VIEWPOINT

ARTIFICIAL INTELLIGENCE AND PEDIATRIC CARE

FDA Draft Guidelines for AI and the Need for Ethical Frameworks

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On January 6, 2025, the US Food and Drug Administration (FDA) released new draft guidance on use of artificial intelligence (AI) in the drug and biological product life cycle.[1] "Considerations for the Use of Artificial Intelligence to Support Regulatory Decision-Making for Drug and Biological Products"[1] provides a 7-step process to establish credibility of AI models, focusing both on risk assessment and precredibility and postcredibility determinations as illustrated by 2 theoretical examples (identifying risk in subpopulations or assessing fill volume specifications). The draft guidance emphasizes the need to understand model risks, calling for manufacturers to have early discussions with the FDA regarding their proposed credibility assessment plan specific to the question asked and commensurate with the risk. This involves consideration of the contribution of AI-derived evidence relative to other contributing evidence used to inform the question (model influence) and the significance of an adverse outcome resulting from an incorrect decision (decision consequences). Understanding model risk is important because it can set expectations and identify potential challenges early, especially as the potential use of AI in the drug product life cycle is rapidly evolving and might change over the product's life cycle.[1] These guidelines provide an adaptive framework for partnerships between drug and biological product manufacturers and the agency, centered on exemplary questions for developers to address rather than detailed rules.

This draft guidance does not, however, directly address ethical considerations as part of AI-model risks in drug product life cycles. Medical AI models should be patient centered, with due consideration for ethical challenges when used with specific patient populations along with the model-specific credibility risks. Pediatric digital twins (DTs) exemplify the need for both model and population specific ethical guidance.

Delivering on the much-hyped promise of medical AI models requires creating "fit for purpose" models, understanding of the limitations of underlying data, and ensuring AI models projections are "...firmly linked to the status of the patient in data—in other words to the digital twin."[2,3] As a type of AI model, DTs—detailed virtual representations of systems through which a multitude of variables, design choices, and options can be studied through advanced computational analysis to aid in overall decision-making—are widely used in a variety of industries.[1] Health care applications remain in their infancy. Development and uses of health care DTs have accelerated recently, including to plan complex congenital cardiovascular heart surgeries and for drug discovery via AI-powered simulated patients.[4,5] DTs can improve regulatory decision-making, allowing manufacturers to evaluate products across more diverse populations in a safer, more cost-effective manner before clinical trials. The National Academies of Science, Engineering, and Medicine has increasingly recognized the transformative power that dynamic, longitudinal DTs might have for precision medicine if fully developed—even beyond the power to simulate, predict, and optimize health care choices before patient interventions to improve health care outcomes.[6]

DTs and other AI models should be developed with fit for purpose,[2] especially as varying scales of models (eg, cellular, organ, whole human, and population scale) raise distinct considerations.[7] Further, creating responsive AI models requires extensive computational resources to integrate and extrapolate multiple large data sources, such as electronic medical records, biobanks, claims, real-time medical device sensors, home environment sensors, and personal wearable devices.[8] Each of these data sources are subject to different regulatory schemes to balance patient privacy, security, and reliability concerns, such that integration requires model-specific consideration to ensure DTs are safe, reliable, and appropriately integrated into existing health care systems. Although the agency's new approach creates an adaptive framework that can begin to facilitate model-specific consideration and will likely be helpful and durable, more ethical guidance is needed to ensure the development and use of AI technologies (including DT synthetic data and in silico clinical trials) occurs in a validated, patient-centered manner.

Pediatric DTs illustrate the importance of more population-specific guidance. Regulations to address ethical challenges could help AI models close clinical trial research gaps in pediatric medicine. Despite improved outcomes for children with decades of regulatory efforts (including the Pediatric Research Equity Act and the Best Pharmaceutical for Children Act), the FDA and American Academy of Pediatrics have recognized the ongoing need for timely approval of innovative drugs for children.[9] Unlike adult medicine where drug discovery often involves large-scale randomized clinical trials (RCTs), many pediatric drugs are prescribed without FDA approval (off label). This evidence gap is most apparent in the neonatal intensive care unit (NICU) where scholars have demonstrated a large proportion of commonly used medications are used off label as well as disappointing clinical trial inclusion rates of eligible NICU infants.[10] In the absence of large RCTs, prescribing choices are often shaped by pharmacokinetic and pharmacodynamic data, extrapolations from adult medicine, observational studies, clinical practice guidelines, and clinical experience. Although "...pediatricians have learned to live with it...,"[9] AI models such as a fit for purpose DT can better integrate these and other real-time sources of information to improve the quality of evidence supporting novel use of drugs for children.

Although pediatric DTs could solve long-standing gaps in pediatric drug and device discovery, they merit additional regulatory guidance because of the breadth of pediatric-specific ethical issues.

For example, informed consent for pediatric DTs must also consider challenges of discordant preferences, duration, and sustainability. Although every state has laws that permit a minor's parent or guardian to provide consent for medical care for their child, parental consent to creation of a DT must also consider the duration of the DT's existence along with its predictive functions. DTs created with a child's data might exist after a child reaches the age of majority, and predictions on progression of conditions without curative treatments also might extend beyond childhood. If a parent consented to share data to create a DT that benefits others, can the child rescind consent once an adult? Can insurance companies use outcomes predicted by a childhood DT to prorate or limit coverage of a condition for an adult? If technical maintenance of a child's DT is discontinued by a company, is there a right to repair that DT? Does the child-patient, parent, hospital, insurance company, or engineering company own the DT? Consent and ownership of data are important questions for development of DTs in general, but the sustainability and duration of use for DTs when applied to children require special consideration. With rapid technologic advances in health care DTs that potentially impact the physician-patient relationship, additional age- and model-specific ethical guidance is important.

"Considerations for the Use of Artificial Intelligence to Support Regulatory Decision-Making for Drug and Biological Products"[1] provides much needed first steps toward a framework for (1) considering questions of uncertainty, accuracy, reliability, and fit for use and (2) facilitating the responsible use of AI in drug and biological product development. Additional guidance is still needed to address broader ethical issues, including patient autonomy and control over DTs within and beyond a particular health care system; potential for manipulation, overreliance, and exploitation/commodification; and digital dignity and silent trials; among others. Actions taken by the Trump Administration (namely, Executive Orders 14148 and 14179) place federal policies to ensure responsible biomedical AI on uncertain footing. Further efforts to promote effective, ethical, and equitable development of AI generally and DTs particularly would be helpful, as digital health equity deserves direct attention—especially for children.

ARTICLE INFORMATION

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