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Applying Artificial Intelligence in Pediatric Clinical Trials: Potential Impacts and Obstacles

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ABBREVIATIONS AI, artificial intelligence; EHR, electronic health record

KEYWORDS artificial intelligence; clinical trials; machine learning; pediatrics; trial design

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Introduction

Recent articles in this *Journal* have discussed the role of artificial intelligence (AI) in research writing and manuscript preparation, recognizing its immense power to streamline the scientific publication workflow as well as addressing concerns for academic integrity and unvalidated output.[1,2] These opportunities and obstacles extend throughout the clinical research landscape. Clinical trials in the pediatric population are particularly challenging and may benefit considerably from AI where both existing and novel therapies are understudied and most drugs continue to be used off-label without adequate dosing, efficacy, and safety data to inform prescribing.[3] Challenges persist with dose and endpoint selection, patient and disease heterogeneity, and patient recruitment.[4] The great potential for AI is to reduce the high cost and time investments of traditional randomized controlled trials by overcoming the many population-specific barriers with innovative strategies.

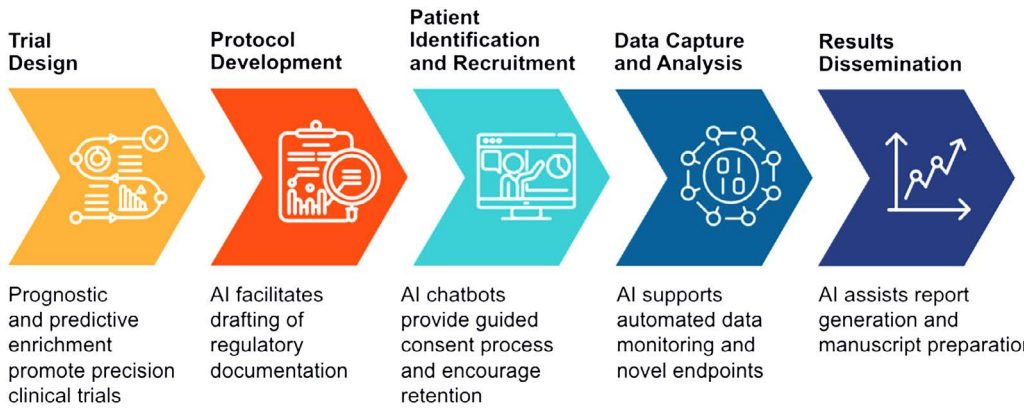
AI has the capability to improve numerous aspects of the clinical trial process to help overcome these hurdles. The spectrum of available methods ranges from traditional regression models to deep learning neural networks that allow for predicting outcomes from complex inputs such as multilayer cross-sectional images or time series electronic health record (EHR) data.[5] Natural language processing and large language models use computational techniques to analyze the content and meaning of text, supporting both data extraction and text generation.[6,7] Such models can collate relevant clinical trial data from multiple studies, facilitating meta-analyses and future trial development.[8] Additionally, they can aid the technical writing required in trial development through drafting protocols, patient consent forms, or review board documentation.[7] Here we discuss potential applications of these methods, collectively referred to as AI, across key areas in pediatric clinical trials (Figure). In presenting the opportunities, we also highlight the critical risks and concerns that must be addressed as novel applications continue to emerge at an accelerated pace. Finally, given the broad potential applications of AI, we will limit our focus primarily on its role in clinical trials, recognizing its transformative potential spans across preclinical drug development, clinical pharmacology, and clinical decision support.[9–11]

Patient and Treatment Selection

Because AI improves the ability to accurately predict patient outcomes, we expect the promise of precision clinical trials to be realized, potentially allowing for shorter, smaller, and more cost-efficient trials.[12] Prognostic enrichment (including patients more likely to have an outcome) and predictive enrichment (including patients more likely to benefit from therapy) are recognized strategies for increasing trial efficiency.[13] As just one of many examples, a recent study applied a mortality risk score to adults with heart failure in 4 community and 5 clinical trial cohorts, finding that selecting higher-risk patients would markedly increase the expected event rate and could reduce trial size by almost 70%.[14] Conversely, in adults with sepsis, prospectively selecting only those patients at moderate risk of death could have resulted in a positive clinical trial of a polyclonal anti–tumor necrosis factor-α fragment antibody by excluding those too sick to benefit from treatment as well as those whose health would have improved regardless of trial arm.[15]

Predictive enrichment techniques have been commonly used in the field of oncology, which has established a data-rich environment with a combination of genetic profiles, tumor markers, and multiple targeted therapies. Studies in adults have combined genomic profiles of a patient's tumor with outcomes from prior trials to predict progression-free survival and select the therapy of most likely benefit.[16,17] The use of AI in pediatric oncology is more nascent with approaches largely based on retrospective analysis of published studies rather than prospective applications.[18] Interestingly, there has been much progress in the more challenging

Figure. Proposed use cases for AI throughout the pediatric clinical trial life cycle.



AI, artificial intelligence.

environment of pediatric septic shock where decisions must be made rapidly, often without rich data. Strategies for prognostic enrichment were reported a decade ago and have evolved rapidly to include both prognostic and predictive strategies within the same cohort.[19,20] Recently, a study of pediatric patients with sepsis generated pediatric sepsis phenotypes with 4 distinct biomarker profiles differing in their clinical trajectories.[21] Consistent with studies in adults, there were children likely to benefit from anti-inflammatory therapies, whereas others might possibly be harmed.[22]

Prognostic and predictive enrichment strategies have the potential to support precision clinical trial design. To ensure benefit across pediatric populations, much work is needed to define disease-specific data patterns that reliably support diagnosis and prognosis. Successful AI will likely incorporate diverse inputs including laboratory and multi-omic data, as well as dynamically tracked data generated both in the course of health care and through wearable technology.[23] As participant selection strategies integrate ever-more data sources, it will be critical to ensure availability of information among those most at risk of inequity, and for whom existing data may be incomplete or inaccurate. Inadvertently excluding those without access to the technologies needed to generate data, or for whom data privacy is paramount, becomes a primary concern to ensure equitable data capture. Indeed, the need for adequate data security is a primary challenge for adopting AI into clinical trials.[24]

Patient Identification and Recruitment

AI has the potential to streamline patient identification and recruitment as well as to facilitate ongoing communication with patients and their families throughout a trial. AI can combine structured data, such as diagnosis codes, with unstructured data from clinical notes to provide a curated population to then manually screen for trial eligibility, significantly improving screening efficiency.[25] Trial-centric strategies, in which a patient population is assessed on criteria for a specific trial, and patient-centric strategies, in which known trials are matched to a specific patient, have both been proposed.[26] One study reviewed 215 pediatric oncology patients across 55 trials and found that AI could cut screening workload by up to 90%.[27] Importantly, AI can maintain both high sensitivity and negative predictive value to ensure identification of all potentially eligible patients.[28] In addition to cohort identification, embedding AI within the EHR can allow for real-time identification of patients for whom timeliness of intervention is critical, such as in the emergency department or intensive care unit.[29,30] Going beyond simply identifying potentially eligible patients, recent studies have used clinical, demographic, and trial characteristics to predict whether patients would agree to consent for a clinical trial.[31,32]

Identifying potential participants and predicting who would be most likely to consent is presumed to decrease resources required for patient recruitment, yet it will be essential to ensure inequity is not perpetuated by integrating bias into the recruitment pipeline. This is a critical risk in the use of AI for recruitment. For example, Ni et al[31] found that Black children and those with income less than 50% of the poverty line were less likely to consent to a clinical trial in a pediatric emergency department than White children and those from households with higher income. Selecting trial participants based on likelihood of consent would exclude Black children and those living in poverty. Women and minorities are consistently underrepresented in clinical trials, and equitable enrollment must actively seek out these groups rather than avoiding approaching them for consent.[33] Encouragingly, an AI tool was able to evaluate how adjusting eligibility criteria could allow for inclusion of more women in a nationwide database of adults with lung cancer, indicating similar analyses should be applied to pediatric populations.[34]

Beyond the existing use cases where AI is used to identify potential cohorts for study, we suggest AI has the potential to disrupt the recruitment process. Generative AI has the capability of interacting through audio, visual, and written interfaces by using language and context specific to the user. We expect the scenario to emerge where children and their guardians can engage with a multimodal chatbot to learn more about the research and to answer questions specific to the potential participant's lived context. Such an interaction could be guided to ensure understanding of the research and completion of a valid consent process. The chatbot could remain available through the life cycle of a trial and be personalized to optimize participant engagement and retention. In addition to solving regulatory hurdles to such a use case, it will be critical to ensure that such technology does not cross the line from being informative to being coercive. As these technologize become more personalized, associated institutional review board and regulatory oversight will be needed to ensure adequate protections for both patient and patient heath information.

Data Capture and Analysis

Clinical trials traditionally require labor-intensive and costly manual data entry for safety and endpoint documentation. AI is already being used to extract real-world data from the EHR, as well as to detect data anomalies that may occur in the data entry process.[35,36] Automated extraction allows for increased complexity of outcomes; in addition to structured clinical data such as length of stay or mortality, AI can analyze disease trajectories, medical images, and clinical notes.[37] The analysis of time-series data, especially from existing monitoring devices and wearable technology, can provide rich information and minimize trial burden on families.[24] Further, AI could be used to define novel trial endpoints. For example, wearable data have shown potential in measuring attention-deficit/hyperactivity disorder and sleep problems in children, and AI analysis of interaction with a digital app may improve autism detection.[38–40] Similarly, AI image interpretation has comparable accuracy to trained specialists in detecting breast cancer screening mammograms and discriminating malignant from benign skin lesions.[41,42]

Today, trial endpoints are typically manually adjudicated. While this can contribute significant cost and time burden to trials, it is a necessary process for minimizing bias and ensuring endpoints are related to the study intervention or procedures.[43] Automating endpoint evaluation could standardize assessment and hasten trial completion.[44] In adult heart failure, AI has demonstrated equivalent performance to a manual adjudication process.[45]

As algorithms for automating measurements multiply, there is increasing urgency for validating AI-generated endpoints for use in clinical trials. Extracting accurate EHR data requires efficient data processing as well as robust methods for dealing with biases in EHR data, including missing data points or patients lost to follow-up.[46,47] As with consent, there is the potential for AI to interact with participants, providers, and investigators to maximize the completeness and quality of data. One might even imagine the scenario where a chatbot engages with a participant to assess patient-reported outcomes in a culturally responsive manner while also considering their age and language ability.

Risks and Limitations

A foundational pillar for advancing AI in clinical trials must be to vet its application with a degree of scrutiny that matches the potential harm to participants and patients. If inequity and error persist in the generation of evidence, structural inequity will continue. The recent Executive Order on the Safe, Secure, and Trustworthy Development and Use of Artificial Intelligence details the critical necessity for adequate oversite and regulation to ensure adherence to best practices and minimization of harm for these rapidly evolving technologies.[48] Using AI to generate technical writings that are subsequently reviewed by personnel with appropriate expertise and training may not warrant regulation. However, AI that affects patient selection or data measurement, analysis, or interpretation will require a regulatory framework to ensure appropriate patient protections and to limit furthering disparities in patient care.[49] Without such oversight, AI trained on existing data in which there are discrepancies in care or outcomes between groups will perpetuate bias.[50] Any use of AI that diminishes trustworthiness and representativeness of clinical trials must be avoided at all costs.

AI tools only perform well if their input data match the clinically relevant population. AI must be trained on diverse cohorts, which will require collaboration and data sharing across medical centers and institutions.[49] Like with drug therapies, in which dosing or efficacy in children should not be merely extrapolated from adult trials, AI must also be validated for population- and disease-specific cohorts prior to deployment. The exponential increase in publications evaluating AI for clinical applications must be accompanied with transparent reporting of model performance with adherence to reporting guidelines such as CONSORT-AI, with careful attention to prospective validation.[51–53] Generative AI is at particular risk for factual errors, and for bias and harm, when responding to clinical questions or developing scientific reports.[54,55] Guardrails will be critical for any application using text generation, and for now, such applications are expected to require manual auditing to ensure the veracity of the provided text.

Overall, there is great potential for AI to streamline the clinical trial, from initial protocol development

through results dissemination and manuscript preparation. Coupling AI with advances in trial design, such as for pragmatic trials and master protocols testing multiple drugs in the same platform, has the potential to facilitate the completion of pediatric clinical trials across therapies and populations.

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