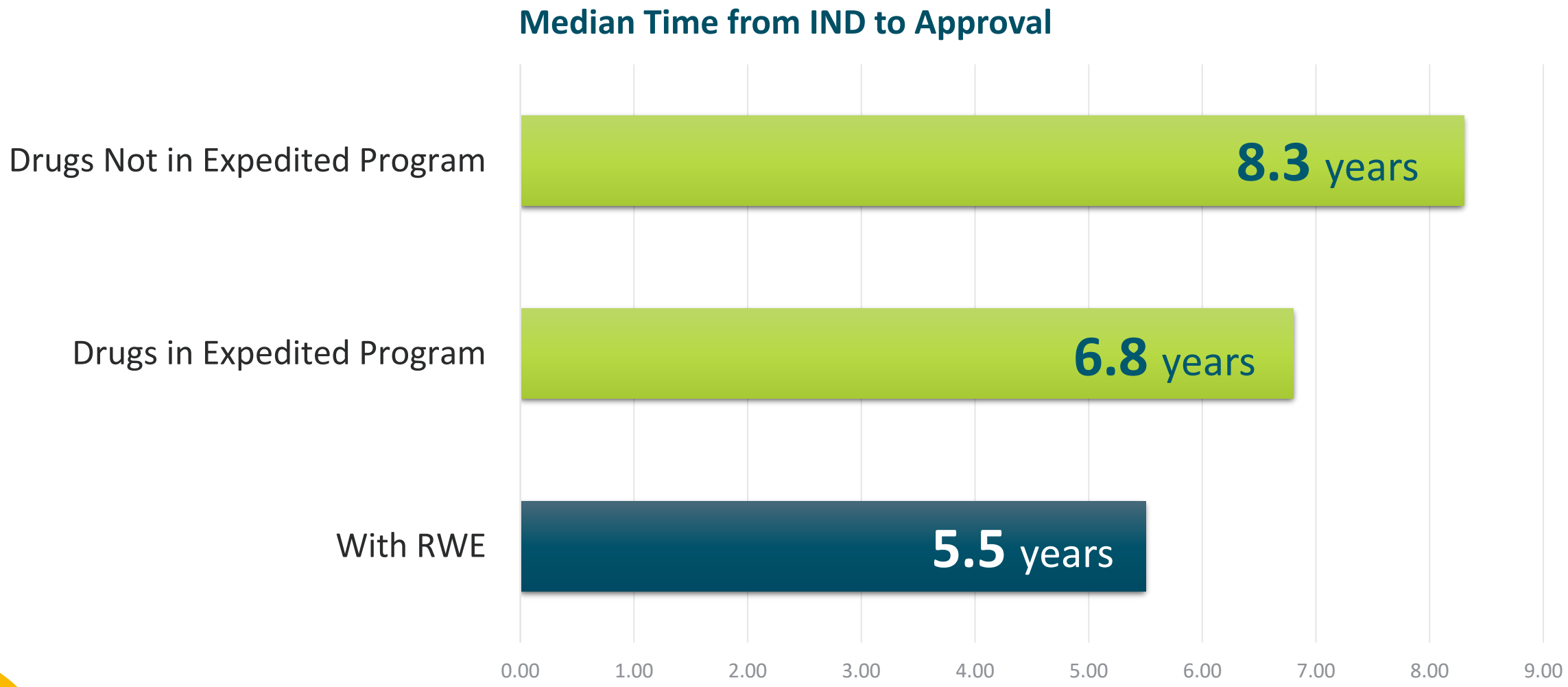
Timeline Impact With Use of RWE



Hwang TJ, Franklin JM, Chen CT, Lauffenburger JC, Gyawali B, Kesselheim AS, Darrow JJ. Efficacy, safety, and regulatory approval of Food and Drug Administration–designated breakthrough and nonbreakthrough cancer medicines. *Journal of Clinical Oncology*. 2018 Jun 20;36(18):1805-12.

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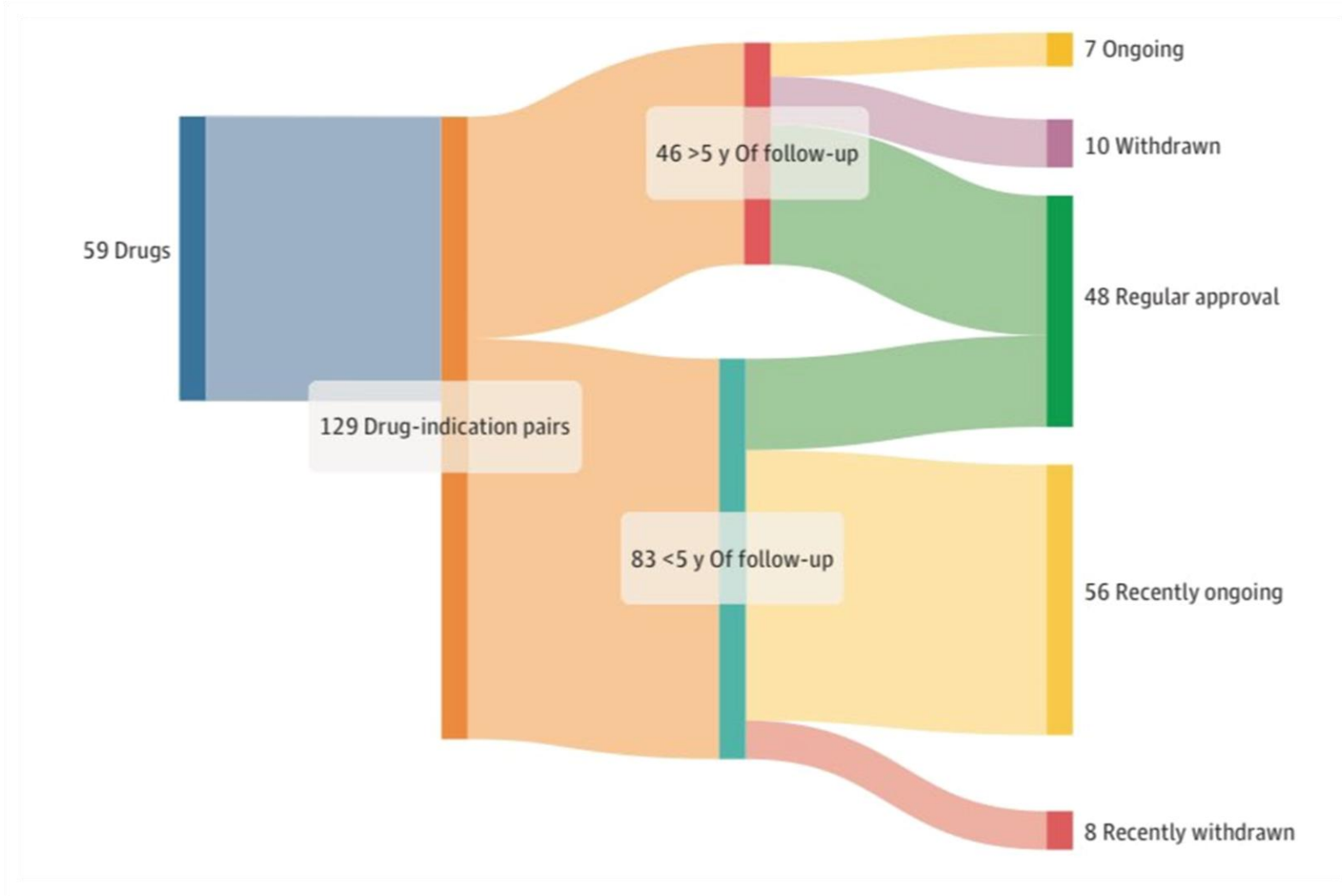
Oncology Drugs Granted AA & Outcome (2013-23)



Oncology drugs granted accelerated approval and regulatory outcome, based on follow-up time.

Liu IT, Kesselheim AS, Cliff ER. Clinical benefit and regulatory outcomes of cancer drugs receiving accelerated approval. *JAMA*. 2024 May 7;331(17):1471-9.

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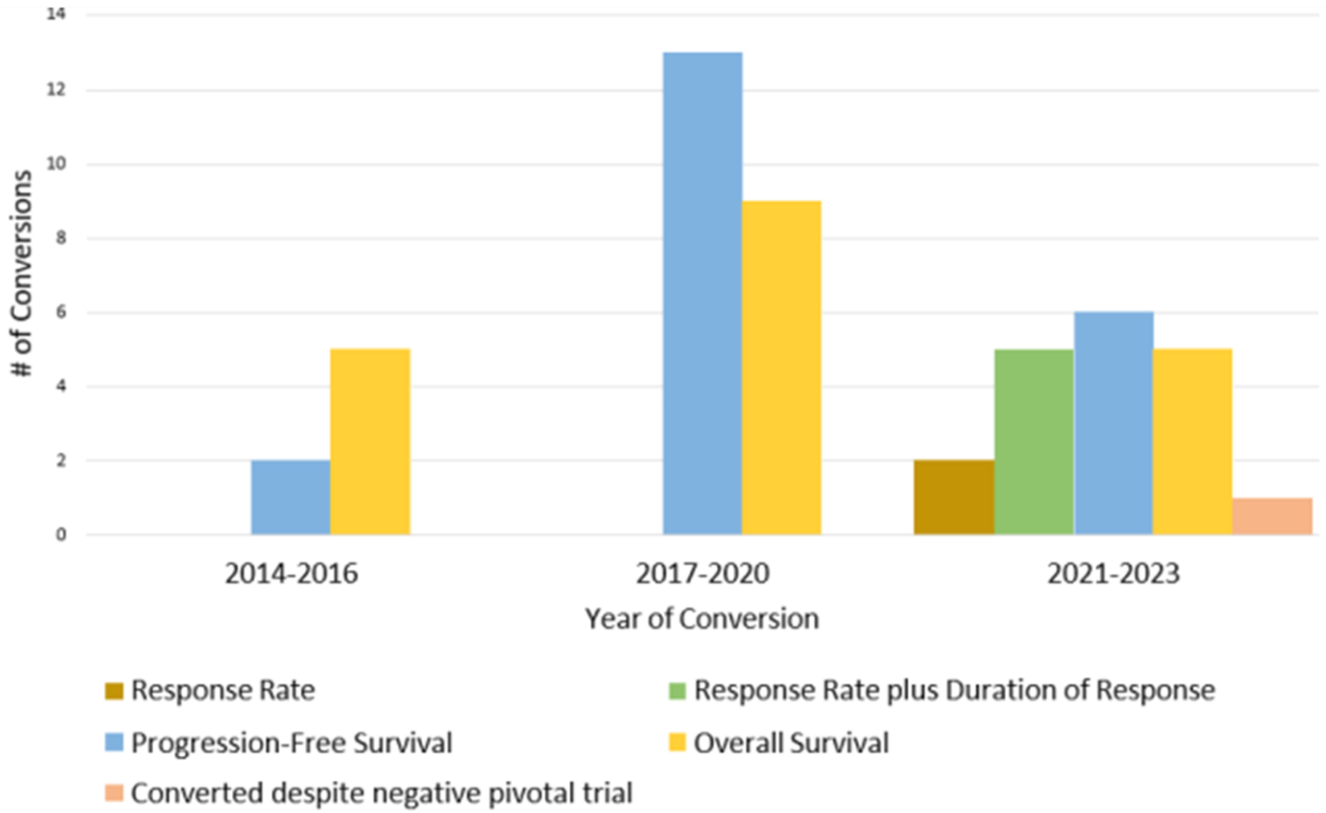
Confirmatory Trial Endpoints Used for Conversion to Regular Approval



Accelerated approvals for cancer indications converted to regular approval with trial endpoint used to support conversion.

Liu IT, Kesselheim AS, Cliff ER. Clinical benefit and regulatory outcomes of cancer drugs receiving accelerated approval. *JAMA*. 2024 May 7;331(17):1471-9.

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FDA Accelerated Approval Statistics (as on 29 Oct 2024)

ONGOING ONCOLOGY AA:

64

ONCOLOGY AA WITH VERIFIED CLINICAL BENEFIT:

106

WITHDRAWN ONCOLOGY AA:

30

Accelerated Approval Program | FDA

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RCT Duplicate Initiative

- Aimed to compare RCT findings with non-interventional RWE findings that emulate trial designs as closely as possible.
- Focus on developing a consistent, transparent, and reproducible process acceptable to regulators.
- Goals of the Initiative:
  - **Transparent RWE Development**: Predefine and preregister all study measures for a single primary analysis.
  - **Quantify Concordance**: Assess how often RWE studies align with RCT conclusions.
  - **Identify Influencing Factors**: Examine the factors that affect whether RCTs and RWE yield similar results.

Franklin JM, Patorno E, Desai RJ, Glynn RJ, Martin D, Quinto K, Pawar A, Bessette LG, Lee H, Garry EM, Gautam N. Emulating randomized clinical trials with nonrandomized real-world evidence studies: first results from the RCT DUPLICATE initiative. *Circulation*. 2021 Mar 9;143(10):1002-13.

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RCT Duplicate Initiative

METHODS:
Replicated 10 RCTs using US commercial and Medicare claims data, applying pre-specified inclusion/exclusion criteria, endpoints, and propensity score matching to control for confounders.

RESULTS:
6 out of 10 replications had regulatory conclusions aligned, and 8 out of 10 had hazard ratio estimates within the 95% CI from the corresponding RCTs.

CONCLUSIONS:
Concordance between RCT and RWE findings varies, with active comparators improving validity, but further emulations are needed to better understand when RWE matches RCT outcomes.

Franklin JM, Patorno E, Desai RJ, Glynn RJ, Martin D, Quinto K, Pawar A, Bessette LG, Lee H, Garry EM, Gautam N. Emulating randomized clinical trials with nonrandomized real-world evidence studies: first results from the RCT DUPLICATE initiative. *Circulation*. 2021 Mar 9;143(10):1002-13.

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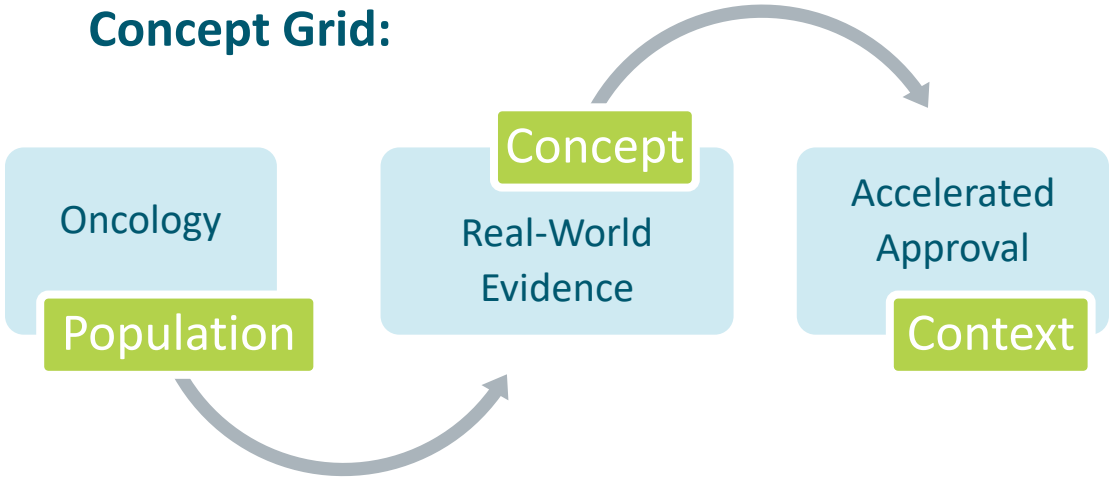
RWE & AA in Oncology: A Scoping review

Research Question:

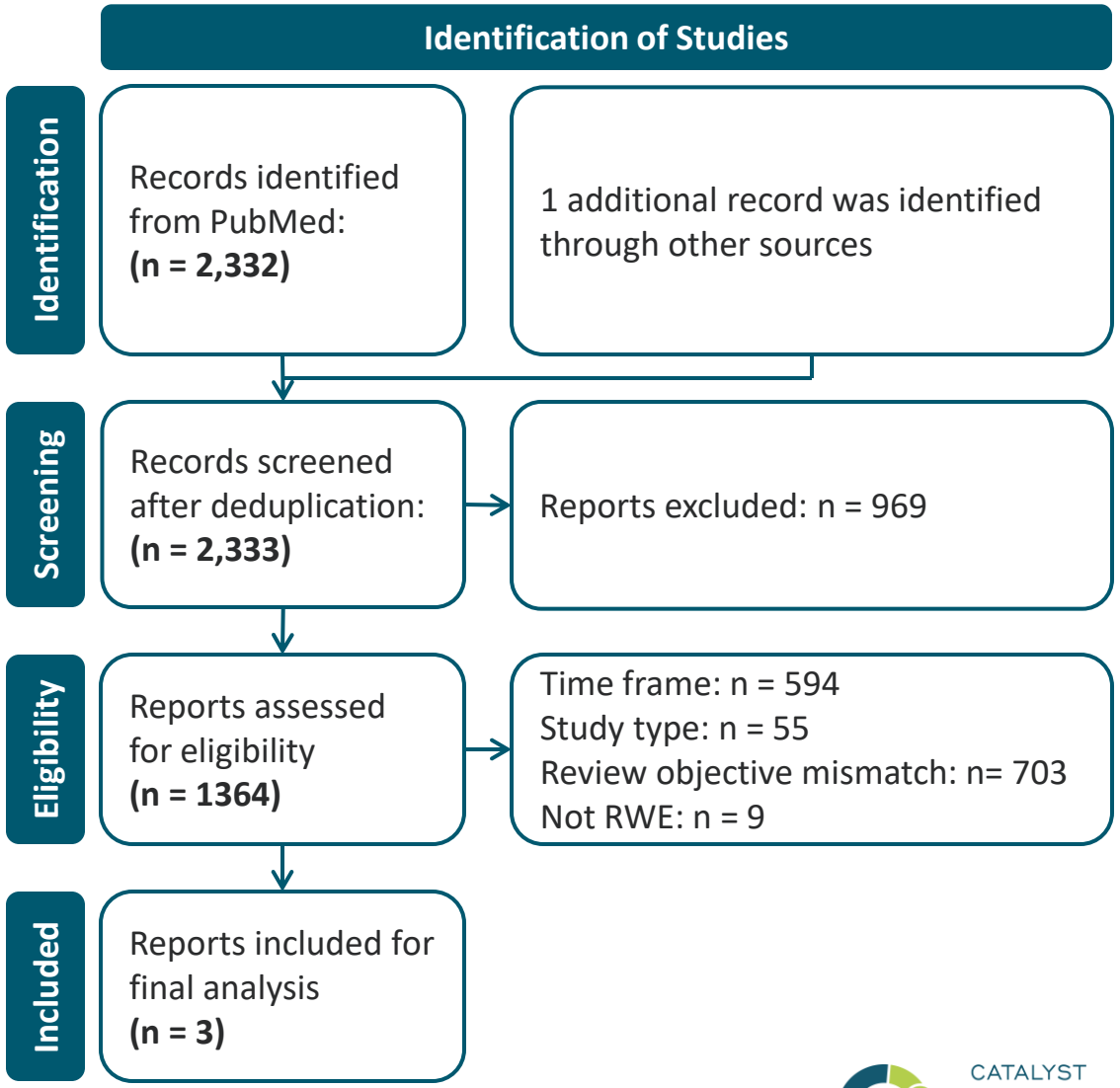
How can Real-World Evidence support and enhance the Accelerated Approval process for oncology drugs ?

Concept Grid:



RWE Keywords:

"Retrospective," "observational," "real world," "chart review," "claims," "electronic medical record," "natural history" with oncology context for FDA and EMA



Scoping Review Results

- **Report Characteristics**
  - Number of Studies - 3
    - **Study type**: 1 SLR, 1 FDA summary, 1 observational cohort study
    - **Country**: 2 US, 1 not applicable
- **Record Characteristics**

Author	Title	Study Design	Study Population	Remarks
Bird et al. 2020	Idelalisib for Treatment of Relapsed Follicular Lymphoma and Chronic Lymphocytic Leukemia: A Comparison of Treatment Outcomes in Clinical Trial Participants vs Medicare Beneficiaries.	Comparative observational study using clinical trial data vs. Medicare Beneficiaries Data	Patients with Relapsed Follicular Lymphoma and Chronic Lymphocytic Leukemia	RWE study was mutually exclusive from clinical trial data that was used for accelerated approval of the study drug
Singh et al. 2024	FDA Approval Summary: Alpelisib for PIK3CA-Related Overgrowth Spectrum.	Site-based retrospective non-interventional medical chart review	Pediatric and adult male and female patients with PIK3CA-Related Overgrowth Spectrum (PROS)	Very limited direct relevance with oncology

Bird ST, Tian F, Flowers N, Przepiorka D, Wang R, Jung TH, Kessler Z, Woods C, Kim B, Miller BW, Wernecke M. Idelalisib for treatment of relapsed follicular lymphoma and chronic lymphocytic leukemia: a comparison of treatment outcomes in clinical trial participants vs medicare beneficiaries. *JAMA oncology*. 2020 Feb 1;6(2):248-54.
Singh S, Bradford D, Li X, Mishra-Kalyani PS, Shen YL, Wang L, Zhao H, Xiong Y, Liu J, Charlab R, Kraft J. FDA Approval Summary: Alpelisib for PIK3CA-Related Overgrowth Spectrum. *Clinical Cancer Research*. 2024 Jan 5;30(1):23-8.

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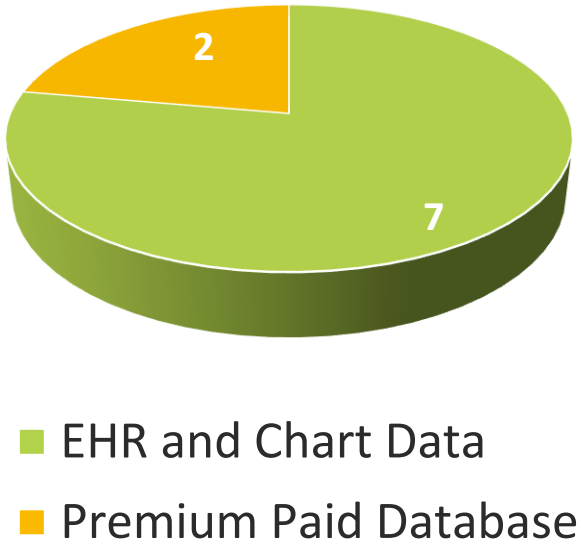
Further Insights (cont'd...)

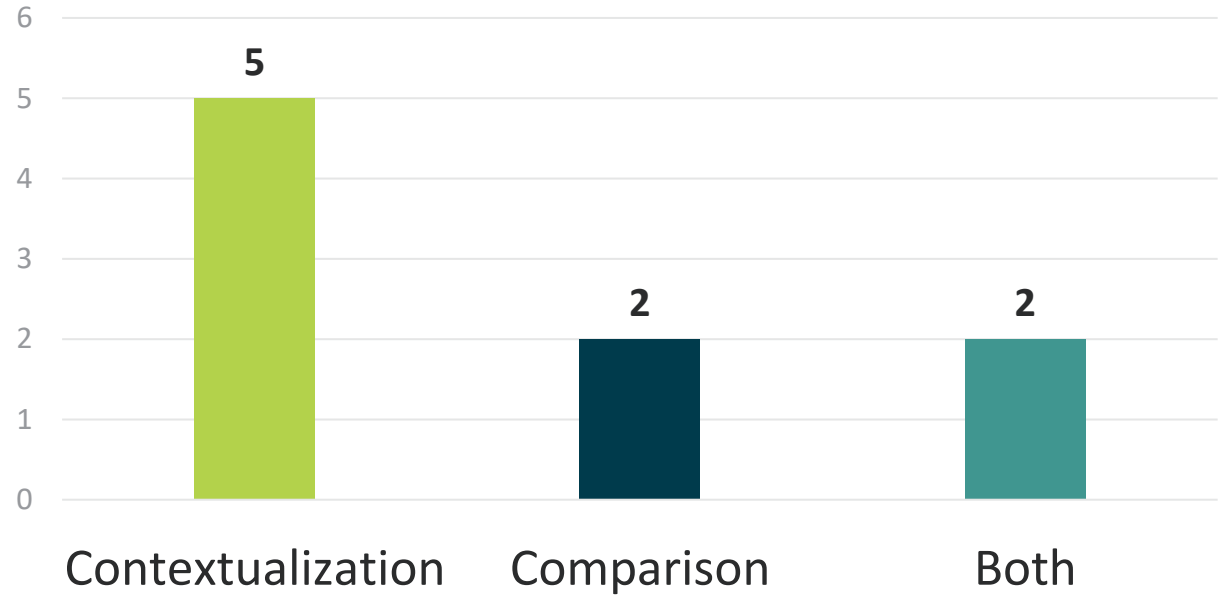
Arondekar et al. 2022

- 11 total NDA/BLA approval by FDA used RWE (2 -sNDA/sBLA)
- 9 received accelerated approvals for the oncology products (between 2015-2020)

RWE Source



RWE Purpose



Arondekar B, Duh MS, Bhak RH, DerSarkissian M, Huynh L, Wang K, Wojciehowski J, Wu M, Wornson B, Niyazov A, Demetri GD. Real-world evidence in support of oncology product registration: a systematic review of new drug application and biologics license application approvals from 2015–2020. *Clinical Cancer Research*. 2022 Jan 1;28(1):27-35.

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Recommendations and Conclusions

ESTABLISH	ADVOCATE	ADOPT	PROMOTE	ENHANCE
Establish advanced standards for RWE to ensure credible, regulatory-ready data for AA submissions.	Advocate for clear, RWE-focused guidelines from regulators to enhance AA submission quality.	Adopt AI/ML tools to streamline data processing and ensure high-quality RWE for AA.	Promote a collaborative platform to share successful RWE AA cases and best practices.	Enhance team proficiency with targeted training on RWE standards, regulatory needs, and AI tools for AA.

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Thank you

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