



Identifying Therapeutic Alternatives for Affordability Reviews

Guidance for State Prescription Drug Affordability Boards (PDABs)

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Executive Summary

As state Prescription Drug Affordability Boards (PDABs) evaluate the affordability of certain prescription drugs, several state laws require PDABs to classify therapeutic alternatives for drugs under affordability review. We outline a methodology for using medical professional associations' clinical guidelines to identify therapeutic alternatives for these selected drugs, building on a similar process we proposed for use in Medicare drug price negotiation.¹ We include ways to overcome challenging cases encountered through use of this methodology, namely, multi-drug regimens and strong guideline recommendations based on low-quality evidence. Limitations include the impact of clinical guideline committee biases and publication timelines that cannot account for newly-approved drugs.

Background

Identifying therapeutic alternatives will be a crucial step for PDABs as they evaluate the affordability of prescription drugs.² Though a drug's clearest alternatives may be within the same mechanistic class, experts have suggested that wider consideration of drugs treating the same condition could more comprehensively illustrate the comparative value of the drug under review.³ The therapeutic alternatives selected for comparison to selected drugs might have implications for PDABs' final affordability determinations.

Other entities involved in the value assessment of prescription drugs are similarly tasked with identifying therapeutic alternatives. For example, the Centers for Medicare and Medicaid (CMS) includes consideration of therapeutic alternatives in its negotiation of drug prices for Medicare.⁴ Countries that conduct health technology assessments (HTAs) also identify therapeutic alternatives to

¹ Mooney H, Martin M, Bendicksen L, Kesselheim AS, Rome BN, Lalani HS. Identifying Therapeutic Alternatives in CMS Drug Negotiation: The Case of Etanercept. *JMCP*. Published online December 13, 2023;1-8. doi:[10.18553/jmcp.2023.23209](https://doi.org/10.18553/jmcp.2023.23209)

² Bendicksen L, Rome BN, Avorn J, Kesselheim AS. Pursuing Value-Based Prices for Drugs: A Comprehensive Comparison of State Prescription Drug-Pricing Boards. *The Milbank Quarterly*. 2021;99(4):1162-1197. doi:[10.1111/1468-0009.12533](https://doi.org/10.1111/1468-0009.12533)

³ Lin JK, Barnes JI, Doshi JA. The Medicare Drug Price Negotiation Program: Considerations for Therapeutic Alternatives. *Health Affairs Forefront*. Published online July 18, 2023. doi:[10.1377/forefront.20230717.330058](https://doi.org/10.1377/forefront.20230717.330058)

⁴ Centers for Medicare & Medicaid Services (CMS). Medicare Drug Price Negotiation Program: Revised Guidance, Implementation of Sections 1191 – 1198 of the Social Security Act for Initial Price Applicability Year 2026. 2023.

<https://www.cms.gov/files/document/revised-medicare-drug-price-negotiation-program-guidance-june-2023.pdf>

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analyze the value of newly-approved drugs.⁵ HTA agencies differ in their approaches to using these therapeutic alternatives in their assessments, with some agencies comparing new technologies to the standard of care, the lowest cost alternative, or “all relevant” alternatives.⁶ In the US, the Institution for Clinical and Economic Review (ICER) also engages in evidence reviews for prescription drugs, including the identification of therapeutic alternatives.⁷ PDABs face additional challenges in that they might be identifying therapeutic alternatives for drugs already on the market with established clinical practice patterns. Nonetheless, the processes of these other organizations may be a valuable resource as states develop their own methodology.

Method for Identifying Therapeutic Alternatives

States can use resources from the US Food and Drug Administration (FDA) to identify relevant clinical guidelines. The FDA approves prescription drugs for the treatment of specific conditions, or “indications.” For each drug selected for affordability review, states can identify the most recent clinical guidelines issued by US medical professional associations for each of these FDA-approved indications.⁸ For example, if a drug is approved by the FDA to treat rheumatoid arthritis, the guidelines of interest would be the 2021 American College of Rheumatology Guidelines for the Treatment of Rheumatoid Arthritis.⁹

Clinical guidelines combine a review of evidence for possible treatment options with clinical judgments by a panel of experts to outline treatment recommendations for clinical decision-making. Guideline bodies adjust the strength of their recommendations based on the quality of evidence supporting different treatment options. Typical frameworks for evidence evaluation include the Grading of Recommendation Assessment, Development, and Evaluation (GRADE) or Strength of Recommendation Taxonomy (SORT) criteria.^{11,12} Evidence reviewed can also include factors such as cost and patient input.¹⁰ When using clinical guidelines to determine therapeutic alternatives, **states may consider focusing only on guideline recommendations supported by “high” or “moderate” strength of evidence under GRADE criteria or Level I strength of evidence under SORT criteria.**

Inclusion and Exclusion Criteria

PDABs may consider various criteria to identify the appropriate scope of health care interventions considered therapeutic alternatives for drugs under affordability review. These criteria could include:¹¹

- Including all drugs within the **same mechanistic or pharmacologic class** as the drug under review, unless the guidelines explicitly recommend these within-class options be used differently.
- Including a drug in a different mechanistic or pharmacologic class if either of the following apply:

⁵ World Health Organization (WHO). Health technology assessment. 2023. <https://www.who.int/health-topics/health-technology-assessment>

⁶ Dehnen J, Petry D, Bercher J, Kruse F. Quantitative and Qualitative Analysis of Differences in AMNOG outcomes between IQWiG and G-BA Between 2011-2018. *Value in Health*. 2019;22:S789. doi:10.1016/j.jval.2019.09.2067

⁷ Institute for Clinical & Economic Review (ICER). About Us. 2023. <https://icer.org/who-we-are/>

⁸ Information on a drug’s FDA-approved indications, including its most recent label, is available in the Drugs@FDA database. <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm>

⁹ Fraenkel L, Bathon JM, England BR, et al. 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Care & Research*. 2021;73(7):924-939. doi:10.1002/acr.24596

¹⁰ *Ibid.*

¹¹ Mooney H, Martin M, Bendicksen L, Kesselheim AS, Rome BN, Lalani HS. Identifying Therapeutic Alternatives in CMS Drug Negotiation: The Case of Etanercept. *JMCP*. Published online December 13, 2023:1-8. doi:10.18553/jmcp.2023.23209

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1. The drug is **recommended in the same treatment line** as the drug under review (i.e., if a drug is recommended at a similar disease stage or treatment progression to the drug under review).
 2. The drug is recommended in a **different treatment line than the drug under review based on low-quality evidence**. If the guidelines do not indicate strong evidence that a potential therapeutic alternative should be used before or after the drug under review, this drug could be considered a therapeutic alternative due to insufficient evidence that it is prescribed in a different position in the treatment pathway.
- Including drugs outlined in clinical guidelines for **off-label use** or drugs without FDA-approval for the specific indication, since many medications are used with evidence-based justification to treat conditions for which the manufacturer has not sought an FDA-approved indication (e.g., in oncology).
 - Excluding non-pharmacologic therapeutic alternatives, such as medical devices or procedures; this aligns with the approach that is being taken by CMS.¹²

Supplementing Clinical Guidelines

The most recent clinical guidelines for the relevant indications might not consider all available treatment options. For example, the most recent American College of Rheumatology Guidelines for the Treatment of Rheumatoid Arthritis were published in June 2021.¹³ States can use resources that are updated frequently, including UpToDate or DynaMed, or search for new clinical trials listed via ClinicalTrials.gov to supplement clinical guidelines with newer information.^{14,15,16}

For alternatives approved by the FDA after the publication of clinical guidelines to qualify as therapeutic alternatives, states may **consider limiting inclusion to newer drugs that share an approved indication with the drug under review**. In addition, the drug's official labeling should not specify that patients must fail the drug under review as a prerequisite for use.

Methodological Challenges

Clinical guidelines combine a review of indication-specific evidence with the consensus of leading experts to characterize treatment options for a given condition, making them an important resource for PDABs to use to standardize the identification of therapeutic alternatives. However, using clinical guidelines may still present challenges, including two scenarios outlined below.

Strong Recommendations Based on Low-Quality Evidence

PDABs may encounter a strong guideline recommendation for a drug based on low-quality evidence.

- **Example:** The rheumatoid arthritis guidelines make a “strong” recommendation for the use of methotrexate before use of a biologic disease-modifying antirheumatic drug (DMARD) (e.g., tumor necrosis factor (TNF) inhibitors).¹⁷ “Very low” quality evidence forms the basis of this

¹² CMS. 2023.

¹³ Fraenkel et al. 2021

¹⁴ UpToDate. <https://www.uptodate.com/contents/search>

¹⁵ DynaMed. <https://www.dynamed.com>

¹⁶ ClinicalTrials.gov. National Library of Medicine. <https://clinicaltrials.gov/>

¹⁷ Fraenkel et al. 2021

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recommendation, which is justified based on methotrexate’s “established efficacy and safety as a first-line DMARD and low cost” not superior evidence of methotrexate’s safety or efficacy.¹⁸

- **Implications:** Given that only low-quality evidence separates methotrexate and TNF inhibitors in the treatment of rheumatoid arthritis, PDABs could determine that methotrexate and TNF inhibitors are therapeutic alternatives. Given the low cost of methotrexate, retailing for less than \$15 per monthly prescription, compared with biologic treatment options for rheumatoid arthritis, which can exceed \$10,000 in annual treatment costs, this choice could greatly impact the outcome of an affordability review.^{19,20} This decision could reasonably reflect the evidence evaluated by the clinical guideline committee, but the strength of the recommendation also indicates that setting these drugs as therapeutic alternatives might oppose typical clinical practice.

Multi-Drug Regimens

States may also have to assess guideline recommendations for multi-drug regimens (i.e., treatments consisting of two or more active ingredients administered for the same condition) to identify appropriate therapeutic alternatives.

- **Example:** Combination therapies are common in the treatment of many conditions, including HIV. As evidenced by the 2023 Department of Health and Human Services guidance, HIV treatment combinations vary based on patient experience, patient population, and co-infection.²¹ Combination therapies can be administered as fixed-dose combination regimens (e.g., multiple ingredients in a single pill) or as separate drugs administered simultaneously. In the context of health conditions in which combination therapies are common, states will have to decide whether to treat single-drug regimens as therapeutic alternatives to multi-drug regimens.
- **Implications:** Antiretroviral therapy for the treatment of HIV is an example of a multi-drug regimen.²² There may be many different ways to combine different products based on the guidelines, and states must decide whether to compare individual ingredients or whether to consider combination therapies as separate therapeutic alternatives.

Bias and Limitations of Clinical Guidelines

State PDABs should be aware of certain biases and limitations that may influence guideline recommendations:

- **Conflicts of Interest:** Clinical guideline recommendations might be affected by committee member conflicts of interest.²³ Studies have demonstrated a high frequency of financial conflicts

¹⁸ *Ibid.*

¹⁹ GoodRx. Methotrexate Prices, Coupons & Savings Tips. 2023.

https://www.goodrx.com/methotrexate?form=tablet&dosage=2.5mg&quantity=16&label_override=methotrexate

²⁰ San-Juan-Rodriguez A, Piro VM, Good CB, Gellad WF, Hernandez I. Trends in list prices, net prices, and discounts of self-administered injectable tumor necrosis factor inhibitors. *JMCP*. 2021;27(1):112-117. doi:[10.18553/jmcp.2021.27.1.112](https://doi.org/10.18553/jmcp.2021.27.1.112)

²¹ Department of Health and Human Services (HHS). Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. 2023. <https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv>

²² *Ibid.*

²³ Institute of Medicine Committee on Conflict of Interest in Medical Research, Education, and Practice. Conflicts of Interest and Development of Clinical Practice Guidelines. In: *Conflict of Interest in Medical Research, Education, and Practice*. National Academies Press (US); 2009. doi:[10.17226/12598](https://doi.org/10.17226/12598)

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of interest among guideline committee members, and many of these relationships are not included in conflict-of-interest disclosures.^{24,25}

- **Status Quo Bias:** Clinical guideline recommendations might be subject to “status quo bias,” meaning that guideline bodies might be biased towards established treatment options over newer drugs.²⁶ For example, newer drugs may be recommended as second-line treatment following established treatment options even if newer evidence supports their use as first-line treatment.

Boards could address these limitations by using supplementary materials to inform therapeutic alternative decision-making, including stakeholder engagement. Continued awareness of potential conflicts of interest in all materials considered during the affordability review will further strengthen PDAB methodologies.

²⁴ Khan R, Scaffidi MA, Rumman A, Grindal AW, Plener IS, Grover SC. Prevalence of Financial Conflicts of Interest Among Authors of Clinical Guidelines Related to High-Revenue Medications. *JAMA Internal Medicine*. 2018;178(12):1712-1715. doi:[10.1001/jamainternmed.2018.5106](https://doi.org/10.1001/jamainternmed.2018.5106)

²⁵ CMS. What is the Open Payments Program? Updated February 1, 2024. <https://www.cms.gov/priorities/key-initiatives/open-payments>

²⁶ Camilleri AR, Sah S. Amplification of the status quo bias among physicians making medical decisions. *Applied Cognitive Psychology*. 2021;35(6):1374-1386. doi:[10.1002/acp.3868](https://doi.org/10.1002/acp.3868)