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How to Balance Accelerated Approvals and Uncertainties: Public Preference and risk management

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Accelerated approval provides choices under major public health crisis

- In face of major public health crises, decisions **neither can nor should await flawless data**
- Rather, they must be made under "**acceptable uncertainty**," grounded in the most reliable evidence currently available, through a prudent balancing of risks and benefits -- ***Lackey, Leila et al. Therapeutic innovation & regulatory science, 2021***

	Identifying the Causative	Preclinical Trials	Clinical Trials	Regulatory Approval
Fluarix® [1] (10+ years)	**7 years (1933-1940)**	**2 years (2008-2010)**	**2 years (2010-2012)**	**2012.12 approved**
Vaxzevria®[2] (15 months)	**2 months (2020.01-2020.03)**	**1 months (2020.03-2020.04)**	**7 months (2020.04-2020.11)**	**2020.12 EUA**
CoronaVac®[3] (13 months)	**1 months (2020.01-2020.02)**	**2 months (2020.02-2020.04)**	**8 months (2020.04-2020.12)**	**2020.06 EUA**

	Vaccine Efficacy (95%CI)		Vaccine Safety(SAEs)	
	Phase III (%)	Real-World Data (%)	Phase III	Real-World Data
Fluarix® [1]	49.8 (41.8-56.9) [width: **15.1**]	-	<1%	Guillain-Barré syndrome is rare (approximately 1 case per 100,000 vaccine recipients).
Vaxzevria®[4,5]	66·7 (57·4-74·0) [width: **16.6**]	74.5 (68.4-79.4) [width: 11]	0.9%	TTS: Occurring in 1 to 2 per 100,000 people vaccinated
CoronaVac®[6.7]	83·5 (65·4-92·1) [width: **26.7**]	65.9 (65.2-66.6) [width: 1.4]	0%	-

Lackey, Leila et al.

[1]McKeage K. Drugs. 2013 Sep;73(14):1587-94. [2]Mahase E. BMJ. 2021;372:n86. Published 2021 Jan 12. [3]CoronaVac. (2025, October 23). Wikipedia. https://en.wikipedia.org/wiki/CoronaVac[4]Voysey M et al.Lancet. 2021 Mar 6;397(10277):881-891. [5]Lopez Bernal J et al.N Engl J Med. 2021 Aug 12;385(7):585-594.[6]Tanriover MD et al.Lancet. 2022 Jan 29;399(10323):436.[7]Jara A et al.N Engl J Med. 2021 Sep 2;385(10):875-884.

Accelerated approval both accepts and introduces uncertainties to the public

Accelerated approval improves vaccine accessibility in terms of time, but clinical trials with limited duration and sample size may lead to significant uncertainty.

- Vaxzevria@ was developed in November 2020,. The research team created the vaccine in record time, turning a process that usually takes 10 years into just 10 months, a "global miracle."
- On April 30, AstraZeneca first acknowledged in court documents that its COVID-19 vaccine may cause rare blood clots with thrombocytopenia syndrome (TTS) in a small number of cases.
- However, AstraZeneca stated that the withdrawal of Vaxzevria was purely a business decision and that its timing was unrelated to the court case or the acknowledgment of rare side effects.

1 https://mp.weixin.qq.com/s/wCPwxH3FGSGe3D7x6GbewQ 2 https://www.biospace.com/article/astrazeneca-withdraws-covid-19-vaccine-worldwide-as-demand-craters/

BRF -- “uncertainties are uncertain”

- In 2009, FDA initiated a structured Benefit-Risk Framework (BRF) , **but uncertainties are mainly presented in a narrative way**
- Facing uncertainty, the FDA adopts a careful yet flexible approach, **emphasizing data**, **ongoing monitoring**, and **transparency**

Example

STN:125742

Proper Name: COVID-19 Vaccine, mRNA

Tradename: COMIRNATY

Manufacturer: BioNTech Manufacturing GmbH

Benefit uncertainty: longer-term duration of protection, significantly Immunocompromised not well represented in the clinical trial, and effectiveness against SARS-CoV-2 variants

Risk: lack of precise estimates for excess risk across various age and gender Subgroups, subclinical cases, longer-term outcomes and prognoses

Risk management: safety surveillance led by FDA/CDC continues for adolescents 12-15, post-approval studies to further evaluate safety specifically for vaccine-associated myocarditis and pericarditis and their long-term sequelae

Table 31. Risk-Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• COVID-19 is associated with significant morbidity, mortality (over 7 million deaths worldwide to date) and long-term sequelae among survivors. In the U.S., COVID-19 has been responsible for 1.2 million deaths to date with a cumulative COVID-19-associated hospitalization rate of 77.8 per 100,000 people for the 2024-2025 season, as of June 28, 2025, with the highest hospitalization rates in individuals over 65 years of age (317.4 per 100,000 people). • SARS-CoV-2 continues to evolve, particularly in the spike protein’s receptor-binding domain. Successive waves of variants, including Delta, Omicron BA.1, BA.5, XBB.1.5, and JN.1, have demonstrated increased transmissibility and, in some cases, greater ability to evade immunity from prior infection or vaccination. The trajectory of SARS-CoV-2 continues to remain unpredictable, including the potential emergence of variants with greater immune escape or virulence. • A large percentage of the U.S. population has developed immunity through vaccination, prior infection, or a combination thereof. While this has contributed to reduced rates of severe disease, it complicates assessments of vaccine effectiveness over time. The durability of immunity and the impact of waning immune protection on future disease burden are not fully known. • Updated vaccine formulae continue to show relative vaccine effectiveness (i.e., added benefit) in a population with high prevalence of seropositivity.	• COVID-19 continues to pose a substantial public health threat, both from acute infections and long-term complications. COVID-19 burden, including hospitalizations and deaths, are high among individuals over 65 years of age and in infants and young children. • Vaccination remains a cornerstone of the public health response, with updated formulae improving effectiveness against currently circulating variants. • Due to ongoing SARS-CoV-2 evolution and despite widespread seropositivity, it is important to continue surveillance and to maintain flexibility in vaccine development and public health planning.
Unmet Medical Need	• COVID-19 remains a serious illness, particularly for older adults, young infants and children, and individuals with underlying health conditions. While many individuals recover within 1-2 weeks, some experience prolonged symptoms or develop post-acute sequelae known as Long COVID, contributing to long-term morbidity. Children may also experience a serious medical condition associated with COVID-19 called Multisystem Inflammatory Syndrome in Children (MIS-C). The ability of current treatments to prevent Long COVID and MIS-C remains unclear. • Antiviral medications and monoclonal antibodies have been approved or authorized for the management of individuals with COVID-19; these therapeutics are more effective when taken soon after disease onset and are generally more effective against mild to moderate COVID-19. The age of the patient and the presence or absence of immunity from natural infection and prior COVID-19 immunization may also affect the benefit of using these treatments for COVID-19. • Currently, four COVID-19 vaccines (Spikevax, mNexspike, Comirnaty, and Nuvaxovid) have received FDA approval for prevention of COVID-19, but while Pfizer-BioNTech COVID-19 Vaccine, is authorized for use in children as young as 6	• Although treatments exist for those infected with SARS-CoV-2, they are generally not effective in severe disease; additionally, treatments may not prevent complications from COVID-19, including Long COVID and MIS-C. • Vaccines provide important protection from COVID-19. • There is only one COVID-19 vaccine recently approved (July 2025) for infants and children less than 12 years of age.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
	months of age under EUA, there is only one COVID-19 vaccine that was recently approved for children under 12 years of age (July 2025).	

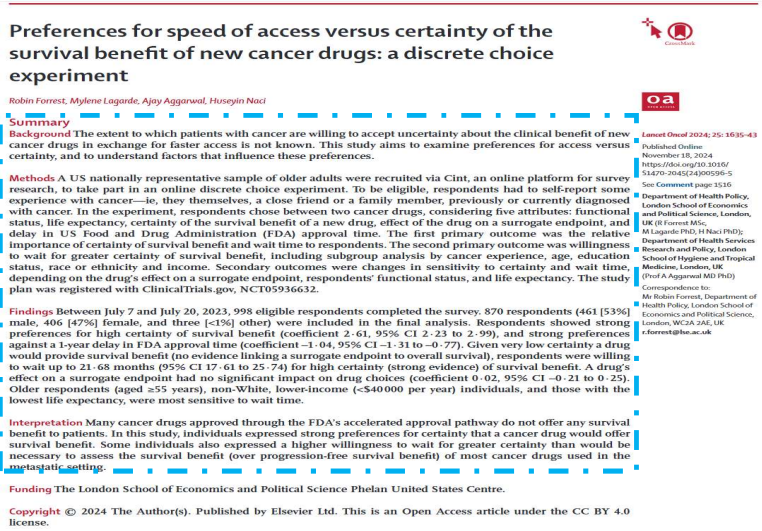
Clinical Benefit	• Effectiveness of a single dose (10 µg) of Comirnaty in children 5 years through 11 years of age irrespective of prior COVID-19 vaccination is based on:
	  ◦ Immunogenicity of a single dose (10 µg) of Comirnaty (XBB.1.5 monovalent formulation) in COVID-19 vaccine-naive children 5 years through 11 years of age with evidence of prior SARS-CoV-2 as evaluated in Study 1048 SSE
	  ◦ Immunogenicity of an additional single dose (10 µg) of Comirnaty (Original monovalent) in previously vaccinated individuals 5 years through 11 years of age as evaluated in Study 1007 Booster Phase
	  ◦ Immunogenicity of an additional single dose (10 µg) of a bivalent vaccine (Original and Omicron BA.1) in previously vaccinated individuals 5 years through 11 years of age as evaluated in Study 1046 SSD
	• The original 2-dose series evaluation in COVID-19 vaccine-naïve individuals is analogous to a single dose in vaccine-naïve individuals with evidence of previous SARS-CoV-2 exposure. Thus, effectiveness of a single dose (10 µg) of Comirnaty in children 5 years through 11 years of age irrespective of prior COVID-19 vaccination is also supported by Study 1007 data including:
	  ◦ Immunogenicity following 2 doses of Comirnaty (Original) as compared with the nAb responses following 2 doses of BNT162b2 in young adults (18 years through 25 years old) for whom clinical efficacy was demonstrated in Study C4591001
	  ◦ Efficacy of Comirnaty against confirmed COVID-19 occurring from 7 days post-Dose 2 to prior to Dose 3 during the blinded follow-up period in participants without evidence of past SARS-CoV-2 infection.
	• All studies listed above met their primary pre-specified success criteria.
	• Uncertainties in clinical benefit include: precise estimate of relative vaccine efficacy in children less than 12 years of age, effectiveness against severe disease, durability of protection beyond 6-12 months, effectiveness in preventing asymptomatic infection or transmission, and effectiveness of future formulae (i.e., updated variant compositions) against future circulating variants.
		• The evidence for clinical benefit of a single dose (10 µg) of Comirnaty meets the evidentiary standards for approval (i.e., substantial evidence of effectiveness) for use in individuals 5 years through 11 years of age, irrespective of prior COVID-19 vaccination status, to prevent COVID-19 caused by SARS-CoV-2.

Risk	• The most frequently reported adverse reactions were solicited local adverse reactions of injection site pain and axillary swelling or tenderness and systemic adverse reactions of fatigue, headache, and new or worsened muscle pain. These reactions were generally mild to moderate in severity, occurred within 1-3 days after vaccination, and resolved quickly. Unsolicited AEs within 1-month post-vaccination were generally consistent with solicitated ARs or common childhood illnesses. There were no SAEs reported in the studies submitted to this sBLA which were assessed as related to Comirnaty. • No cases of vaccine-related myocarditis, pericarditis, or anaphylaxis were observed in the studies submitted to this sBLA. This is consistent with the observed epidemiology of vaccine-related myocarditis and pericarditis, which have not been	• In the clinical studies, across individuals 5 years through 11 years of age, and following one or two vaccinations, local and/or systemic solicited adverse reactions following vaccination were generally mild to moderate and of short duration (mean 1-3 days). Relevant related adverse events have been added to the USPI as described. There were no other new safety concerns identified in study data reviewed in this application which were not already identified in the current Comirnaty (Original monovalent) USPI.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
	shown to occur at higher frequency in children under 12 years of age. However, these events remain recognized potential risks for the vaccine class.	
Risk Management	• Labeling for Comirnaty describes the common and uncommon (but potentially serious) risks associated with the vaccine, which are unchanged based on the data reviewed in this sBLA for children 5 years through 11 years of age, as no new safety signals were identified. The Comirnaty prescribing information includes warning statements for severe allergic reactions and myocarditis/pericarditis. • Postmarketing monitoring for AEs using both passive and active surveillance systems will be used to assess for emergence of any new safety concerns.	• Risk mitigation strategies for Comirnaty in individuals 5 years of age and older are unchanged based on the review of this sBLA and include communication of risks and benefits through labeling, directed counseling prior to vaccination according to individual risks and benefits, and a pharmacovigilance plan to further evaluate risks.

11.2 Risk-Benefit Summary and Assessment

US public prefer slower approval with lower uncertainty towards anti-cancer drugs



Preferences for speed of access versus certainty of the survival benefit of new cancer drugs: a discrete choice experiment

Robin Forrest, Mylene Lagarde, Ajay Aggarwal, Huseyin Naci

Summary

Background The extent to which patients with cancer are willing to accept uncertainty about the clinical benefit of new cancer drugs in exchange for faster access is not known. This study aims to examine preferences for access versus certainty, and to understand factors that influence these preferences.

Methods A US nationally representative sample of older adults were recruited via Cint, an online platform for survey research, to take part in an online discrete choice experiment. To be eligible, respondents had to self-report some experience with cancer—ie, they themselves, a close friend or a family member, previously or currently diagnosed with cancer. In the experiment, respondents chose between two cancer drugs, considering five attributes: functional status, life expectancy, certainty of the survival benefit of a new drug, effect of the drug on a surrogate endpoint, and delay in US Food and Drug Administration (FDA) approval time. The first primary outcome was the relative importance of certainty of survival benefit and wait time to respondents. The second primary outcome was willingness to wait for greater certainty of survival benefit, including subgroup analysis by cancer experience, age, education status, race or ethnicity and income. Secondary outcomes were changes in sensitivity to certainty and wait time, depending on the drug's effect on a surrogate endpoint, respondents' functional status, and life expectancy. The study plan was registered with ClinicalTrials.gov, NCT05936632.

Findings Between July 7 and July 20, 2023, 998 eligible respondents completed the survey. 870 respondents (461 [53%] male, 406 [47%] female, and three [<1%] other) were included in the final analysis. Respondents showed strong preferences for high certainty of survival benefit (coefficient 2·61, 95% CI 2·23 to 2·99), and strong preferences against a 1-year delay in FDA approval time (coefficient −1·04, 95% CI −1·31 to −0·77). Given very low certainty a drug would provide survival benefit (no evidence linking a surrogate endpoint to overall survival), respondents were willing to wait up to 21·68 months (95% CI 17·61 to 25·74) for high certainty (strong evidence) of survival benefit. A drug's effect on a surrogate endpoint had no significant impact on drug choices (coefficient 0·02, 95% CI −0·21 to 0·25). Older respondents (aged ≥55 years), non-White, lower-income (<$40 000 per year) individuals, and those with the lowest life expectancy, were most sensitive to wait time.

Interpretation Many cancer drugs approved through the FDA's accelerated approval pathway do not offer any survival benefit to patients. In this study, individuals expressed strong preferences for certainty that a cancer drug would offer survival benefit. Some individuals also expressed a higher willingness to wait for greater certainty than would be necessary to assess the survival benefit (over progression-free survival benefit) of most cancer drugs used in the metastatic setting.

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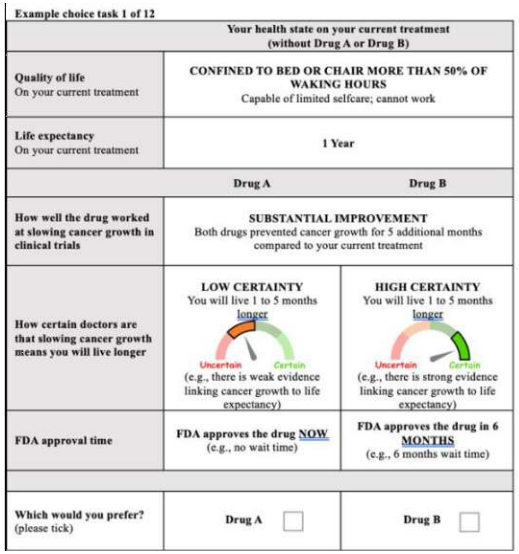

Example choice task 1 of 12

	Your health state on your current treatment (without Drug A or Drug B)	
Quality of life On your current treatment	CONFINED TO BED OR CHAIR MORE THAN 50% OF WAKING HOURS Capable of limited selfcare; cannot work	
Life expectancy On your current treatment	1 Year	
	Drug A	**Drug B**
How well the drug worked at slowing cancer growth in clinical trials	SUBSTANTIAL IMPROVEMENT Both drugs prevented cancer growth for 5 additional months compared to your current treatment	
How certain doctors are that slowing cancer growth means you will live longer	LOW CERTAINTY You will live 1 to 5 months longer Uncertain Certain (e.g., there is weak evidence linking cancer growth to life expectancy)	HIGH CERTAINTY You will live 1 to 5 months longer Uncertain Certain (e.g., there is strong evidence linking cancer growth to life expectancy)
FDA approval time	FDA approves the drug NOW (e.g., no wait time)	FDA approves the drug in 6 MONTHS (e.g., 6 months wait time)
Which would you prefer? (please tick)	Drug A ☐	Drug B ☐

Example choice task 2 of 12

	Your health state on your current treatment (without Drug A or Drug B)	
Quality of life On your current treatment	UP AND ABOUT MORE THAN 50% OF WAKING HOURS Can walk around; cannot work	
Life expectancy On your current treatment	3 Years	
	Drug A	**Drug B**
How well the drug worked at slowing cancer growth in clinical trials	MODERATE IMPROVEMENT Both drugs prevented cancer growth by 3 additional months compared to your current treatment	
How certain doctors are that slowing cancer growth means you will live longer	MODERATE CERTAINTY You will live 1 to 5 months longer Uncertain Certain (e.g., there is some evidence linking cancer growth to life expectancy)	VERY LOW CERTAINTY You will live 1 to 5 months longer Uncertain Certain (e.g., there is no evidence linking cancer growth to life expectancy)
FDA approval time	FDA approves the drug in 1 year (e.g., 12 months wait time)	FDA approves the drug in 6 months (e.g., 6 months wait time)
Which would you prefer? (please tick)	Drug A ☐	Drug B ☐

- **Background:** This study examines how much uncertainty cancer patients are willing to accept for faster access to new drugs and what factors affect these preferences.
- **Methods:** Online discrete choice experiment (DCE), choosing between two cancer drugs based on five attributes: survival benefit certainty, FDA approval delay, and others.
- **Participants:** US adults with personal or family cancer experience
- **Sample Size:** 900+
- **Results:** Respondents **preferred high certainty of survival benefit** and **a 1-year FDA approval delay**. They were willing to **wait up to 21.68 months** for higher certainty of survival benefit.
- **Conclusions:** Respondents strongly valued certainty in survival benefits and were willing to wait longer, particularly for metastatic cancer drugs. Many FDA-approved drugs offer no survival benefit, highlighting the need for certainty.

Study ongoing: Chinese public trade-off between vaccine speed & certainty

- **Study design**: Single-profile DCE
- **Participants**: Adults, children, elderly, pregnant women, and immunocompromised individuals (including HIV-positive)
- **Other stakeholders**:
  - **Vaccine developers**: Executives, R&D teams, marketing, and supply chain staff;
  - **Regulators**: Review and approval officials, health commissions, CDC, and regional procurement bodies;
  - **Vaccine givers**: Frontline doctors, pediatric specialists, and community immunization staff.
- **Sample size**: **1200+**.
- **Expected completion date:** March 2026
- **Expected publicity**: ***VIF world 2026, Mar, Shanghai***

Benefit vs. Uncertainty		
	Infection risk if you are NOT vaccinated:	
Disease-related mortality	A substantial proportion of people may die.	
Transmissibility	Rapid spread, potentially triggering a national or global epidemic	
	The following vaccine is now offered to you:	
Relative efficacy	Substantially reduces disease risk	
Relative efficacy range	±30%	
Safety	Serious adverse events occur occasionally	
Safety range	±0.1%	
Cost	Completely free	
Approval time	Vaccine available almost immediately	
Would you choose to be vaccinated?	☐ yes	☐ no

When making your vaccination decision, which vaccine attribute do you prioritize?

Relative efficacy	Relative efficacy range	Safety	Safety range	Cost	Approval time
☐	☐	☐	☐	☐	☐

Example choice task

Recommendations for a quasi-quantitative BRF and risk management

A) Standardize Health Metrics: Employ QALY/DALY as a unified measure to quantify health trade-offs in the "speed-certainty" balance for vaccines, thereby supporting cost-effectiveness analyses.

B) Establish Dynamic Risk Thresholds: Create a model for "acceptable uncertainty thresholds" linked to pandemic severity, providing flexible decision-making bases for emergency authorizations across different scenarios.

C) Incorporate Real-World Data: Utilize post-marketing real-world evidence for sensitivity analyses, quantifying the effects of uncertainty on predicted outcomes to enhance model robustness and reliability.

D) Implement Real-Time Risk Monitoring: Establish continuous monitoring using real-time data to adjust risk management strategies, ensuring quick responses to emerging risks and adaptive decision-making in ongoing pandemic situations.

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Thanks!