Forthcoming in Kevin C. Elliott and Ted Richards (eds.), *The Routledge Handbook of Values and Science*. Routledge.

FDA Evidentiary Standards and the need to Attend to Stakeholders' Values

Inmaculada de Melo-Martín
Weill Cornell Medicine—Cornell University

Abstract

Although it seems both ethically and epistemically appropriate to engage with publics to ensure that values used in research consider the interests of relevant stakeholders, doing so successfully faces serious challenges. Because values play central roles in drug and medical device research, using the USA Food and Drug Administration's (FDA) attempts to incorporate stakeholders' values can offer insights into these problems. I point out challenges regarding the incorporation of what are arguably legitimate but conflicting values from relevant stakeholders. Identifying these challenges is necessary to determine what strategies might be more likely to address them.

Introduction

Contextual value judgments play important and beneficial roles in scientific reasoning (Douglas 2009; Elliott 2017; Longino 1990). Although it is neither possible nor desirable to prevent non-epistemic values from operating in science, legitimate concerns exist about whose values should be guiding research (de Melo-Martín 2024). Arguably, judgments about which values to endorse or incorporate in research should not be left to scientists alone as this would give them disproportionate power in shaping science that informs policy decisions (Pielke 2007; Betz 2013). Since scientists have no special expertise or authority in making these judgments and are unrepresentative of the diverse stakeholders affected by science, it is questionable that they alone should decide what values to use when conducting research. Because there can be some reasonable disagreements about social, political, and ethical values, in pluralistic societies all stakeholders should have some say in determining which values to endorse or prioritize in cases of conflict.

To address this value-imposition concern, many philosophers of science have called for identifying democratic and deliberative processes that facilitate that relevant parties, rather than just scientists, can determine what values should guide scientific research (Intemann 2015; Elliott 2017; Schroeder 2021; Lusk 2021). Often these proposals advocate engaging relevant stakeholders in various ways, including community-based advisory boards, citizen panels, deliberative polling from relevant communities, or seeking consensus (Intemann 2015; Elliott 2017; Douglas 2009; Schroeder 2021). Such engagement is especially relevant in the context of the biomedical sciences, where failing to attend to relevant stakeholders can have particularly negative implications (Porter 2022). Patients and their caregivers have direct experiences with illness and medical care: the specific challenges they face in their daily lives, the most

concerning aspects of the disease, the interventions that would be more helpful, and the concessions they are willing to make in managing their disease. It therefore makes sense to involve them in various phases of clinical research (Domecq et al. 2014). For instance, clinical trial success critically depends on ensuring the participation of an adequately informed and appropriately diverse group of patients. Insufficient or skewed participation is a common problem in clinical research (Desai 2020). Trials might impose too high a burden for patients, too many visits or interventions, inclusion and exclusion criteria might be unnecessarily restrictive, excessive length, or unreasonable benefits-risks profiles from the patients' perspectives (Poongothai et al. 2023). These factors hinder participation and result in reduced statistical power, inconclusive results, and misalignment between the internal and external validity of clinical trials (Poongothai et al. 2023). Collaborations with relevant patient groups can minimize these problems (Crocker et al. 2018). Importantly, these collaborations can challenge not only research priorities or product development but also scientific methodology (Epstein 1996).

Although it seems both ethically and epistemically appropriate to identify democratic procedures that would ensure that the values shaping research represent the interests of relevant stakeholders, doing so successfully faces serious practical and theoretical challenges (Le Bihan 2024). Here, I use the USA Food and Drug Administration's (FDA) attempts to incorporate stakeholders' values to show some of these challenges. Values play central roles in drug and medical device research. For instance, inductive risk judgments are central to drug development and approval processes, where decisions about how much evidence or what type of evidence is needed to determine safety or efficacy affect how quickly such evidence can be gathered –and thus, how fast drugs can arrive to the market. I point out challenges regarding the incorporation of what are arguably legitimate but conflicting values from relevant stakeholders. Certainly, many of those calling for public engagement as a way to address the value imposition concern have recognized challenges when stakeholders have a plurality of legitimate values (Intemann 2015; Elliott 2017; Schroeder 2021; Kitcher 2011; Lusk 2021). However, I believe that the implications of those challenges for such engagement proposals have not been sufficiently appreciated. I first offer a brief overview of the FDA's role in drug development and approval processes and its attempts to incorporate the legitimate values of relevant stakeholders. I then discuss several of the challenges such attempts face and conclude with some suggestions about how to move forward.

The FDA: Attending to Stakeholders' Values

The FDA is one of the most respected and powerful public agencies in the world (Carpenter 2010). As of October 2024, the FDA was responsible for the oversight of more than $3.9 trillion worth of food, tobacco, and medical products produced in the U.S. and abroad (FDA 2024). Only drugs explicitly declared safe and effective for their intended uses by the FDA can be legally marketed in the US. Hence, although the FDA's formal authority applies only to the United States and its territories, its decisions have global reach, as any international drug company wishing to introduce products to the US market is required to obtain FDA approval. Moreover, many other regulatory agencies all over the world have used the FDA as a model for their approval processes (Gaudillière and Hess 2013).

After its foundation in 1906, the FDA gradually increased its gatekeeping powers over pharmaceutical markets (Carpenter 2010). It originally verified drug composition through laboratory tests to prevent adulteration and fraud. In 1938, after the sulfanilamide elixir tragedy, Congress passed the Federal Food, Drug, and Cosmetic Act, that gave the FDA authority to require drug manufacturers to prove the safety of their products (Carpenter 2010). A new pharmaceutical catastrophe –thalidomide—led Congress in 1962 to pass the Kefauver-Harris Drug Amendments. For the first time, drug manufacturers were required to show not only the safety of their products but also their efficacy. In particular, sponsors were required to provide "substantial evidence" of effectiveness based on well-controlled clinical studies. The Kefauver-Harris amendments also required FDA approval before a drug could be marketed in the United States.

Until recently, the FDA's evidentiary standard for allowing a new drug onto the market was, with some exceptions, two double-blind, randomized-controlled trials (RCT). However, although the RCT is usually considered the gold standard of evidence, it has important drawbacks from the perspective of at least some patients (Epstein 1996; Will and Moreira 2010). RCTs incorporate debiasing methods to secure a like-to-like comparison: allocation of the intervention is randomized, and the interventions are masked (Hackshaw 2009). These debiasing mechanisms, however, impose various costs on patients (Epstein 1996; Will and Moreira 2010). First, patients who participate in trials perceive randomization, masking, and the use of placebos as contrary to their interests. This is particularly the case when studying interventions for life-threatening illnesses. Second, trial protocols often have restrictive inclusion and exclusion criteria, limiting the type of participants who can have access to them. Third, protocols are also quite strict, and many participants find it difficult to adhere to them and drop out before completing the study. Furthermore, due to complexities of design and conduct, RCTs can take a long time to complete, making it difficult for patients in need to access new treatments.

Patient groups have argued for the need to take into account their interests in two important ways (Epstein 2007; Wehling, Viehöver, and Koenen 2015; Flanigan 2017). First, they have insisted on a change of evidentiary standards for drug development and approval in ways that make trials less burdensome and bring innovations to the market faster. Second, they have demanded that their preferences regarding what might be onerous about a disease, how to treat it, or what factors to address should be considered when making decisions about what interventions to develop and approve. Attempting to incorporate stakeholders' values regarding these two concerns -- to accomplish faster access to drugs and to ensure attention to patients' preferences regarding particular interventions—present challenges. Because of space limitations, I will limit my discussion to the issue of faster access to medications. Of course, some of the challenges of attending to these two concerns will be common, but some are specific to each of them. In particular, incorporating some stakeholders' values in the context of speedier access to drugs has direct effects on standards of evidence for safety and effectiveness.

Since the 1980's, the FDA, responding to congressional demands, has attempted to address patients' concerns about faster and easier access to new treatments. It has implemented several expedited programs that allow drugs to be approved provisionally with

reduced evidentiary requirements (Darrow, Avorn, and Kesselheim 2020). For instance, the Fast-Track program permits approval of new interventions for serious and life-threatening conditions without conducting phase 3 trials, and the Accelerated Approval program allows the use of surrogate measures only reasonably likely to predict clinical benefit as end points for the pivotal clinical trials that form the basis for approving a new drug.

These efforts have been further supported by several provisions in the *21st Century Cures Act* (2016), which aim to expedite clinical testing and approval of new drugs and indications. Importantly, these provisions alter the types of data that pharmaceutical and device companies can use to obtain FDA approval or to meet post-approval requirements. In particular, one of the sections (Sec. 3021) directs the FDA to consider the use of complex innovative trial designs (CID) in the development and regulatory decision-making of drugs and biological products (FDA 2020). Although the FDA does not offer a definition of CID, it takes them to include trial designs that have rarely or never been used to date to provide substantial evidence of effectiveness in new drug or biologics applications. Some examples are trial designs that formally borrow external or historical information or control arm data from previous studies to expand upon concurrent controls.

Another section of the Cures Act (Sec. 3022) supports the use of "real world evidence" in the approval of a new indication of an already approved drug or to satisfy post-approval requirements. The Act defines real world evidence (RWE) as data regarding the usage, or the potential benefits or risks of a drug derived from sources other than randomized clinical trials. Such sources include healthcare information from electronic health records, billing databases, product and disease registries, patient input, and observational studies. Collecting these types of data is frequently less onerous than conducting an RCT and they can be collected in situations where RCTs are unfeasible. Moreover, RWE draws upon various data sources that incorporate the experiences of broader patient cohorts. Patient groups, and other stakeholders, lobbied Congress regarding these provisions and public comment documents on the draft of the Bill show that patient groups expressed support for these changes to evidentiary standards (Hwang, Sachs, and Kesselheim 2017).

Incorporating Stakeholders' Values: Challenges

As mentioned earlier, the recognition that contextual values play relevant roles in scientific research has led to concerns about the disproportionate power that scientists could have in shaping research. Strategies to ensure incorporation of relevant stakeholders' values offer a way to address these concerns. But such incorporation presents at least two interrelated challenges: what to do when a relevant stakeholder has conflicting values and how to address conflicts of values among pertinent stakeholders.

Current patients are clearly relevant stakeholders in decisions about drug development and approval. They have interests in ensuring fast access to medications, particularly when drugs can be lifesaving or improve their quality of life in significant ways. When they participate in clinical trials, they also have an interest in the use of evidence that is less onerous. RWE and surrogate endpoints, for instance, often require less time to collect than traditional clinical outcome data. These alternative measures are also helpful when dealing with conditions that have small patient populations and where enrolling enough participants in traditional phase III

trials might be difficult (Wedam et al. 2020). Likewise, existing patients with few other options to treat their diseases, might have strong preferences that are inconsistent with masking, randomization, or the use of placebos (Ali et al. 2021). The FDA's regulations allowing sources of evidence other than those produced by RCTs are a way to attend to these legitimate interests.

However, although patients want faster access to needed drugs, they also want them to be safe and effective.[1] Some evidence indicates that these different legitimate interests can conflict. For example, accelerated approval is now common in oncology, with about one-third of all oncology drug approvals using the pathway (Scott et al. 2023). The surrogate measures that are usually used for accelerated approvals of cancer treatments include tumour response rate and progression-free survival. But these surrogate endpoints correlate poorly with overall survival (Gyawali, Hey, and Kesselheim 2020). A significant amount of evidence shows that most of the drugs approved by this pathway ultimately fail to demonstrate benefit in overall survival or quality of life in confirmatory trials (Liu, Kesselheim, and Cliff 2024; Gyawali, Hey, and Kesselheim 2019). For many of these drugs the FDA has requested withdrawals because of the lack of benefit (Preziosi and Priefer 2024). These problems also occur with non-oncology drugs (Omae et al. 2022).

It is true that the FDA usually requires post-approval confirmatory studies to validate true clinical benefit to either convert the drug to standard approval or remove it from the market. Such trials should ideally be conducted in a reasonable timeframe to limit harms to patients and should use meaningful clinical endpoints rather than unvalidated surrogate ones. However, evidence shows that post-approval trials are often delayed, in some cases for years after approval (Mao, Alexander, and Li 2024). Furthermore, when conducted, many of the confirmatory trials continue using surrogate measures, sometimes the same surrogate points used for accelerated approval. Additionally, medications approved by special pathways are often integrated into clinical practice before confirmation of benefit for original indications (Naci et al. 2017). This means that, for years, patients are exposed to drugs that might have no clinical benefit and could have significant adverse effects, waste time and money, and are prevented from pursuit of other alternatives, potentially including palliation (Mostaghim, Gagne, and Kesselheim 2017; Lynch and Bateman-House 2020).

This conflict is highlighted when one considers another stakeholder in the drug development and approval processes: drug manufacturers. Although drug manufacturers arguably have an interest in bringing safe and effective products to the market, as publicly traded corporations, they are structured to value shareholder interests over those of patients when those interests clash. Their main mission is to sell profitable drugs, whether or not those drugs are optimally useful in treating diseases, and a variety of market and regulatory mechanisms incentivize pharmaceutical companies attention to profits over the health patients (Torreele 2024; Madl 2019). Importantly, the interests of patients in obtaining faster access to effective drugs serve drug manufacturers' interests well. Pharmaceutical companies also have

[1] Depending on their circumstances, individuals might give more weight to some of these interests than others, but they clearly have these various, conflicting, interests.

an interest in getting innovative products to the market as fast as possible, as this increases profits. For the same reason, they have an interest in cutting development costs. Accelerated approvals are consistent with these interests. Given that companies benefit financially from accelerated approvals, this creates an incentive for them to engage with patient groups that also seek faster drug approval. Indeed, some evidence suggests that the interests of patients can be co-opted in ways that have been underappreciated (Holman and Geislar 2018; Tempini and Teira 2019). After all, drug manufacturers face few negative consequences when obtaining accelerated approval for their drugs.

This conflict in values –faster access to possibly beneficial treatments vs more robust evidence of safety and efficacy—is at the heart of the FDA accelerated approval program as well as other special pathways that aim to bring needed therapies to patients faster. Although, these programs can be modified to help better balance these divergent patient's interest (Fashoyin-Aje et al. 2022; Andreoletti and Blasimme 2023), simply calling for inclusion of patients' values when making these decisions will not solve the problem, as patients' values in this context are actually in conflict. Hence, to the extent that patients have a legitimate interest in maintaining standards of evidence more likely to produce safe and effective treatments, this would impose limits on how fast treatments can be brought to the market. The difficulty in managing this conflict can even be observed in the Cures Act mandates. Although Congress asks the FDA to use RWE, novel clinical trials, and patient experience data in the approval process to get drugs to patients faster, it also stipulates that the various amendments the Cures Act makes to the Federal Food, Drug, and Cosmetic Act are not intended to alter the "substantial evidence standard".

Current patients, however, are not the only relevant stakeholders when it comes to the incorporation of values in drug research and approval. Arguably, citizens and healthcare providers are also appropriate stakeholders whose interests should be considered when making decisions about drug development and approval. And

although the interests of these various stakeholders can converge, conflicts are also likely. For instance, in a controversial decision in 2021, the FDA granted accelerated approval to aducanumab, a drug indicated for the treatment of Alzheimer's disease (AD) (Alexander et al. 2021). The approval was based on a unvalidated surrogate outcome: reduction in beta-amyloid plaques. Many considered this evidence insufficient as proof of clinical benefit and aducanumab was also associated with significant risks including brain swelling and haemorrhage in more than one-third of patients who received the dose approved by the FDA (Rabinovici 2021). According to some evidence, Alzheimer's patient groups pushed for the approval of the drug (Hu 2023). This seems understandable given that AD is a devastating disease that leads to irreversible cognitive and functional decline and one for which no drug had ever been approved for modification of its course. Indeed, the FDA emphasized that patients and their families were willing to accept the uncertainty and risks associated with aducanumab treatment in exchange for earlier access to a potentially effective drug (Dunn, Stein, and Cavazzoni 2021).

But, although the accelerated approval of aducanumab serves the interests of patients suffering from AD in accessing a drug that might slow the disease, the interests of other stakeholders are arguably also relevant. Citizens who are not yet but might become future patients also have an interest in ensuring that drugs are brought to the market only after robust

evidence of safety and efficacy. This makes the special approval pathways concerning because, as mentioned earlier, evidence shows that confirmatory trials fail to demonstrate benefit for many of the drugs approved by these pathways (Liu, Kesselheim, and Cliff 2024; Gyawali, Hey, and Kesselheim 2019), with many of them being withdrawn because of the lack of benefit (Preziosi and Priefer 2024; Omae et al. 2022). In some cases, withdrawal from the market can happen relatively quickly, minimizing harms to patients. This was the case with aducanumab. In January 2024, Biogen, the maker of aducanumab announced that it would stop developing and selling the drug. After its accelerated approval in 2021, Biogen launched an international postmarketing study designed to evaluate its real-world safety and effectiveness in US clinical practice. However, the trial was terminated in May 2022 because it failed to meet clinical projections (Heidebrink and Paulson 2024). Not uncommonly, however, confirmatory trials are delayed and when conducted, they may suffer from limitations similar to those of preapproval studies (Woloshin et al. 2017). Hence, drugs can be in the market for years despite uncertain clinical benefit and lack of information about adverse effects, putting patients at risk of harm. Furthermore, once the drugs are in the market, they are integrated into clinical practice and used for off-label indications, which expands their use even when evidence of efficacy for original indication has not being confirmed (Naci et al. 2017).

Citizens also have an interest in ensuring affordability and appropriate use of their tax money. Accelerated approved drugs often have extremely high costs. Biogen, for instance, initially charged $56,000 yearly (Chiong et al. 2022). This price did not include costs related to infusion services, the necessary fees for increased physician follow-up, or the additional studies needed to monitor for risks associated with use of the drug. The price of cancer drugs receiving accelerated approval can be even higher, with many of them priced at more than $100,000 per year before confirmatory trials have been completed (Frank, Shahzad, and Emanuel 2022).

This, of course, presents problems for individuals who need to use the drugs in question. But it constitutes a problem also for citizens in general. For example, Medicare and Medicaid spend millions of dollars covering the costs of accelerated approval drugs and beneficiaries of these programs spend millions of dollars in out-of-pocket spending on these drugs (Skydel et al. 2022; Shahzad, Naci, and Wagner 2021). A recent study of 38 drugs that received FDA accelerated approval from 2012 to 2017 found that the Centers for Medicare & Medicaid spent nearly $68 billion through 2020 (Skydel et al. 2022). Importantly, 59% of the spending was for drugs with confirmatory trials that only evaluated surrogate end points. Likewise, Medicare has paid millions of dollars for drugs that were either voluntarily withdrawn by the manufacturers or recommended by the FDA for withdrawal (Shahzad, Naci, and Wagner 2021). Furthermore, when drugs granted accelerated approval are placed on treatment guidelines, they are then covered by private insurance providers (Rodriguez et al. 2021). This clearly benefits patients who need the drugs but also exposes them to high out-of-pocket costs and importantly also exposes others to higher insurance premiums. Increased out-of-pocket expenses are not only a financial burden for patients, they also often reduce levels of patient compliance and lead to unfavourable outcomes (Gellad and Kesselheim 2017). Ultimately, the high costs of drugs for which clinical benefit is uncertain and sometimes inexistent puts burdens on public services that are unsustainable.

Healthcare providers are also relevant stakeholders whose values should be considered in decisions regarding drug development and approval processes. They have a fiduciary duty to prioritize patients' health and wellbeing and also a duty to nurture the trust of their patients. Insofar as drugs approved by accelerated pathways are incorporated into clinical practice before sufficient evidence of safety and efficacy, clinicians run the risk of prescribing medications that are harmful to their patients. Harms can be the result of unknown side effects, the use of medications that are ineffective and whose use prevent patients from taking other measures, or because of wasted financial resources. But prescription of medications with uncertain safety and benefit profile risks undermining patients' warranted trust in clinicians.

Ensuring that patients have appropriate information regarding uncertainties in this context can minimize some of the harms mentioned. Providing patients with appropriate information is, however, challenging for clinicians. First, evidence suggests that clinicians often lack familiarity with drug and medical device regulatory practices, believe that the evidence supporting FDA approvals is more rigorous than it often is, and are unaware when medical products have expedited approvals (Dhruva et al. 2024). In many cases, labels for medications that have received accelerated approval fail to include this information or to describe the surrogate marker(s) that supported the accelerated approval (Ballreich et al. 2023). Second, accelerated approvals increase decisional burdens on clinicians who need to ensure robust discussions regarding the ambiguity of clinical benefits for drugs approved by special pathways and must help patients make risk-benefit decisions in situations of greater uncertainty. Such decisions are particularly difficult in cases like that of aducanumab because clinical trials were very selective, excluding participants with comorbidities that are common in the AD population (Anderson et al. 2021). These exclusions make it harder for clinicians to determine when the risk-benefit balance is reasonable when advising patients suffering from conditions that were excluded because of the possibility of increased risks. Indeed, some studies have shown that many clinicians were unlikely to prescribe the drug (Dhruva et al. 2023).

Considerations about familiarity with FDA regulatory practices and the additional time spent with patients trying to determine whether particular drugs approved by special pathways are appropriate are arguably important when determining accelerated approvals. Likewise, questions about how clinicians should deal with the burdens on patients associated with prescribing drugs of unproven benefit but with high costs that are either not covered by insurance or that involve elevated out-of-pocket expenses, and concerns about undermining trust in the doctor-patient relationship, are also relevant when making decisions about drug development and approval processes. The interests of clinicians can conflict with those of patients who seek faster access to needed medications. More challenging still is that clinicians are confronted with the conflicting interests of current patients who want access to novel therapeutics as fast as possible and those of future patients who would benefit from drug approvals with less uncertainty about their risks and potential clinical benefits.

Concluding Remarks

Incorporating the interests of various stakeholders into scientific research seems an appropriate goal both on epistemic and ethical grounds. Nonetheless, the FDA's attempts to do so illustrate

the challenges involved. Not uncommonly, debates about engaging publics to incorporate values in science presuppose that some values are clearly legitimate and should be included while others are illegitimate and should be excluded. Those cases might still be challenging as disagreements might actually exist about what the legitimate and illegitimate values in fact are (de Melo-Martín 2024).

Here, however, I have called attention to what I believe is a harder challenge to address. In the context of drug development and approval processes, the FDA is charged with attending to various values of relevant stakeholders that arguably are all legitimate but that conflict. While current patients suffering from diseases with few options have an interest in faster access drugs and in less burdensome means of gathering evidence, they ultimately also want drugs that will help them with their diseases, and this might require more robust evidentiary standards. Future patients have interest in ensuring that drugs are marketed only after sufficient evidence of safety and efficacy. Clinicians want to ensure that they prescribe drugs that help their patients. Citizens have an interest in an appropriate use of their tax dollars. Attending to some of these values necessarily calls for putting other legitimate stakeholders' values aside.

Of course, decisions about managing these conflicts are possible. After all, we manage conflicts among legitimate values in many other contexts such as funding priorities. But calling for the incorporation of stakeholders' values in science does not, by itself, constitute a solution. Certainly, bringing relevant stakeholders together might provide relevant information about the values at stake and can allow them to deliberate (K Intemann 2015a; Schroeder 2021), even if it would still be the case that in some instances, it will simply not be possible to incorporate all legitimate values of all relevant stakeholders. Proposals for incorporating legitimate stakeholder values have focused primarily in proposing mechanisms to determine which or whose values ought to be incorporated into scientific research (Intemann 2015; Schroeder 2021), under the assumption that not all values are legitimate. When all the values are legitimate, these proposals are insufficient. More attention needs to ge given to proposing strategies to manage the legitimate but conflicting values of relevant stakeholders (Laursen, Gonnerman, and Crowley 2021). Likewise, the existence of a plurality of legitimate values might also be a reason for researchers and funders to be more open to conducting and supporting research shaped by alternative values (Hilligardt 2023). Although this option will require difficult decisions about resource allocation, at least in some cases it might be the only way to ensure that important interests are not neglected when conducting research.

Acknowledgments: This work was supported by the National Center for Advancing Translational Science of the National Institute of Health under Grant UL1TR002384.

References

21st Century Cures Act. H.R. 34, 114th Congress. 2016. *https://www.gpo.gov/fdsys/pkg/BILLS-114hr34enr/pdf/BILLS-114hr34enr.pdf*

Alexander, GC, DS Knopman, SS Emerson, B Ovbiagele, RJ Kryscio, JS Perlmutter, and AS Kesselheim. 2021. "Revisiting FDA Approval of Aducanumab." *New England Journal of Medicine* 385: 769-771. https://doi.org/10.1056/NEJMp2110468.

Ali, S, G Hopkin, N Poonai, L Richer, M Yaskina, A Heath, TP Klassen, C McCabe, KidsCAN PERC Innovative Pediat, and KidsCAN PERC Innovative. 2021. "A novel preference-informed complementary trial (PICT) design for clinical trial research influenced by strong patient preferences." *TRIALS* 22 (1). https://doi.org/10.1186/s13063-021-05164-1.

Anderson, TS, JZ Ayanian, J Souza, and BE Landon. 2021. "Representativeness of Participants Eligible to Be Enrolled in Clinical Trials of Aducanumab for Alzheimer Disease Compared With Medicare Beneficiaries With Alzheimer Disease and Mild Cognitive Impairment." *JAMA* 326: 1627-1629. https://doi.org/10.1001/jama.2021.15286.

Andreoletti, M, and A Blasimme. 2023. "Accelerated drug approval: Meeting the ethical yardstick." *Bioethics* 37: 647-655. https://doi.org/10.1111/bioe.13191.

Ballreich, J, M Socal, CL Bennett, A Xuan, A Trujillo, and G Anderson. 2023. "Accelerated approval drug labels often lack information for clinical decision-making." *Pharmacotherapy* 43 (4): 300-304. https://doi.org/10.1002/phar.2789.

Betz, Gregor. 2013. "In defense of the value free ideal." *European Journal of the Philosophy of Science* 3 (2): 207-220.

Carpenter, Daniel P. 2010. *Reputation and Power: Organizational Image and Pharmaceutical Regulation at the FDA*. Princeton University Press.

Chiong, W, BD Tolchin, RJ Bonnie, KM Busl, S Cruz-Flores, LG Epstein, EP Greene, J Illes, M Kirschen, DG Larriviere, S Mantri, MA Rubin, BJ Stern, LP Taylor, and Ethics Law Humanities Comm. 2022. "Decisions With Patients and Families Regarding Aducanumab in Alzheimer Disease, With Recommendations for Consent AAN Position Statement." *Neurology* 98: 154-159. https://doi.org/10.1212/WNL.0000000000013053.

Congress. 2016. 21st Century Cures Act, H.R. 34, 114th Congress.

Crocker, JC, I Ricci-Cabello, A Parker, JA Hirst, A Chant, S Petit-Zeman, D Evans, and S Rees. 2018. "Impact of patient and public involvement on enrolment and retention in clinical trials: systematic review and meta-analysis." *BMJ* 363:k4738. https://doi.org/10.1136/bmj.k4738.

Darrow, J. J., J. Avorn, and A. S. Kesselheim. 2020. "FDA Approval and Regulation of Pharmaceuticals, 1983-2018." *JAMA* 323 (2): 164-176. https://doi.org/10.1001/jama.2019.20288. <Go to ISI>://WOS:000509352900014.

de Melo-Martín, I. 2024. "Concerns about Contextual Values in Science and the Legitimate/Illegitimate Distinction." *Philosophy of Science* 91: 851-868. https://doi.org/10.1017/psa.2024.20.

Desai, Mira. 2020. "Recruitment and retention of participants in clinical studies: Critical issues and challenges." *Perspectives in Clinical Research* 11: 51-53. https://doi.org/10.4103/picr.PICR_6_20.

Dhruva, SS, AS Kesselheim, S Woloshin, RZ Ji, ZG Lu, JJ Darrow, and RF Redberg. 2023. "Physician Perspectives on the Food and Drug Administration's Decision to Grant Accelerated Approval to Aducanumab for Alzheimer's Disease." *Clinical Pharmacology & Therapeutics* 114: 614-617. https://doi.org/10.1002/cpt.2954.

Dhruva, SS, AS Kesselheim, S Woloshin, RZ Ji, ZG Lu, JJ Darrow, and RF Redberg. 2024. "Physicians' Perspectives on FDA Regulation of Drugs and Medical Devices: A National Survey." *Health Affairs* 43 (1): 27-35. https://doi.org/10.1377/hlthaff.2023.00466.

Domecq, JP, G Prutsky, T Elraiyah, Z Wang, M Nabhan, N Shippee, JP Brito, K Boehmer, R Hasan, B Firwana, P Erwin, D Eton, J Sloan, V Montori, N Asi, A Abu Dabrh, and MH Murad. 2014. "Patient engagement in research: a systematic review." *BMC Health Services Research* 14. https://doi.org/10.1186/1472-6963-14-89.

Douglas, Heather. 2009. *Science, Policy, and the Value-Free Ideal*. University of Pittsburgh Press.

Dunn, B, P Stein, and P Cavazzoni. 2021. "Approval of Aducanumab for Alzheimer Disease-the FDA's Perspective." *JAMA Internal Medicine* 181: 1276-1278. https://doi.org/10.1001/jamainternmed.2021.4607.

Elliott, Kevin C. 2017. *A Tapestry of Values: An Introduction to Values in Science*. Oxford University Press.

Epstein, S. 1996. "Impure science: AIDS, activism, and the politics of knowledge." *Med Soc (Berkeley)*: 1-466. <Go to ISI>://MEDLINE:11619509.

Epstein, Steven. 2007. *Inclusion: The Politics of Difference in Medical Research*. University of Chicago Press.

Fashoyin-Aje, LA, GU Mehta, JA Beaver, and R Pazdur. 2022. "The On- and Off-Ramps of Oncology Accelerated Approval." *New England Journal of Medicine* 387: 1439-1442. https://doi.org/10.1056/NEJMp2208954.

Flanigan, Jessica. 2017. *Pharmaceutical Freedom: Why Patients Have a Right to Self-Medicate*. Oxford University Press.

Food and Drug Administration (FDA) (2020) *Interacting with the FDA on Complex Innovative Trial Designs for Drugs and Biological Products. Guidance for Industry*. Available at https://www.fda.gov/media/130897/download

Food and Drug Administration (FDA). (2024) *FDA at a Glance*. Available at https://www.fda.gov/media/182749/download

Frank, RG, M Shahzad, and EJ Emanuel. 2022. "Accelerated Approval Of Cancer Drugs: No Economic Reward For Drug Makers That Conduct Confirmatory Trials." *Health Affairs* 41: 1273-1280. https://doi.org/10.1377/hlthaff.2022.00119.

Gaudillière, Jean-Paul, and Volker Hess. 2013. *Ways of Regulating Drugs in the 19th and 20th Centuries*. Palgrave MacMillan.

Gellad, WF, and AS Kesselheim. 2017. "Accelerated Approval and Expensive Drugs - A Challenging Combination." *New England Journal of Medicine* 376: 2001-2004. https://doi.org/10.1056/NEJMp1700446.

Gyawali, B, SP Hey, and AS Kesselheim. 2019. "Assessment of the Clinical Benefit of Cancer Drugs Receiving Accelerated Approval." *JAMA Internal Medicine* 179: 906-913. https://doi.org/10.1001/jamainternmed.2019.0462.

---. 2020. "Evaluating the evidence behind the surrogate measures included in the FDA's table of surrogate endpoints as supporting approval of cancer drugs." *EClinicalMedicine* 21:100332, doi: 10.1016/j.eclinm.2020.100332.

Hackshaw, Allan K. 2009. *A Concise Guide to Clinical Trials*. Wiley-Blackwell.

Heidebrink, JL, and HL Paulson. 2024. "Lessons Learned from Approval of Aducanumab for Alzheimer's Disease." *Annual Review of Medicine* 75: 99-111. https://doi.org/10.1146/annurev-med-051022-043645.

Hilligardt, H. 2023. "Partisan Science and the Democratic Legitimacy Ideal." *Synthese* 202 (135). https://doi.org/10.1007/s11229-023-04370-5.

Holman, B., and S. Geislar. 2018. "Sex Drugs and Corporate Ventriloquism: How to Evaluate Science Policies Intended to Manage Industry-Funded Bias." *Philosophy of Science* 85 (5): 869-881. https://www.jstor.org/stable/26627752.

Hu, Jon. 2023. "Alzheimer's Drug Approvals Show We Need a Reevaluation of Patient Advocacy." *Stat*, Dec. 18, 2023. https://www.statnews.com/2023/12/18/patient-advocacy-alzheimers-lecanemab-aducanamab-fda/.

Hwang, T. J., R. E. Sachs, and A. S. Kesselheim. 2017. "Public Participation in Drafting of the 21st Century Cures Act." *Journal of Law Medicine & Ethics* 45 (2): 212-220. https://doi.org/10.1177/1073110517720650.

Intemann, K. 2015. "Distinguishing between Legitimate And Illegitimate Values In Climate Modeling." *European Journal for Philosophy of Science* 5 (2): 217-232. https://doi.org/10.1007/s13194-014-0105-6.

Kitcher, Philip. 2011. *Science in a Democratic Society*. Prometheus Books.

Laursen, Bethany K., Chad Gonnerman, and Stephen J. Crowley. 2021. "Improving Philosophical Dialogue Interventions to Better Resolve Problematic Value Pluralism in Collaborative Environmental Science." *Studies in History and Philosophy of Science* 87: 54-71. https://doi.org/10.1016/j.shpsa.2021.02.004.

Le Bihan, S. 2024. "How to Not Secure Public Trust in Science: Representative Values Versus Polarization and Marginalization." *Philosophy Of Science* 91 (5): 1128-1138. https://doi.org/10.1017/psa.2023.119.

Liu, ITT, AS Kesselheim, and ERS Cliff. 2024. "Clinical Benefit and Regulatory Outcomes of Cancer Drugs Receiving Accelerated Approval." *JAMA* 331: 1471-1479. https://doi.org/10.1001/jama.2024.2396.

Longino, Helen E. 1990. *Science as Social Knowledge: Values and Objectivity in Scientific Inquiry*. Princeton University Press.

Lusk, Greg. 2021. "Does Democracy Require Value-Neutral Science? Analyzing the Legitimacy of Scientific Information in the Political Sphere." *Studies in History and Philosophy of Science* 90: 102-110. https://doi.org/10.1016/j.shpsa.2021.08.009.

Lynch, HF, and A Bateman-House. 2020. "Facilitating Both Evidence and Access: Improving FDA's Accelerated Approval and Expanded Access Pathways." *Journal Of Law Medicine & Ethics* 48: 365-372. https://doi.org/10.1177/1073110520935352.

Madl, AC. 2019. "Using Value-Agnostic Incentives to Promote Pharmaceutical Innovation." *Stanford Law Review* 71 (5): 1305-1351.

Mao, Xiangyun, G Caleb Alexander, and Guanqiao Li. 2024. "Accelerated Approvals: Early-Phase Success or Premature Authorization?" *Cancer Cell*. 42(11), 1799-1802. https://doi.org/10.1016/j.ccell.2024.09.005.

Mostaghim, SR, JJ Gagne, and AS Kesselheim. 2017. "Safety Related Label Changes for New Drugs After Approval in the US Through Expedited Regulatory Pathways: Retrospective Cohort Study." *BMJ* 358:j3837. doi:10.1136/bmj.j3837.

Naci, H, OJ Wouters, R Gupta, and JPA Ioannidis. 2017. "Timing and Characteristics of Cumulative Evidence Available on Novel Therapeutic Agents Receiving Food and Drug Administration Accelerated Approval." *Milbank Quarterly* 95: 261-290. https://doi.org/10.1111/1468-0009.12261.

Omae, K, A Onishi, E Sahker, and TA Furukawa. 2022. "US Food and Drug Administration Accelerated Approval Program for Nononcology Drug Indications between 1992 and 2018." *JAMA Network Open* 5(9):e2230973. https://doi.org/10.1001/jamanetworkopen.2022.30973.

Pielke, R. A. 2007. *The Honest Broker: Making Sense of Science in Policy And Politics*. Cambridge University Press.

Poongothai, Subramani, Ranjit Mohan Anjana, Ramasamy Aarthy, Ranjit Unnikrishnan, K M Venkat Narayan, Mohammed K Ali, Kulasegaran Karkuzhali, and Viswanathan Mohan.

2023. "Strategies for Participant Retention in Long Term Clinical Trials: A Participant-Centric Approaches." *Perspectives in Clinical Research* 14: 3-9. https://doi.org/10.4103/picr.picr_161_21.

Porter, Laura D. 2022. "The Importance of Patient Engagement to Improve Healthcare Research and Safety." *Global Journal on Quality and Safety in Healthcare* 5: 27-30. https://doi.org/10.36401/JQSH-22-X1.

Preziosi, AJ, and R Priefer. 2024. "Oncology's Trial and Error: Analysis of the FDA Withdrawn Aaccelerated Approvals." *Life Sciences* 346:122615. https://doi.org/10.1016/j.lfs.2024.122615.

Rabinovici, GD. 2021. "Controversy and Progress in Alzheimer's Disease - FDA Approval of Aducanumab." *New England Journal of Medicine* 385: 771-774. https://doi.org/10.1056/NEJMp2111320.

Rodriguez, R, R Brunner, S Spencer, and DM Qato. 2021. "Time to inclusion in clinical guidance documents for non-oncological orphan drugs and biologics with expedited FDA designations: a retrospective survival analysis." *BMJ OPEN* 11(12):e057744. https://doi.org/10.1136/bmjopen-2021-057744.

Schroeder, S. A. 2021. "Democratic Values: A Better Foundation for Public Trust in Science." *British Journal for the Philosophy of Science* 72 (2): 545-562. https://doi.org/10.1093/bjps/axz023.

Scott, EC, AC Baines, YT Gong, R Moore, GE Pamuk, H Saber, A Subedee, MD Thompson, WM Xiao, R Pazdur, VA Rao, J Schneider, and JA Beaver. 2023. "Trends in the Approval f Cancer Therapies by the FDA in the Twenty-First Century." *Nature Reviews Drug Discovery* 22: 625-640. https://doi.org/10.1038/s41573-023-00723-4.

Shahzad, M, H Naci, and AK Wagner. 2021. "Estimated Medicare Spending on Cancer Drug Indications With a Confirmed Lack of Clinical Benefit After US Food and Drug Administration Accelerated Approval." *JAMA Internal Medicine* 181: 1673-1675. https://doi.org/10.1001/jamainternmed.2021.5989.

Skydel, JJ, AC Egilman, JD Wallach, R Ramachandran, R Gupta, and JS Ross. 2022. "Spending by the Centers for Medicare & Medicaid Services Before and After Confirmation of Benefit for Drugs Granted US Food and Drug Administration Accelerated Approval, 2012 to 2017." *JAMA Health Forum* 33(5):e221158. https://doi.org/10.1001/jamahealthforum.2022.1158.

Tempini, Niccolo, and David Teira. 2019. "Is the genie out of the bottle? Digital platforms and the future of clinical trials." *Economy and Society* 48 (1): 77-106. https://doi.org/10.1080/03085147.2018.1547496.

Torreele, E. 2024. "Why Are Our Medicines So Expensive? Spoiler: Not for The Reasons You Are Being Told…." *European Journal of General Practice* 30(1):2308006. https://doi.org/10.1080/13814788.2024.2308006.

Wedam, S, L Fashoyin-Aje, E Bloomquist, SH Tang, R Sridhara, KB Goldberg, MR Theoret, L Amiri-Kordestani, R Pazdur, and JA Beaver. 2020. "FDA Approval Summary: Palbociclib for Male Patients with Metastatic Breast Cancer." *Clinical Cancer Research* 26 (6): 1208-1212. https://doi.org/10.1158/1078-0432.CCR-19-2580.

Wehling, Peter, Willy Viehöver, and Sophia Koenen. 2015. *The Public Shaping of Medical Research: Patient Associations, Health Movements and Biomedicine*. Taylor & Francis Group.

Will, Catherine, and Tiago Moreira. 2010. *Medical Proofs, Social Experiments: Clinical Trials in Shifting Contexts*. Ashgate.

Woloshin, S, LM Schwartz, B White, and TJ Moore. 2017. "The Fate of FDA Postapproval Studies." *New England Journal Of Medicine* 377: 1114-1117. https://doi.org/10.1056/NEJMp1705800.