



**THE FUTURE OF MEDICINE: LEGISLATION TO ENCOURAGE INNOVATION AND
IMPROVE OVERSIGHT**

**Testimony Before
Committee on Energy and Commerce
Subcommittee on Health**

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March 17, 2022

THE FUTURE OF MEDICINE: LEGISLATION TO ENCOURAGE INNOVATION AND IMPROVE OVERSIGHT

Testimony of Jeff Allen, PhD President & CEO Friends of Cancer Research

Good morning, Chairman Pallone, Chairwoman Eshoo, Ranking Members McMorris-Rogers and Guthrie, and Members of the committee. I am Dr. Jeff Allen, President and CEO of Friends of Cancer Research, a cancer research advocacy organization dedicated to accelerating science & technology from bench to bedside. I would like to thank all Members and the staff of this committee for putting together this important hearing. It is an honor to testify before you today and provide our perspective on several topics included in bills being considered by the committee.

Today represents a unique opportunity to address a diverse set of issues critical to developing a new paradigm for new medicines. Over the past several years healthcare has faced unprecedented pressure on a local and global level in the form of COVID-19. While this has resulted in tragic losses and unimaginable challenges, we are now left to identify the shortcomings, build on the successes, and design a future for health that is able to protect from future pandemics, but also make much needed progress against longstanding challenges like cancer, neurological disease, and the over 6500 rare diseases that have no treatments.¹ I appreciate the opportunity to highlight several areas that will be key for progress related to research and regulation of new medical products that are being discussed today.

Supporting Innovative Research and Regulatory Infrastructure

The route to developing new medicines is long, complex and at times unpredictable. The National Institutes of Health (NIH) is the engine of discovery and enables research toward better health. The NIH

¹ Kaufmann, P, Pariser, AR and Austin, C. From scientific discovery to treatments for rare diseases – the view from the National Center for Advancing Translational Sciences – Office of Rare Diseases Research. *Orphanet J Rare Dis* 13, 196 (2018). <https://doi.org/10.1186/s13023-018-0936-x>

also provides a critical component of research explaining biological underpinnings of diseases and uncovering new ways to treat them. In some cases, these discoveries can translate into potential new medicines and ultimately manufactured into treatments available to patients worldwide. However, this is a process that reportedly takes upwards of 12 years and costs over \$1 billion.²

In order to expedite typical timeframes and improve the government's capability to speed research, President Biden has proposed the establishment of the Advanced Research Projects Agency for Health (ARPA-H). With bipartisan collaboration, Congress has recently identified funds for ARPA-H and this committee has taken on the important work to authorize ARPA-H through separate legislation. ARPA-H will serve a unique role of catalyzing progress in biomedical research by focusing on transformational capabilities and proof-of-concept innovations that have broad applicability across multiple disease areas. This will enable ARPA-H to focus on different components of the biomedical research process and deploy an approach that would be distinct from other organizations. To be successful, no matter the location of ARPA-H, the independence and operational processes established through authorizing language will be key.

An additional effort to enhance infrastructure and accessibility to new medicines is through the 21st Century Cures Initiative (Cures 2.0). The proposed bill builds on numerous provisions in its predecessor that have been highly effective at promoting development and facilitating access to innovative therapies. The Cures 2.0 bill will take key steps to improve public health, support patients and caregivers, advance regulation and reimbursement, and bolster the national research infrastructure.

A specific opportunity through the Cures 2.0 bill could be to include provisions that complement the innovative regulatory programs for transformative therapies, such as the breakthrough therapy designation (BTD) and regenerative medicine advanced therapy (RMAT) designation to enable faster,

² Adams, CP and Brantner, VV. *Health Economics*, 19 (2010), 130–141. doi: 10.1002/hec.1454

more efficient coverage decisions to ensure Medicare beneficiaries have appropriate and timely access to new innovative treatments. A key success feature of the Breakthrough Therapy Designation has been the increased collaboration and interactions between developers and regulators to expedite the development of potentially transformative treatments for serious or life-threatening illnesses. A similar approach could be taken for qualifying technologies that may require unique payment considerations to streamline coverage decisions and enable a more seamless process between an approval by the Food and Drug Administration (FDA) and coverage determination by the Center for Medicare and Medicaid Services (CMS), where the available evidence supports such an approach.

Modernizing Clinical Trials to Promote Inclusivity and Representativeness

While efficient processes and a robust research infrastructure are necessary to support the development of new treatments for patients in need, another essential component will be modernizations to make clinical trials more inclusive, accessible, and equitable.

Barriers to the conduct of and recruitment to clinical trials present perennial challenges to the development of new medical products. For several decades, the average enrollment of adults with cancer into clinical trials has hovered around 2-8%.³ These participation rates have been accompanied by numerous efforts to raise awareness about trials and increase educational outreach to patients and medical providers. While such efforts have likely identified many prospective participants, the criteria for determination of patient eligibility for the trials themselves have largely remained unchanged.

Overly restrictive eligibility criteria can limit access to clinical trials as part of cancer care, impede

³ Unger, JM, Hershman, DL, Till, C , et.al. When Offered to Participate”: A Systematic Review and Meta-Analysis of Patient Agreement to Participate in Cancer Clinical Trials, *JNCI: Journal of the National Cancer Institute*, 113 (3), 2021 March, 244–257, <https://doi.org/10.1093/jnci/djaa155>

enrollment thereby slowing drug development, and cause trials to be less reflective of the patient population that will eventually use new medicines once approved.⁴

Eligibility criteria do play an important role in protecting patients and a relatively homogenous population can be beneficial when attempting to isolate the effect of a drug. However, trial eligibility criteria are often established based on past trials, rather than evaluating and prospectively designing optimal eligibility criteria based on the properties of the drug and the patient population that is being sought. This “cut and paste” approach may contribute to unnecessary exclusion of patients, and may be a barrier to inclusion of more diverse patient populations in clinical trials. For example, routine lab tests are used to identify potential confounding conditions, such as abnormal kidney or liver function, that may make trial participation potentially unsuitable for a patient. The acceptable reference ranges for normal values have been based on averages, and over the years, these averages have come from the most frequent trial participants – similarly aged Caucasian males.⁵ This can effectively exclude a more diverse and representative population, whose metabolic factors may not match those historic participants, but still represent normal biologic functioning to permit clinical trial participation.

Addressing challenges due to restrictive eligibility criteria requires all stakeholders in the oncology clinical trial space to implement changes and increase opportunities for trial participation – and progress is being made. One such multi-stakeholder effort was our partnership with the American Society of Clinical Oncology (ASCO) to launch a collaborative effort alongside expert advisors from clinical research, industry, the FDA, the National Cancer Institute, and other advocacy organizations. The objective was to establish multiple subject-specific working groups to develop recommendations for ways in which

⁴ Jin S, Pazdur R, Sridhara R. Re-Evaluating Eligibility Criteria for Oncology Clinical Trials: Analysis of Investigational New Drug Applications in 2015. *J Clin Oncol*. 2017 Nov 20;35(33):3745-3752. doi: [10.1200/JCO.2017.73.4186](https://doi.org/10.1200/JCO.2017.73.4186)

⁵ Spira AI, Stewart MD, Jones S, et al. Modernizing Clinical Trial Eligibility Criteria: Recommendations of the ASCO-Friends of Cancer Research Laboratory Reference Ranges and Testing Intervals Work Group. *Clin Cancer Res*. 2021 May 1;27(9):2416-2423. doi: 10.1158/1078-0432.CCR-20-3853. Epub 2021 Feb 9. PMID: 33563636; PMCID: PMC8102342.

eligibility criteria could be expanded in cancer clinical trials.^{6,7} Subsequently, our findings were published in the peer-reviewed literature and informed several recently finalized FDA guidance documents on how eligibility criteria might be broadened,^{8,9,10,11} and updated NCI trial templates to help ensure that eligibility criteria routinely start broad and then narrow as appropriate, rather than carrying over previous trial parameters.¹² These efforts can help engage trial sponsors within the pharmaceutical industry and academic research centers to expand eligibility and take steps to not exclude potential patients who could benefit from their products.

Several of the bills included in today's hearing provide new opportunities for increased transparency and promote the inclusion of more diverse and representative enrollment in clinical trials. When looking more broadly at ways to make clinical research more accessible, eligibility criteria is just one opportunity. However, expanding the criteria for trial entry will allow more people to have access to clinical research as part of their care, allow drug developers, medical practitioners, and patients to gain insights for a more representative population, and increase the number of patients who can participate in trials. Tangible and collaborative steps to modify clinical trial constructs can help raise historic rates for trial accrual and speed up trial enrollment – ultimately resulting in new medicines making it to patients sooner.

⁶ Kim E, Bruinooge S, Roberts S, et al., 2017, Broadening Eligibility Criteria to Make Clinical Trials More Representative: American Society of Clinical Oncology and Friends of Cancer Research Joint Research Statement, *J Clin Oncol*, 35(33): 3737-3744. DOI: [10.1200/JCO.2017.73.7916](https://doi.org/10.1200/JCO.2017.73.7916)

⁷ Kim ES, Uldrick TS, Schenkel C, et al. Continuing to Broaden Eligibility Criteria to Make Clinical Trials More Representative and Inclusive: ASCO-Friends of Cancer Research Joint Research Statement. *Clin Cancer Res*. 2021 May 1;27(9):2394-2399. doi: 10.1158/1078-0432.CCR-20-3852. Epub 2021 Feb 9. PMID: 33563632.

⁸ FDA Guidance: Cancer Clinical Trial Eligibility Criteria: Minimum Age Considerations for Inclusion of Pediatric Patients, <https://www.fda.gov/media/121318/download>

⁹ FDA Guidance: Cancer Clinical Trial Eligibility Criteria: Patients with Organ Dysfunction or Prior or Concurrent Malignancies, <https://www.fda.gov/media/123745/download>

¹⁰ FDA Guidance: Cancer Clinical Trial Eligibility Criteria: Brain Metastases, <https://www.fda.gov/media/121317/download>

¹¹ FDA Guidance: Cancer Clinical Trial Eligibility Criteria: Patients with HIV, Hepatitis B Virus, or Hepatitis C Virus Infections, <https://www.fda.gov/media/121319/download>

¹² Broadening/Modernizing Eligibility Criteria for National Cancer Institute (NCI) Sponsored Clinical Trials, https://ctep.cancer.gov/protocolDevelopment/docs/CTEP_Broadened_Eligibility_Criteria_Guidance.pdf

Optimizing the Accelerated Approval Pathway

The Accelerated Approval pathway has been an important regulatory mechanism for FDA to allow for earlier approval of safe and effective drugs that treat serious and life-threatening illnesses than would occur through the traditional approval program. The pathway allows for the approval of a drug based on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict clinical benefit. Earlier approval enables quicker access to new safe and effective drugs and is reserved for drugs that treat serious or life-threatening conditions where the risks associated with no or delayed treatment have negative consequences.

The Accelerated Approval pathway broadly applies to all drug classes and is used across clinical divisions within the FDA. However, Accelerated Approval has been most frequently used in oncology. In the past 10 years (2010- June 2021), 80% (138/168) of FDA's Accelerated Approvals were granted for oncology indications.¹³ This is due in large part to the availability of measurable endpoints, such as tumor shrinkage, that can be directly associated with the activity of a drug. Cancer researchers have also made significant efforts to standardize tumor response measures which has helped ensure the consistent application of endpoints like response rates and improve in the interpretability of clinical trial results. The robust experience of Accelerated Approval in oncology, which is a unique therapeutic setting given an extensive infrastructure for conducting research and aggregating data, can be used to inform the use of Accelerated Approval in other diseases. Accelerated Approval has extended or, in certain cases, saved patients' lives through earlier access to novel therapies. One assessment of oncology treatments concluded that therapies receiving Accelerated Approval were made available a median of 3.4 years

¹³ US Food and Drug Administration. CDER Drug and Biologic Accelerated Approvals Based on a Surrogate Endpoint As of June 30, 2021. <https://www.fda.gov/media/151146/download>. Accessed online 09/15/2021.

earlier than if approval were based on a full clinical endpoint, such as overall survival.¹⁴

Products approved through the Accelerated Approval pathway are subject to post approval study requirements to verify the anticipated effect of the drug and to further characterize the associated risks and clinical benefits. Based on post approval confirmatory studies, the FDA may grant full approval to the drug or, if post approval studies fail to demonstrate benefit (or other evidence demonstrates the product is not shown to be safe and effective), the approval may be withdrawn. In evaluating the total number of indications that have received Accelerated Approval, 49.3% of all indications and 44.2% of cancer indications have been converted to full approval based upon subsequent evidence. Conversely, 9.9% of all accelerated approvals and 9.0% of oncology accelerated approvals have been withdrawn. This yields 42.8% (115/282, all indications) and 46.8% (89/190, oncology indications) that have neither been converted to a full approval or withdrawn (Table 1). Together this indicates a highly favorable success rate for confirmation of benefit and demonstrates the importance of timely post approval studies.

Table 1. Regulatory Outcomes of Accelerated Approval Drugs

Accelerated Approval Indications	Total with Accelerated Approval	Total Converted to Full Approval	Total Withdrawn	Total Pending Action
All ¹⁵	282	139 (49.3.0%)	28 (9.9%)	115 (40.8%)
All Approved Over 5-Years ¹⁴	66	34 (51.5%)	14 (21.2%%)	18 (27.7%%)

¹⁴ Beaver JA, Howie LJ, Pelosof L, et al. A 25-Year Experience of US Food and Drug Administration Accelerated Approval of Malignant Hematology and Oncology Drugs and Biologics: A Review. *JAMA Oncol.* 2018;4(6):849–856. doi:10.1001/jamaoncol.2017.5618. Accessed online 10/1/2020.

¹⁵ Kaltenboeck A, Mehlman A, Pearson S. Strengthening the Accelerated Approval Pathway: An Analysis of Potential Policy Reforms and Their Impact on Uncertainty, Access, Innovation, and Costs. Apr 26, 2021. <https://icer.org/wp-content/uploads/2021/04/Strengthening-the-Accelerated-Approval-Pathway--ICER-White-Paper--April-2021.pdf> (accessed August 5, 2021).

Oncology ¹⁶	190	84 (44.2%)	17 (9.0%)	89 (46.8%)
Oncology Products Over 5-Years ¹⁷	33	19 (57.6%)	5 (15.2%)	9 (27.3%)

Post approval confirmatory studies are required to verify and describe the anticipated effect and to further characterize the long-term outcomes associated with the drug.¹⁷ Because these studies require collection of additional clinical data and may involve the conduct of additional clinical trials, they require additional time for completion. For drugs that have received Accelerated Approval for oncology indications, conversion to full approval took a median time of 3.1 years, while withdrawals took 3.8 years to generate the evidence necessary for action. For the indications that have not yet been converted or withdrawn, the median time since their approval is 1.8 years (Table 2). It is important to note that because 72% (64/89) of pending oncology indications having been approved in the last 2 years, it may be unrealistic to expect their post approval studies to be completed already (Figure 1).

As technology and science evolve it's important to ensure to that the Accelerated Approval pathway continues to serve it's intended purpose. These data indicate that the Accelerated Approval pathway has enabled patients with serious diseases to have access to new medicines years earlier. Key to continued success is both early planning for when Accelerated Approval may be used, and transparency to robust post approval evidence generation. Together this will enhance confidence in the Accelerated Approval process and bolster the ability to address unmet needs for the people that need it most.

¹⁶ Friends of Cancer Research: <https://friendsofcancerresearch.org/drug-development-dashboard> (accessed March 10, 2022).

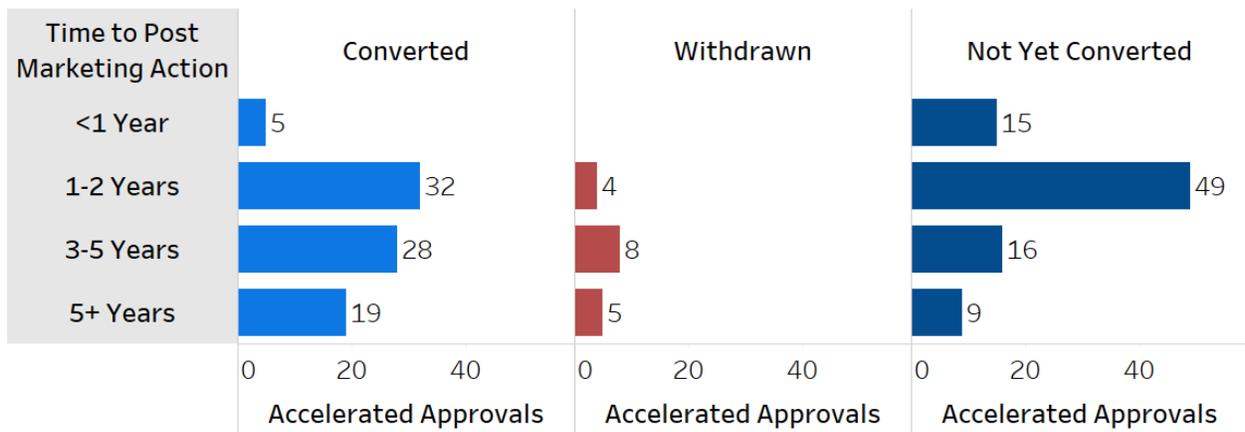
¹⁷ FDA Guidance: Expedited Programs for Serious Conditions – Drugs and Biologics, <https://www.fda.gov/media/86377/download>

Table 2. Median Years between Accelerated Approval and Follow-up Action (1992-June 2021)

Accelerated Approval Indications	Converted	Withdrawn	Pending*
All (n=278)	3.2	6.9	1.8
Oncology (n=190)	3.1	3.8	1.8

*Median time calculation for Accelerated Approvals pending action = time between accelerated approval and the date of this analysis (January 31, 2022).

Figure 1. All Oncology Accelerated Approvals' Time to Follow-up Action.



Facilitating High-Quality Evidence Generation

Accelerated Approval allows patient access to therapies that have demonstrated an initial treatment effect, potentially before a randomized trial that fully establishes clinical benefit is completed. Approval prior to established clinical benefit can potentially introduce loss of clinical equipoise that may interfere with continued drug development and timely completion of post marketing requirements to confirm clinical benefit. For example, patients may be reluctant to enroll in trials where they may be randomized

to receive a perceived inferior therapy, or they may discontinue participating in ongoing clinical trials once the product is accessible on the market after it has received Accelerated Approval. Because these are real challenges encountered for drugs receiving Accelerated Approval, strategies such as earlier initiation of confirmatory trials have been pursued. Similarly, the use of alternative trial designs or leveraging data from clinical practice (real-world data) is being explored.

As previously noted, under 10% of adult patients with cancer are enrolled in a clinical trial as part of their care. Therefore, the vast majority of experience with cancer drugs occurs outside of clinical trials in typical medical practices or the so-called “real-world”. Relatively recent advances in information technology and data capture have allowed for the collection of significantly more data from medical practice than historically has been available. Much of this information is collected for administrative purposes, such as billing, and is therefore not intentionally structured for research. However, real-world data could be leveraged as a research tool to generate evidence about approved medical products in widespread use.

To explore the opportunities and challenge to using real-world data for research, we partnered with several leading healthcare data organizations to characterize patient populations treated for non-small cell lung cancer and evaluate how real-world data could inform outcome measures. Through a series of collaborative pilot projects, we were able to show that it is possible to align on key data elements across different data sources and implement common study protocols. This enabled the identification of similar directionality in treatment effects for both immunotherapy and chemotherapy as had previously been seen in clinical trials.¹⁸ While consistency and reproducibility of findings can add confidence in the results, several challenges with aligning different data sources remain that will need to be further

¹⁸ Stewart M, Norden A, Dreyer N, et.al. An Exploratory Analysis of Real-World End Points for Assessing Outcomes Among Immunotherapy-Treated Patients with Advanced Non-Small-Cell Lung Cancer. *JCO Clinical Cancer Informatics*. 2019 July Special Article. 1-15. Doi: 10.1200/cci.18.00155.

evaluated to optimize the use of real-world data. Challenges that can make interpretation of results difficult include missing data points, differences in care patterns, variation in subsequent therapies and follow-up time, and differences in outcome measures/endpoints compared to more structured research studies.

Despite these challenges, there are significant opportunities for future utilization of real-world evidence to supplement data obtained from clinical trials. For example, data obtained from real-world practice provides important information regarding patients that differ from the relatively homogenous population that may have been included in the initial clinical trials. Real-world data can help provide insights into the impact that factors such as comorbidities, stage of disease, clinical characteristics, and demographics such as age, sex, race and ethnicity can have on outcomes.¹⁹ While in most cases this not intended as a substitute for the data that can be developed through a traditional clinical study, with continued refinement to methodologies, real-world data will provide a growing amount of important information about the safety and effective use of medical products over time.

Conclusion

While there are certainly challenges ahead, scientific advancement has brought us to a time of great opportunity. For the people who currently depend on safe and effective medicines, for those who are holding strong for the breakthroughs to come, and for every future patient, there isn't time to waste. Through the leadership of this committee, we can enable a strong research and evidence infrastructure, implement clinical trials that are more inclusive, and ensure that avenues are available for timely access

¹⁹ Rivera, D.R., Henk, H.J., Garrett-Mayer, E., et.al. (2022), The Friends of Cancer Research Real-World Data Collaboration Pilot 2.0: Methodological Recommendations from Oncology Case Studies. *Clin Pharmacol Ther*, 111: 283-292. <https://doi.org/10.1002/cpt.2453>

to promising new safe and effective medicines that can transform the lives of millions of Americans who need new treatments and cures.

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About Friends of Cancer Research

Friends of Cancer Research is working to accelerate policy change, support groundbreaking science, and deliver new therapies to patients quickly and safely. Once we set a goal, we talk, we listen, we advocate, and we leave no stone unturned for patients. That's how breakthroughs transpire. That's how better policies happen. That's how patients get what they need. www.friendsofcancerresearch.org

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