



August 21, 2023

Chiquita Brooks-LaSure  
Administrator  
Centers for Medicare & Medicaid Services  
Department of Health and Human Services  
7500 Security Blvd.  
Baltimore, MD 21244-1850

**Re: CMS National Coverage Analysis Evidence Review and Coverage with Evidence Development**

Dear Administrator Brooks-LaSure,

On behalf of the more than 25 million Americans living with one of the over 7,000 known rare diseases, the National Organization for Rare Disorders (NORD) thanks the Centers for Medicare and Medicaid Services (CMS) for the opportunity to provide comments on the draft guidance documents “CMS National Coverage Analysis Evidence Review” and “Coverage with Evidence Development.”

NORD is a unique federation of non-profits and health organizations dedicated to improving the health and well-being of people with rare diseases by driving advances in care, research, and policy. NORD was founded 40 years ago, after the passage of the Orphan Drug Act (ODA), to formalize the coalition of patient advocacy groups that were instrumental in passing that landmark law. Since that time, NORD has been advancing rare disease research and funding to support the development of effective treatments and cures; raising awareness and addressing key knowledge gaps; and advocating for policies that support the availability of and access to safe and effective therapies.

At NORD, we believe all patients should have access to quality, accessible, and affordable health care coverage that is best suited to meet their medical needs. As the draft guidance indicates, the NCD process can help rare disease patients gain more timely and affordable access to new and innovative medical products that have been shown to be reasonable and necessary and should therefore be covered by the Medicare program. Such timely and affordable access is vital to our community. Approximately 11.5% of individuals enrolled in Medicare are rare disease patients, according to 2019 data.<sup>1</sup> Furthermore, rare disease patients often rely on both orphan and non-orphan products as a part of their treatment regimen.<sup>2</sup> Among Medicare beneficiaries, those with rare diseases spend on average approximately \$28,185 more in direct medical costs under Medicare each year compared to those without rare diseases.<sup>3</sup> This is true even though as many as 95% of the more than 7,000 known rare diseases have no FDA-approved therapy for that specific condition.

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<sup>1</sup> Yang, G., Cintina, I., Pariser, A. *et al.* The national economic burden of rare disease in the United States in 2019. *Orphanet J Rare Dis* 17, 163 (2022). <https://doi.org/10.1186/s13023-022-02299-5>.

<sup>2</sup> Depping, M. K., Uhlenbusch, N., von Kodolitsch, Y., Klose, H. F. E., Mautner, V. F., & Löwe, B. (2021). Supportive care needs of patients with rare chronic diseases: multi-method, cross-sectional study. *Orphanet journal of rare diseases*, 16(1), 44. <https://doi.org/10.1186/s13023-020-01660-w>

<sup>3</sup> Yang, G., Cintina, I., Pariser, A. *et al.* The national economic burden of rare disease in the United States in 2019. *Orphanet J Rare Dis* 17, 163 (2022). <https://doi.org/10.1186/s13023-022-02299-5>.

Because timely, data-driven, and transparent evidence generation and coverage decisions are critical to the rare disease community, NORD supports CMS's intent to increase the transparency and predictability of National Coverage Determinations (NCDs) and the coverage with evidence development (CED) paradigm, and to use pre-market studies and other available data sources to the extent possible when making coverage decisions. However, the challenges of rare disease drug development result in unique issues and data limitations that must be considered in the NCD framework and CED process. Without appropriately accounting for these realities, rare disease patients will be at greater risk for wrongful coverage denials, resulting in negative health outcomes, increased out-of-pocket costs, and ultimately greater overall costs for the healthcare system.<sup>4</sup> Informed by our 40 years of experience working constructively with all key stakeholders to help ensure the availability of and access to life-altering therapies to the rare-disease community, NORD is pleased to offer the specific recommendations below to make the draft guidance more applicable to the unique realities of rare disease patients.

**Recommendation 1: Strengthen the alignment between CMS and FDA to ensure timely, consistent, and data-driven FDA approval or licensure, and predictable and transparent coverage decisions**

Recommendation 1a: Collaborate closely with FDA to ensure Medicare populations are appropriately represented in pivotal trials for medical products. NORD appreciates that FDA and CMS operate under distinct Congressional mandates and statutory standards,<sup>5</sup> and that in certain situations, CEDs can play a key role in determining that a therapy is reasonable and necessary for Medicare patients. However, the limited patient populations and overall scarcity of data for most rare diseases make greater standardization and alignment across FDA and CMS data collection efforts imperative to maximize efficiencies, avoid duplication of effort, and allow for timely approval and coverage decisions.

NORD agrees with CMS that such alignment is hampered by data limitations. Many clinical trials still lack appropriate representation of diverse patient populations, including those that are Medicare eligible. Although people over 65 years of age constitute a significant fraction of the patient population for many acute and chronic diseases, they are often underrepresented in clinical trials. Similarly, individuals with disabilities or specific chronic diseases that make them Medicare-eligible are often underrepresented in clinical research.<sup>6,7</sup> This lack of clinical trial diversity has several root causes - and it negatively impacts both FDA's and CMS's ability to fulfill their respective mandates.<sup>8</sup>

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<sup>4</sup> U.S. Department of Health and Human Services. (2021, October 22). *NIH study suggests people with rare diseases face significantly higher health care costs*. National Institutes of Health. <https://www.nih.gov/news-events/news-releases/nih-study-suggests-people-rare-diseases-face-significantly-higher-health-care-costs>

<sup>5</sup> *Press release CMS statement: Response to Alzheimer's Association's request to reconsider the final national coverage determination*. CMS. (2023, February 22). <https://www.cms.gov/newsroom/press-releases/cms-statement-response-alzheimers-associations-request-reconsider-final-national-coverage>

<sup>6</sup> Beatty, L. (2023, August 16). *The definition of clinical trial diversity must include disabled people*. STAT. <https://www.statnews.com/2023/08/17/clinical-trials-diversity-disabled-people/#:~:text=Despite%20constituting%20the%20largest%20minority,heavily%20excluded%20from%20the%20process.>

<sup>7</sup> Csaba P Kovesdy, Clinical trials in end-stage renal disease—priorities and challenges, *Nephrology Dialysis Transplantation*, Volume 34, Issue 7, July 2019, Pages 1084–1089, <https://doi.org/10.1093/ndt/gfz088>

<sup>8</sup> Beatty, L. (2023, August 16). *The definition of clinical trial diversity must include disabled people*. STAT. <https://www.statnews.com/2023/08/17/clinical-trials-diversity-disabled-people/#:~:text=Despite%20constituting%20the%20largest%20minority,heavily%20excluded%20from%20the%20process.>

In recent years, FDA has increasingly tried to encourage sponsors to increase the diversity in clinical trials underpinning FDA approvals or licensures. Some of these strategies, including clinical trial diversity plans and FDA diversity reporting mandates, were codified through the Food and Drug Omnibus Reform Act (FDORA) of 2022, enshrining an ever-greater emphasis on diversity and representation into law.<sup>9,10</sup> Yet, successful implementation of these new mandates will require new approaches for trial recruitment and retention. Given CMS’s long history of successful outreach to and engagement with Medicare populations, NORD urges CMS to work closely with FDA to help identify practical strategies and best practices to increase recruitment and retention of diverse populations, including Medicare-eligible patients, and ensure more adequate representation of Medicare populations moving forward.

As one tangible example of strategies to increase equitable trial recruitment and retention, FDA recently released a draft guidance for industry on conducting decentralized trials and how these trials can help increase trial diversity through strategies such as remote trial participation in the patient’s own home.<sup>11</sup> As the experience with decentralized clinical trial adoption during the COVID-19 pandemic demonstrates, this can be a useful tool to increase equitable trial participation. However, ensuring these trials adequately account for and meet the unique needs of older adults and other Medicare populations will be key to their success. Depending on the implementation, strategies such as innovative remote or digital health technologies, increasing use of local healthcare facilities, and use of telehealth can work to either increase or decrease trial accessibility for Medicare populations. CMS should work closely with FDA to ensure decentralized trials in fact positively impact access and representation for Medicare populations.

Recommendation 1b: Work closely with FDA to align evidence generation for accelerated approval products to ensure efficient CEDs, adequate access, and timely conversion to traditional approval. The accelerated approval pathway has been and continues to be vital for rare disease patients.<sup>12</sup> For example, among 252 FDA-approved new orphan drugs and indications approved from 2008 to 2021, about a quarter were approved through accelerated approval.<sup>13</sup> As a 2011 study of oncology drugs demonstrates, drugs receiving accelerated approval are available to patients’ years earlier than they otherwise would – at a median 3.9 years faster than oncology drugs with immediate traditional approval.<sup>14</sup>

Products approved through accelerated approval rely on surrogate or intermediate clinical endpoints such as CD4 T-cell counts for HIV/AIDS products, tumor size for oncology products, or blood pressure for

<sup>9</sup> Center for Drug Evaluation and Research. (2023). *Guidance Recap Podcast | Podcast for Patients — Enhancing the Diversity of Clinical Trial Populations—Eligibility Criteria, Enrollment Practices, and Trial Designs*. U.S. Food and Drug Administration.

<https://www.fda.gov/drugs/guidances-drugs/guidance-recap-podcast-podcast-patients-enhancing-diversity-clinical-trial-populations-eligibility#:~:text=To%20enroll%20participants%20from%20diverse,populations%20receive%20their%20health%20care.>

<sup>10</sup> Siddiqui, F., & Livornese, D. L. (2023, January 24). *Under FDORA, FDA to require most drug and device trials to submit Diversity Action Plans*. FDA Law Blog. <https://www.thefdalawblog.com/2023/01/under-fdora-fda-to-require-most-drug-and-device-trials-to-submit-diversity-action-plans/>

<sup>11</sup> U.S. Department of Health and Human Services. (2023, April 24). Diversity and inclusion in clinical trials. National Institute of Minority Health and Health Disparities. <https://www.nimhd.nih.gov/resources/understanding-health-disparities/diversity-and-inclusion-in-clinical-trials.html#:~:text=People%20may%20experience%20the%20same,can%20benefit%20from%20scientific%20advances.>

<sup>12</sup> NORD, Temkin, E. & Trihn, J. FDA’s Accelerated Approval Pathway: A Rare Disease Perspective. [https://rarediseases.org/wp-content/uploads/2022/10/NRD-2182-Policy-Report\\_Accelerated-Approval\\_FNL.pdf](https://rarediseases.org/wp-content/uploads/2022/10/NRD-2182-Policy-Report_Accelerated-Approval_FNL.pdf)

<sup>13</sup> Monge AN, Sigelman DW, Temple RJ, Chahal HS. Use of US Food and Drug Administration Expedited Drug Development and Review Programs by Orphan and Nonorphan Novel Drugs Approved From 2008 to 2021. *JAMA Netw Open*. 2022;5(11):e2239336. doi:10.1001/jamanetworkopen.2022.39336

<sup>14</sup> Johnson, J., Ning, Y., Farrell, A. J., Justice, R., Keegan, P., Pazdur, R., Accelerated Approval of Oncology Products: The Food and Drug Administration Experience, *JNCI: Journal of the National Cancer Institute*, Volume 103, Issue 8, 20 April 2011, Pages 636–644, <https://doi.org/10.1093/jnci/djr062>

cardiovascular products. Sponsors must have demonstrated that the surrogate or intermediate clinical endpoint is reasonably likely to predict clinical benefit, but the final validation of this correlation within the specific context of use has not yet been completed. At the time of accelerated approval, FDA specifies which confirmatory trials are required for conversion to traditional approval, and in what time frame. Nearly all accelerated approval drugs are ultimately able to confirm clinical benefit and are eventually converted to traditional approvals. For instance, more than three out of four drugs that received accelerated approval from 1992 to 2016 have already been successfully converted to traditional approvals.<sup>15</sup> Only about 10 percent of the 278 accelerated approval drugs approved from 1992 to now are currently past their original confirmatory trial completion date.<sup>16</sup> Among them, more than half are less than a year past their confirmatory trial date and only four drugs are five or more years late.<sup>17</sup>

As these data show, most sponsors meet FDA's requirements for post-market evidence generation, and most accelerated approval drugs are swiftly converted to traditional approval. Delays in confirmatory trial enrollment are one of the key reasons confirmatory trial dates are missed.<sup>18,19</sup> These enrollment challenges can have several distinct root causes, which each may warrant their own solutions.<sup>20</sup> For instance, transitioning confirmatory trials into earlier disease stages or population subgroups that do not have ready access to the approved drug can help overcome enrollment challenges that stem from a lack of incentives to participate in a confirmatory trial once a drug is approved and available outside of the confines of the trial; however, this approach may not always be feasible, and it may not be the only – or at times most appropriate – approach. For instance, efforts to modernize and decentralize trials can reduce the burden for patients and hence minimize the disincentives weighing against participation in confirmatory trials.

At the same time, patients face increasing barriers to coverage and reimbursement of drugs approved through accelerated approval.<sup>21,22</sup> This makes life-saving drugs essentially unaffordable for too many patients and threatens to undermine the integrity and intent of the accelerated approval pathway. NORD urges CMS to work with FDA to maximize alignment of the relevant evidence generation frameworks, and to find creative solutions to close any remaining post-market data gaps. This will help ensure the product's clinical benefit specifically for Medicare populations is appropriately demonstrated, and the same evidence generated through post-market trials can be used to meet both FDA's and CMS' data needs. If done effectively, such approaches will benefit both confirmatory trial enrollment and NCDs simultaneously, helping ensure patients have and retain timely access to the therapies they need while protecting the intent of accelerated approval.

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<sup>15</sup> NORD, Temkin, E. & Trihn, J. FDA's Accelerated Approval Pathway: A Rare Disease Perspective. [https://rarediseases.org/wp-content/uploads/2022/10/NRD-2182-Policy-Report\\_Accelerated-Approval\\_FNL.pdf](https://rarediseases.org/wp-content/uploads/2022/10/NRD-2182-Policy-Report_Accelerated-Approval_FNL.pdf)

<sup>16</sup> Health and Human Services (2022, September 29). *Delays in Confirmatory Trials for Drug Applications Granted FDA's Accelerated Approval Raise Concerns*. Office of Inspector General. Retrieved May 15, 2023, from <https://oig.hhs.gov/oei/reports/OEI-01-21-00401.asp>

<sup>17</sup> *Id.*

<sup>18</sup> Health and Human Services (2022, September 29). *Delays in Confirmatory Trials for Drug Applications Granted FDA's Accelerated Approval Raise Concerns*. Office of Inspector General. Retrieved May 15, 2023, from <https://oig.hhs.gov/oei/reports/OEI-01-21-00401.asp>

<sup>19</sup> NORD, Temkin, E. & Trihn, J. FDA's Accelerated Approval Pathway: A Rare Disease Perspective. [https://rarediseases.org/wp-content/uploads/2022/10/NRD-2182-Policy-Report\\_Accelerated-Approval\\_FNL.pdf](https://rarediseases.org/wp-content/uploads/2022/10/NRD-2182-Policy-Report_Accelerated-Approval_FNL.pdf)

<sup>20</sup> *Id.*

<sup>21</sup> Oregon Health Authority, 2022-2027 Medicaid 1115 Demonstration Application, (February 18, 2022), <https://www.oregon.gov/oha/HSD/Medicaid-Policy/Documents/2022-2027-Waiver-Application-Final.pdf>

<sup>22</sup> Centers for Medicare & Medicaid Services, Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (CAG-00460N), (January 11, 2022), <https://www.cms.gov/medicare-coverage-database/view/ncal-decisionmemo.aspx?proposed=Y&NCAId=305>



## Recommendation 2: Reduce the burden for rare disease patients participating in NCDs with CED

CEDs can allow Medicare beneficiaries access to FDA-approved therapies while additional data are collected and before NCDs are completed, although they can be burdensome and unduly hinder patient access to needed therapies.<sup>23</sup> Based on a recent review of 27 CED programs, requirements among therapies have been highly variable. Only a few CED data collection requirements have been successfully retired because adequate evidence was collected to support - or revoke – coverage decisions.<sup>24</sup> To date, the majority of CEDs have relied on one, or often more than one, clinical trials for evidence generation, and some CEDs rely on registries in addition to - or rarely in lieu of - clinical trials. CED programs have varied in duration from 1 to 16 years, potentially creating burdensome and potentially protracted data collection efforts and ultimately delaying access to therapies.<sup>25</sup>

Many rare disease patients are geographically dispersed, medically complex, and struggle with the logistics of trial or registry participation.<sup>26</sup> According to some estimates, more than 25% of rare disease trials that were terminated between 2016 and 2020 were halted due to insufficient patient participation rates.<sup>27</sup> Participation in CED trials can be quite burdensome for patients, particularly for rare disease patients and patients from historically underrepresented populations.<sup>28</sup> Randomized controlled trials for CEDs are difficult to scale and can create barriers to equitable patient access.<sup>29</sup> These studies are typically conducted in academic medical centers or large hospitals centered in densely populated areas, which can complicate access for rural and historically underserved populations.<sup>30</sup>

Alternative trial methods, such as decentralized trials, can be useful levers in increasing trial participation in patient populations who would otherwise be unable to participate in the CED.<sup>31</sup> Strategies such as greater reliance on registries to support CEDs may also help ease the burden on participants and increase equitable recruitment and retention, in particular if the data collection efforts are targeted specifically to the most impactful open questions regarding clinical benefit and the studies are designed with the unique needs and access barriers of the impacted populations in mind.<sup>32</sup> Collaboration with patient advocacy

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<sup>23</sup> Buch, L., & Von Eisenburg, M. (2022, June 24). NCDs, part I: Overview of ncds, CED, and potential access barriers. Avalere. <https://avalere.com/podcasts/ncds-part-i-overview-of-ncds-ced-and-potential-access-barriers-2>

<sup>24</sup> Zeitler, E. P., & Gilstrap, L. G. (2022, April 7). Coverage with evidence development: Where&nbsp;are we now?. AJMC. <https://www.ajmc.com/view/coverage-with-evidence-development-where-are-we-now->

<sup>25</sup> *Id.*

<sup>26</sup> Rath, A., Salamon, V., Peixoto, S. *et al.* A systematic literature review of evidence-based clinical practice for rare diseases: what are the perceived and real barriers for improving the evidence and how can they be overcome?. *Trials* **18**, 556 (2017). <https://doi.org/10.1186/s13063-017-2287-7>

<sup>27</sup> Ben Adams. (2021). *More than a quarter of rare disease trials are culled due to low patient rates: report*. Fierce Biotech. <https://www.fiercebiotech.com/cro/more-than-a-quarter-rare-disease-trials-are-culled-due-to-low-patient-rates-report>

<sup>28</sup> Alliance report: Medicare using “coverage with evidence development” to ration patient access to FDA-approved treatments. Alliance for Aging Research. (2023, February 14). <https://www.agingresearch.org/news/alliance-report-medicare-using-coverage-with-evidence-development-to-ration-patient-access-to-fda-approved-treatments/>

<sup>29</sup> Von Eisenburg, M., & Harrington, S. (2022, June 24). *NCDs, part II: Evidence development to fulfill CED requirements*. Avalere. <https://avalere.com/podcasts/ncds-part-ii-evidence-development-to-fulfill-ced-requirements-2>

<sup>30</sup> Alliance report: Medicare using “coverage with evidence development” to ration patient access to FDA-approved treatments. Alliance for Aging Research. (2023, February 14). <https://www.agingresearch.org/news/alliance-report-medicare-using-coverage-with-evidence-development-to-ration-patient-access-to-fda-approved-treatments/>

<sup>31</sup> Moore, J., Goodson, N., Wicks, P. *et al.* What role can decentralized trial designs play to improve rare disease studies?. *Orphanet J Rare Dis* **17**, 240 (2022). <https://doi.org/10.1186/s13023-022-02388-5>

<sup>32</sup> Von Eisenburg, M., & Harrington, S. (2022, June 24). NCDs, part II: Evidence development to fulfill CED requirements. Avalere. <https://avalere.com/podcasts/ncds-part-ii-evidence-development-to-fulfill-ced-requirements-2>

groups and the patient community is vital to minimize patient burden and determine appropriate endpoints that can help strengthen the participation and utility of the data.<sup>33</sup>

As these data show, CED requirements must be carefully balanced to ensure equitable access to novel therapies. Reducing the burden for participants is particularly important as barriers to equitable patient participation and the inherent limited patient populations for most rare diseases also hamper the ability of CEDs to timely generate robust and relevant evidence supporting clinical benefit. This is particularly important if medium or long-term outcomes require extended periods of follow-up. Proactive, intentional outreach to the relevant patient population for the product under CED will allow for a diverse range of impacted patients to participate in the CED process in a way that will help inform evaluators perspective of use of the product outside of a clinical trial setting.

### **Recommendation 3: Provide sufficient flexibility in the evidence generation framework to adequately account for the unique challenges in evidence generation for rare diseases**

As stated in the guidance, CMS intends to rely on the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) methodology in assessing NCD evidence for key study characteristics including risk of bias, precision, consistency, and directness.<sup>34</sup> NORD strongly supports the use of rigorous, consistent, and transparent criteria to evaluate whether strong evidence supports that a therapy is necessary and reasonable for Medicare patients. This will ultimately increase the timeliness and predictability of coverage decisions. However, although the GRADE approach has been widely adopted, it may not be suitable without adaptations in all circumstances, including for some rare diseases.<sup>35</sup>

As the scientific literature demonstrates, overall paucity of peer-reviewed studies, including scarcity of large randomized controlled trials, lack of replicate studies, and patients that receive multiple (and varying) therapies simultaneously to manage their complex medical needs, are well-known challenges when applying the GRADE methodology to rare diseases.<sup>36</sup> Similarly, the common phenotypic and/or genotypic heterogeneity in rare diseases, and the limited precision of effect estimates based on small sample sizes in rare disease studies make application of GRADE to rare diseases uniquely challenging.<sup>37</sup>

The unique challenges associated with rare disease research complicate both traditional randomized, double-blinded, placebo-controlled trials as well as alternative research approaches including observational studies, single-arm trials, and studies with external control arms. Real-world data including

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<sup>33</sup> Rath, A., Salamon, V., Peixoto, S. *et al.* A systematic literature review of evidence-based clinical practice for rare diseases: what are the perceived and real barriers for improving the evidence and how can they be overcome?. *Trials* **18**, 556 (2017). <https://doi.org/10.1186/s13063-017-2287-7>

<sup>34</sup> Department of Health and Human Services. CMS National Coverage Evidence Review. June 2023.

<sup>35</sup> Pai M, Iorio A, Meerpohl J, Taruscio D, Laricchiuta P, Mincaroni P, Morciano C, Leo CG, Sabina S, Akl E, Treweek S, Djulbegovic B, Schunemann H; Consortium for the RARE-Bestpractices. Developing methodology for the creation of clinical practice guidelines for rare diseases: A report from RARE-Bestpractices. *Rare Dis.* 2015 Sep 29;3(1):e1058463. doi: 10.1080/21675511.2015.1058463. PMID: PMC4590012.

<sup>36</sup> *Id.*

<sup>37</sup> *Id.*

post-market data collected through investigational or observational studies can provide vital additional insights into safety, effectiveness, and optimal use and should not be discounted.<sup>38</sup>

Because the evidence available for rare diseases is often qualitatively and quantitatively different from that for more common diseases, more pragmatic approaches for recommendation generation may be needed. NORD urges CMS to consult the relevant literature that has explored the application of GRADE and other evidence generation approaches to rare diseases.<sup>39,40,41,42,43</sup> An overly rigid application of the GRADE framework would limit the feasibility and applicability of the NCD framework for rare diseases.

NORD again thanks CMS for the opportunity to provide comments on this important draft guidance, and we look forward to continuing the dialogue around NCDs, as well as other strategies to make rare disease drugs on the market accessible and affordable to patients. For questions regarding NORD or the above comments, please contact Mason Barrett, Policy Analyst, at [mbarrett@rarediseases.org](mailto:mbarrett@rarediseases.org) or Hayley Mason, Policy Analyst, at [hmason@rarediseases.org](mailto:hmason@rarediseases.org).

Sincerely,



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<sup>38</sup> Center for Drug Evaluation and Research. (n.d.). Postmarket requirements and commitments. U.S. Food and Drug Administration. <https://www.fda.gov/drugs/drug-approvals-and-databases/postmarket-requirements-and-commitments#:~:text=The%20phrase%20postmarket%20requirements%20and,%2C%20efficacy%2C%20or%20optimal%20use.>

<sup>39</sup> Pai M, Iorio A, Meerpohl J, Taruscio D, Laricchiuta P, Mincaroni P, Morciano C, Leo CG, Sabina S, Akl E, Treweek S, Djulbegovic B, Schunemann H; Consortium for the RARE-Bestpractices. Developing methodology for the creation of clinical practice guidelines for rare diseases: A report from RARE-Bestpractices. *Rare Dis.* 2015 Sep 29;3(1):e1058463. doi: 10.1080/21675511.2015.1058463. PMID: PMC4590012.

<sup>40</sup> Tingley, K., Coyle, D., Graham, I.D. *et al.* Stakeholder perspectives on clinical research related to therapies for rare diseases: therapeutic misconception and the value of research. *Orphanet J Rare Dis* **16**, 26 (2021). <https://doi.org/10.1186/s13023-020-01624-0>

<sup>41</sup> Pai, M., Yeung, C.H.T., Akl, E.A. *et al.* Strategies for eliciting and synthesizing evidence for guidelines in rare diseases. *BMC Med Res Methodol* **19**, 67 (2019). <https://doi.org/10.1186/s12874-019-0713-0>

<sup>42</sup> Scharpf J. The Challenge of Guideline Development When Evidence Is Sparse. *Otolaryngol Head Neck Surg.* 2017 Sep;157(3):383-384. doi: 10.1177/0194599817717676. Epub 2017 Jul 4. PMID: 28675089.

<sup>43</sup> Annemans, L., Makady, A. TRUST4RD: tool for reducing uncertainties in the evidence generation for specialised treatments for rare diseases. *Orphanet J Rare Dis* **15**, 127 (2020). <https://doi.org/10.1186/s13023-020-01370-3>