ACRO Innovate Advocate Collaborate

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Tala Fakhouri
Center for Drug Evaluation and Research
Hussein Ezzeldin
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, Rm. 6330,
Silver Spring, MD 20993–0002

RE: ACRO comment on *Using Artificial Intelligence and Machine Learning in the Development of Drug and Biological Products*
[FDA-2023-N-0743-0001]

Dear Dr. Fakhouri and Dr. Ezzeldin,

The Association of Clinical Research Organizations (ACRO) represents the world's leading clinical research and clinical technology organizations. Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics and medical devices, from pre-clinical, proof of concept and first-in-human studies through post-approval, pharmacovigilance and health data research. ACRO member companies manage or otherwise support a majority of all biopharmaceutical sponsored clinical investigations worldwide and advance clinical outsourcing to improve the quality, efficiency and safety of biomedical research.

ACRO appreciates the opportunity to provide our industry's thinking and recommendations in response to the discussion paper on *Using Artificial Intelligence and Machine Learning in the Development of Drug and Biological Products*. In Section I of this comment, we offer some general recommendations, before addressing the Agency's specific questions in Section II.

Section I: General Recommendations

1. **Endpoint versus Exploratory**: ACRO suggests that the regulatory framework for AI/ML should primarily govern use cases involving AI/ML that directly impact determinants of effectiveness and safety, such as in endpoint collection, patient safety improvement, and in enhancing data quality. AI/ML applications aimed at improving operational efficiency and for exploratory purposes should, in general, be excluded from the regulatory framework.

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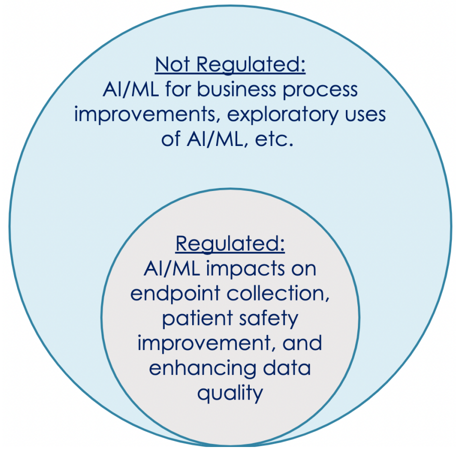

2. **Governance and Oversight**: Industry should establish strong internal governance and oversight mechanisms for monitoring the development of AI/ML models. ACRO recommends the following principles:
   - Create a dedicated internal governance framework for AI.
   - Establish dedicated teams, including an AI ethics board, responsible for implementing AI strategy.
   - Develop an AI handbook to integrate AI use into organizational policies.

3. **Accountability and Risk Assessments**: Effective accountability and risk assessment frameworks are necessary for controlling the deployment of AI/ML models. The FDA should provide stakeholder-informed guidelines on assessing risks and implementing accountability structures. Considerations include:
   - Develop risk assessment scales and utilize impact assessments to identify and mitigate risks.
   - Include AI monitoring within existing accountability structures.
   - Establish accountability documentation, such as impact assessments, audit functions, monitoring procedures, management plans, and AI acquisition and procurement policies. Ensure that IP and copyright related issues are assessed.

4. **Human Oversight**: Ensuring clear human oversight is essential for monitoring AI models and maintaining proper governance. The FDA should provide stakeholder-informed guidelines on the expected level of human oversight. Recommended areas of oversight include:
   - Incorporate human review and accuracy testing at each stage of the AI life cycle.
   - Provide oversight on the data used for training AI models.
   - Monitor inaccurate AI decisions and establish corrective measures managed and reviewed by humans.
   - Establish policies and protocols for triggering human interventions when necessary.

5. **Transparency**: A transparent framework is vital for governing and monitoring AI models. A uniform mandate on transparency will facilitate regulatory compliance for both the agency and ACRO member teams. Consider the following ideas:
   - Articulate the organization's risk appetite, methodologies, and frameworks in an AI impact assessment document.
   - Draft notices, policies, and procedures, disclaimer statements outlining the purpose of AI systems, underlying datasets, decision-making processes, and subject rights related to AI systems.
   - Ensure transparency frameworks focus on outcomes that protect patient safety and data integrity, rather than explanations of the inner workings of the systems.

6. **Explainability of AI/ML Models**: Research suggests that explainability and AI model performance come with certain tradeoffs[1]. ACRO believes that the totality of evidence or interpretability of the model are better indicators for good and sound model performance. Given the tradeoffs, ACRO recommends a risk-based approach to focus on outcomes and results rather than expecting detailed explainability of AI/ML tools.

<u>Section I: In Closing</u>

ACRO appreciates the FDA's dedication to ensuring the safe and effective use of AI/ML in drug development. We believe that addressing the questions raised in this request for feedback will contribute to the establishment of a robust regulatory framework that fosters innovation while safeguarding patient safety and data integrity. We remain committed to collaborating with the FDA and other stakeholders to address these important considerations.

Thank you for considering our feedback. We are available for further discussions or clarification if needed.

Respectfully Submitted,

Douglas Peddicord
Executive Director, ACRO

[1] Forough Poursabzi-Sangdeh, Daniel G Goldstein, Jake M Hofman, Jennifer Wortman Wortman Vaughan, and Hanna Wallach. 2021. Manipulating and Measuring Model Interpretability. In Proceedings of the 2021 CHI Conference on Human Factors in Computing Systems (CHI '21). Association for Computing Machinery, New York, NY, USA, Article 237, 1–52. https://doi.org/10.1145/3411764.3445315

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Section II: Appendix - ACRO's Responses to the FDA's Questions Listed in Discussion Paper

Human-led Governance, Accountability, and Transparency

1. What specific use cases or applications of AI/ML need additional regulatory clarity?

ACRO recognizes the importance of regulatory clarity in use cases that directly impact clinical trial endpoints, enhance the quality of submission data, and prioritize patient safety. These areas are critical to the success of clinical trials and the development of safe and effective treatments. We believe that providing clear guidelines and regulations for AI/ML applications in these use cases will ensure consistent standards and facilitate innovation in the life sciences industry.

However, we would like to emphasize that there are other areas where AI/ML can be utilized in clinical operations to drive efficiencies, optimize site and patient recruitment, and enhance operational processes. These use cases primarily focus on improving internal workflows, resource allocation, and operational decision-making, without directly affecting regulatory submissions or patient safety. In these non-submission-related areas, we recommend that FDA refrain from regulatory oversight.

ACRO believes that by differentiating between use cases that directly impact regulatory endpoints and those that focus on operational efficiencies, the FDA can provide targeted regulatory guidance and foster innovation in the clinical trial domain. This approach would strike a balance between ensuring patient safety, data integrity, and regulatory compliance, while allowing for the exploration of AI/ML technologies to drive process improvements within the clinical research ecosystem.

2. What does transparency mean in the use of AI/ML?

In the context of AI/ML in clinical trials, transparency refers to the extent to which relevant information about the AI/ML model is effectively communicated to regulatory authorities, trial sponsors, and other stakeholders to the extent consistent with applicable law governing intellectual property.

Transparency encompasses **clear and comprehensive documentation** of the model's purpose, data sources, algorithmic approach, key decisions made during its development, and any deviations from established protocols, as permitted.

Appropriate transparency is vital for ensuring trust, accountability, and regulatory compliance in the application of AI/ML technologies. It enables relevant stakeholders to understand the underlying processes and assumptions of the model, facilitating critical evaluation of its reliability, safety, and effectiveness.

Transparent reporting of the AI/ML model's development and performance allows regulators and trial sponsors to assess its suitability for the intended use and evaluate potential risks and benefits.

Transparency in AI/ML also includes providing information as permitted on the sources and quality of the training data, potential biases, and steps taken to address bias and ensure representativeness. This ensures that the data used to train the AI/ML model aligns with the target population and avoids unfair or discriminatory outcomes.

Furthermore, transparency allows for critical review and validation, aiding in the identification of potential limitations, risks, or errors.

ACRO believes that transparency is a foundational principle for responsible and ethical use of AI/ML in clinical trials. Clear and comprehensive documentation of the output of the AI/ML model from a patient safety and a data integrity perspective are essential to foster trust, support regulatory decision-making, and promote collaboration among stakeholders.

3. What are the main barriers and facilitators of transparency?

Barriers to transparency in AI/ML use in clinical trials stem from various factors:

- **The complexity of AI/ML algorithms** poses a significant challenge, as these models can be intricate and difficult to comprehend for non-technical stakeholders.
- Additionally, concerns related to **intellectual property** can hinder transparency. Companies may be hesitant to disclose proprietary algorithms or trade secrets. Balancing the need for transparency with the protection of intellectual property rights is an important consideration, since protection of intellectual property rights is necessary to promote innovation.
- Addressing source data issues including privacy in training the model can make model building burdensome.
- Ensuring replicability of results is a key challenge in model building and scaling.
- Furthermore, the **lack of standardized reporting frameworks** poses a challenge to transparency.

On the other hand, several factors can act as facilitators of transparency in the use of AI/ML in clinical trials:

- Regulatory guidance that encourages the **disclosure of AI/ML models** used in clinical trials plays a crucial role in facilitating transparency. Ongoing dialogue between the agency and the industry concerning how the reporting on AI models is done would be helpful.
- **Establishing clear accountability** mechanisms is another facilitator. When there are clear roles and responsibilities assigned to different stakeholders involved in the development and use of AI/ML models, transparency can be enhanced. This includes defining the

responsibilities of AI/ML developers, sponsors, and regulatory authorities in ensuring transparency throughout the clinical trial process.

- **Industry collaboration** is also essential in promoting transparency. By fostering collaboration among stakeholders, including pharmaceutical companies, contract research organizations, academic institutions, and regulatory bodies, we can work together to develop transparent reporting standards, share best practices, and address common challenges. Collaborative efforts can help establish a culture of transparency within the industry.

ACRO believes that overcoming the barriers to transparency where appropriate, balancing the need for transparency with the need for intellectual property protection for innovation, and leveraging the facilitators mentioned above will be crucial in promoting the responsible and transparent use of AI/ML in clinical trials. By addressing these challenges and encouraging a collaborative approach, we can enhance transparency, build trust among stakeholders, and support the advancement of innovative and ethical clinical trial research.

4. What are some of the good practices for providing risk-based, meaningful human involvement when AI/ML is utilized?

Ensuring risk-based, meaningful human involvement is crucial for the safe and effective use of AI/ML in clinical trials. ACRO recommends the following practices to achieve this:

- **Interdisciplinary Teams**: Establish interdisciplinary teams comprising experts in AI/ML, clinical research, and regulatory compliance. These teams can provide diverse perspectives and expertise to ensure comprehensive risk assessment and meaningful human involvement throughout the AI/ML implementation in clinical trials.
- **Risk Management Planning**: Develop and implement risk management plans specifically tailored to the use of AI/ML in clinical trials. These plans should identify and mitigate potential risks associated with AI/ML use in the specific trial context. Risk assessment should consider factors such as data quality, patient safety, regulatory compliance, and ethical considerations. The involvement of relevant stakeholders and experts is essential in designing and implementing effective risk management strategies.
- **Documentation and Oversight**: Maintain clear documentation of key steps, decisions, and rationale for deviations from established protocols. This includes documenting the purpose and intended use of the AI/ML model, as well as any modifications or updates throughout the clinical trial. Oversight structures should be established to ensure human review and accuracy testing at each stage of the AI/ML lifecycle. This ensures that human involvement is meaningful, allowing for appropriate risk assessment and intervention when necessary.
- **Collaboration and Training**: Promote industry collaboration and knowledge-sharing to develop best practices for risk-based, meaningful human involvement. Encourage training programs and initiatives to enhance the understanding of AI/ML among stakeholders involved in clinical trials. This will foster a shared understanding of the

benefits, limitations, and risks associated with AI/ML and facilitate effective collaboration between AI/ML experts and clinical trial professionals.
- **Regulatory Guidance**: Seek clear regulatory guidance from the FDA on risk-based human involvement requirements for AI/ML in clinical trials. Well-defined guidelines will help organizations ensure appropriate human oversight, accountability, and risk mitigation strategies throughout the development and implementation of AI/ML models. ACRO encourages the FDA to engage in ongoing dialogue with industry to address the unique considerations.

By implementing these good practices, clinical trial and technology organizations can effectively provide risk-based, meaningful human involvement when utilizing AI/ML. ACRO believes that interdisciplinary collaboration, robust risk management planning, clear documentation and oversight, collaboration and training, and regulatory guidance will collectively contribute to the safe and effective use of AI/ML in clinical trials.

5. What processes are in place to enhance/enable traceability and auditability?

To enhance traceability and auditability of AI/ML in clinical trials, ACRO suggests the following processes:
- **Standardized Documentation Practices**: Implement standardized documentation practices that capture essential information about AI/ML models. This documentation should include the purpose and context of the model, details of its development, key decisions made during the development process, and any modifications made over time. By maintaining comprehensive documentation, organizations can establish a clear audit trail and facilitate traceability of AI/ML models throughout their lifecycle.
- **Utilization of Electronic Systems**: Utilize electronic systems specifically designed to capture and record important information related to AI/ML models. These systems should provide an audit trail that documents the inputs, algorithmic decisions, and output generation processes. By leveraging electronic systems, organizations can streamline data collection, ensure accuracy and consistency, and facilitate efficient auditability of AI/ML models.
- **Version Control and Change Management**: Employ robust version control and change management procedures for AI/ML models. This includes maintaining a record of model iterations, documenting modifications made during the development process, and tracking the evolution of the model over time. By implementing effective version control and change management, organizations can easily trace the history of AI/ML models, understand the impact of modifications, and ensure reproducibility and reliability.
- **Data Provenance**: Facilitate data provenance by recording metadata that tracks the origin and history of the data used in AI/ML models. This includes documenting information such as data sources, data collection methods, data preprocessing steps, and any data transformations performed. By capturing data provenance, organizations

can establish the lineage of data, ensure data quality and reliability, and enable comprehensive auditing of AI/ML models.

ACRO believes that implementing these processes will enhance the traceability and auditability of AI/ML in clinical trials. By adopting standardized documentation practices, utilizing electronic systems, implementing version control and change management procedures, and capturing data provenance, organizations can ensure transparency, accountability, and reproducibility in the utilization of AI/ML.

6. How are pre-specification activities managed, and changes captured and monitored, to ensure the safe and effective use of AI/ML in drug development?

Pre-specification activities play a crucial role in ensuring the safe and effective use of AI/ML in drug development, including risk-benefit considerations. ACRO recommends the following practices for managing pre-specification activities and capturing and monitoring changes:

- **Pre-Specification Planning**: Organizations should establish a robust pre-specification planning process that outlines the purpose, objectives, and intended use of the AI/ML model in drug development. This involves clearly defining the research question, the specific context of use, and the risk considerations associated with the AI/ML model. By engaging relevant stakeholders and conducting thorough pre-specification planning, organizations can establish a solid foundation for the safe and effective use of AI/ML.
- **Documentation and Version Control**: It is essential to document all pre-specification activities, including key decisions made, rationale for those decisions, and any deviations from established protocols. Organizations should maintain a comprehensive record of the pre-specification process and ensure version control to track changes and updates over time. This documentation should capture the purpose, intended use, and modifications of the AI/ML model, enabling traceability and facilitating future monitoring and auditing.
- **Change Management**: Organizations should implement robust change management procedures to track and monitor any changes made to the AI/ML model during the drug development process. This includes documenting the reasons for changes, assessing their potential impact on the model's performance, and ensuring appropriate approvals and oversight. Regular reviews and evaluations should be conducted to assess the necessity and validity of changes, ensuring that they align with the intended use and objectives of the AI/ML model.
- **Ongoing Monitoring and Auditing**: Continuous monitoring and auditing are vital to ensure the safe and effective use of AI/ML in drug development. Organizations should establish processes for ongoing monitoring of the AI/ML model's performance, including data inputs, algorithmic decisions, and outputs. Regular assessments should be conducted to evaluate the model's adherence to pre-specification plans, identify potential risks or issues, and implement corrective measures when necessary. Auditing procedures should also be in place to review the documentation, decision-making

processes, and changes made throughout the development and implementation of the AI/ML model.

By implementing these practices, organizations can effectively manage pre-specification activities, capture and monitor changes, and ensure the safe and effective use of AI/ML in drug development. ACRO believes that a proactive approach to pre-specification planning, documentation, change management, and ongoing monitoring and auditing will contribute to the overall quality, reliability, and transparency of AI/ML in the drug development process.

Quality, Reliability, Representativeness of Data

7. Are there additional data considerations for AI/ML in drug development?

In drug development, several additional data considerations are important when utilizing AI/ML:

- **Addressing Bias**: It is crucial to address bias in the underlying input data used for training AI/ML models. By identifying and mitigating biases, we can prevent the amplification of preexisting biases in the AI/ML model, ensuring fairness and equity in the analysis and decision-making processes.
- **Data Integrity**: Ensuring data integrity is vital to maintain the quality and reliability of AI/ML-generated insights. This includes maintaining data consistency, accuracy, and completeness throughout the data collection, curation, and preprocessing stages. Robust data integrity practices help minimize errors and inconsistencies that could adversely impact the validity and reliability of AI/ML outcomes.
- **Data Privacy and Security**: Protecting data privacy and security is of utmost importance to maintain confidentiality, comply with applicable regulations (such as HIPAA), and safeguard patient information. Implementing appropriate security measures, data anonymization techniques, and access controls are essential to ensure the privacy and security of sensitive data used in AI/ML applications.
- **Data Provenance**: Establishing data provenance is critical to track the origin, transformation, and usage of data inputs in AI/ML models. By capturing metadata and documenting the journey of data, we enhance transparency, traceability, and auditability. Data provenance helps build trust in the AI/ML outputs and enables stakeholders to understand the context and reliability of the data used.
- **Data Relevance and Representativeness**: Ensuring data relevance and representativeness is crucial to the accuracy and generalizability of AI/ML models in drug development. It is important to use datasets that accurately reflect the intended patient population, clinical context, and diversity of real-world scenarios. By ensuring data representativeness, we can enhance the applicability and reliability of AI/ML-generated insights.

By addressing these additional data considerations, stakeholders in drug development can improve the quality, fairness, and reliability of AI/ML applications. ACRO emphasizes the importance of incorporating these considerations into the regulatory framework to ensure the responsible and effective use of AI/ML in advancing drug development.

8. What practices help assure the integrity of AI/ML?

To assure the integrity of AI/ML in clinical trials, ACRO suggests the following practices:

- **Rigorous Data Quality Assurance**: Implementing robust data quality assurance processes is crucial to ensure the integrity of AI/ML. This includes validation, cleaning, and normalization techniques to address data errors, inconsistencies, and outliers. By ensuring data accuracy, completeness, and reliability, the integrity of AI/ML models and their outputs can be maintained.
- **Validation Assessments**: Conducting thorough validation assessments of AI/ML models is essential to ensure their credibility, reliability, and performance for the specific context of use in clinical trials. Validation should include rigorous testing against appropriate reference standards, comparison with gold-standard methodologies, and assessment of the model's generalizability and limitations. This includes implementing mechanisms to detect and mitigate biases in AI/ML models.
- **Independent Verification and Validation**: Performing independent verification and validation of AI/ML algorithms and software code helps ensure the integrity of the models. Independent experts or third-party organizations can assess the algorithms, validate the code, and verify the accuracy and reliability of the AI/ML outputs. This process enhances transparency, accountability, and confidence in the integrity of AI/ML applications.
- **Regulatory Compliance and Data Integrity Guidelines**: Incorporating regulatory compliance and adherence to relevant data integrity guidelines is essential during the development and implementation of AI/ML in clinical trials. Following established regulations and guidelines, such as those provided by regulatory authorities and industry standards, ensures that the data used, algorithms employed, and processes followed maintain the highest standards of integrity and quality.

By implementing these practices, stakeholders in clinical trials can assure the integrity of AI/ML applications, enhancing the reliability and trustworthiness of the generated insights and outcomes.

9. What practices are used to help ensure data privacy and security?

To ensure data privacy and security in AI/ML applications within the context of clinical trials, ACRO suggests the following practices:

- **Stringent Data Access Controls**: Implementing stringent data access controls is crucial to protect sensitive patient information. This includes role-based access controls, data

encryption, and anonymization techniques to limit access to authorized personnel and ensure the confidentiality of patient data.
- **Compliance with Data Protection Regulations**: It is essential to comply with relevant data protection regulations and guidelines, such as the Health Insurance Portability and Accountability Act (HIPAA) and General Data Protection Regulation (GDPR). Adhering to these regulations helps safeguard patient privacy, establish clear data governance frameworks, and ensure appropriate handling of personal health information.
- **Privacy Impact Assessments**: Conducting privacy impact assessments is recommended to identify potential risks associated with AI/ML models handling patient data. These assessments help evaluate the privacy implications of the data processing activities, identify vulnerabilities, and define appropriate mitigation strategies to protect patient privacy.
- **Collaboration with Cybersecurity Experts**: Collaborating with cybersecurity experts can enhance data privacy and security in AI/ML applications. These experts can assist in establishing robust security measures, including network security, data encryption protocols, intrusion detection systems, and incident response plans, to protect against data breaches and unauthorized access to AI/ML systems.

By implementing these practices, stakeholders in clinical trials can effectively safeguard data privacy and security, ensuring the confidentiality and integrity of patient information throughout the AI/ML lifecycle.

10. What practices help address reproducibility and replicability?

To address reproducibility and replicability in AI/ML applications within the context of clinical trials, ACRO suggests the following practices:
- **Documentation of Methodologies and Parameters**: It is crucial to document detailed methodologies used in AI/ML model development. This documentation allows for independent reproduction of the models and facilitates transparency and accountability in the research process.
- **Sharing of Datasets, Code, and Model Specifications**: Encouraging the sharing of datasets, code repositories, and model specifications through open science initiatives and collaborative platforms promotes reproducibility and replicability. This sharing enables researchers to validate and replicate AI/ML models in different research settings, fostering transparency and knowledge exchange.
- **Peer Review and Validation**: Encouraging peer review and validation of AI/ML models is essential to ensure their replicability and robustness. Peer review provides an external assessment of the models' methodologies, data handling, and statistical approaches, enhancing the scientific rigor and reliability of the findings.
- **Sensitivity Analyses and External Validations**: Conducting sensitivity analyses and external validations helps assess the generalizability and robustness of AI/ML models.

These analyses involve testing the models with different datasets or variations in model parameters to evaluate their performance and reliability across diverse settings.

By implementing these practices, stakeholders in clinical trials can enhance the reproducibility and replicability of AI/ML models, promoting transparency, scientific integrity, and knowledge advancement.

11. What processes are developers using for bias identification and management?

To address bias in AI/ML applications within the context of clinical trials, developers employ the following processes:

- **Bias Detection Algorithms**: Developers implement bias detection algorithms to identify potential biases in training datasets and model outputs. These algorithms analyze the data to identify patterns and discrepancies that may indicate biased outcomes or unfair treatment.
- **Fairness Assessments**: Conducting fairness assessments is crucial in evaluating the impact of AI/ML models on different demographic groups. Developers assess the fairness of model outputs across various characteristics, such as race, gender, age, or socioeconomic status, to identify and mitigate any identified biases. Disclosure of such assessments would help ensure that the AI/ML models do not disproportionately favor or disadvantage specific population subgroups.
- **Ongoing Model Performance Monitoring**: Developers regularly monitor the performance of AI/ML models to detect and address biases that may arise during model deployment. This monitoring involves analyzing real-world outcomes and comparing them against expected results. If biases are identified, developers can recalibrate the algorithms or introduce corrective measures to minimize their impact and ensure fair and unbiased results.
- **Collaboration with Domain Experts and Stakeholders**: Collaboration with domain experts and diverse stakeholder groups is essential to comprehensively evaluate potential biases and their implications. By engaging with experts from various disciplines and involving representatives from different demographic groups, developers can gain insights into potential biases and consider multiple perspectives in the bias identification and management process.

By implementing these processes, developers in clinical trials can enhance the identification and management of biases in AI/ML applications, promoting fairness, equity, and unbiased decision-making.

Model Development, Performance, Monitoring, Validation

12. What tools, processes, approaches, and best practices are being used to document development and performance of AI/ML in clinical trials?

In clinical trials, the following tools, processes, approaches, and best practices are utilized to document the development and performance of AI/ML:

- **Reporting Frameworks**: The use of reporting frameworks such as CONSORT-AI (Consolidated Standards of Reporting Trials for Artificial Intelligence) and SPIRIT-AI (Standard Protocol Items: Recommendations for Interventional Trials - Artificial Intelligence) is encouraged. These frameworks provide guidelines for comprehensive reporting of AI/ML methods and outcomes, ensuring transparency and facilitating replication of studies.
- **Documentation of AI/ML Models**: It is essential to document the purpose, algorithms, data sources, model specifications, and performance metrics of AI/ML models used in specific trial contexts. This documentation provides crucial information for evaluating the reliability, generalizability, and reproducibility of the models and their impact on trial outcomes.
- **Version Control and Recordkeeping**: Implementing version control systems and maintaining detailed records of model iterations, modifications, and validation results are critical. This ensures traceability and facilitates the tracking of changes made during the development and refinement of AI/ML models. Detailed records enable a clear understanding of the evolution of the models and provide insights into the decision-making processes involved.
- **Independent Verification and Validation**: Engaging independent auditors or validators to verify and validate AI/ML models and their accompanying documentation adds an extra layer of assurance. Independent validation helps ensure the accuracy, reliability, and robustness of the models and their performance metrics, promoting confidence in the results generated by the AI/ML applications.

By utilizing these tools, processes, approaches, and best practices, the documentation of AI/ML development and performance in clinical trials can be comprehensive, transparent, and well-documented, supporting the credibility and reproducibility of the findings.

13. How are model types selected for AI/ML in clinical trials?

The selection of model types for AI/ML in clinical trials involves careful consideration of several factors:

- **Context of Use**: The specific context of use within the clinical trial setting plays a crucial role in determining the appropriate model type. Different trials may require different types of models to address their unique objectives and challenges.

- **Available Data**: The availability, quality, and quantity of data influence the selection of model types. Some models may require larger datasets or specific types of data, such as structured or unstructured data, to perform effectively.
- **Desired Outcomes**: The desired outcomes of the AI/ML application in the clinical trial guide the selection of model types. For example, if the goal is prediction or classification, different models such as logistic regression, decision trees, support vector machines, or neural networks may be considered.
- **Complexity and Interpretability**: The complexity and interpretability of model types are important considerations. Simpler models, such as linear regression or decision trees, may be preferred when interpretability and explainability are critical. In contrast, more complex models like deep learning neural networks may offer higher predictive performance but may be less explainable.
- **Computational Requirements**: Model selection takes into account the computational resources available and the computational requirements of different models. High-performance computing capabilities may be necessary for computationally intensive models like deep learning networks.
- **Regulatory Compliance**: Consideration of regulatory compliance is essential in the selection of model types. Models must comply with applicable regulatory requirements, guidelines, and standards to ensure the integrity, safety, and reliability of the clinical trial data.

Domain expertise and input from interdisciplinary teams comprising data scientists, statisticians, clinicians, and regulatory experts play a vital role in the selection process. Their collective knowledge and experience contribute to informed decision-making and ensure that the selected model types align with the trial objectives, data characteristics, and regulatory considerations.

14. What specific approaches are used to determine the performance of AI/ML models in clinical trials?

The determination of AI/ML model performance in clinical trials involves several specific approaches:

- **Defining Relevant Success Criteria and Performance Measures**: Success criteria and performance measures are established based on the specific trial objectives and endpoints. Common measures include accuracy, sensitivity, specificity, positive predictive value, negative predictive value, and area under the receiver operating characteristic curve (AUC-ROC). These measures assess the model's ability to correctly classify and predict outcomes.
- **Rigorous Validation Studies**: Validation studies are conducted using independent datasets to evaluate the model's performance. Statistical analyses, such as calculating performance metrics and confidence intervals, are applied to assess the model's predictive capabilities. Validation studies help determine the model's generalizability and its performance across different patient populations and trial settings.

- **Cross-Validation Techniques**: Cross-validation is employed to estimate the model's generalization capability. This technique involves splitting the available data into multiple subsets for training and testing. By repeatedly training and evaluating the model on different data subsets, cross-validation provides an estimation of the model's performance and helps identify potential overfitting or underfitting issues.
- **Collaboration with Regulatory Authorities and Trial Sponsors**: Collaboration with regulatory authorities and trial sponsors is essential in establishing thresholds and benchmarks for acceptable AI/ML model performance. These stakeholders provide guidance and requirements to ensure that the performance of AI/ML models meets the necessary standards for clinical trial applications.

These specific approaches collectively contribute to assessing the performance of AI/ML models in clinical trials. They enable rigorous evaluation of the models' predictive capabilities, generalizability, and alignment with trial objectives. Collaboration with regulatory authorities and trial sponsors ensures that the performance assessment follows established guidelines and meets the necessary regulatory standards.

15. How is transparency and explainability evaluated in AI/ML models used in clinical trials?

Transparency and explainability in AI/ML models used in clinical trials are evaluated through the following approaches:

- **Feature Importance Analysis**: By conducting feature importance analysis, researchers can identify the factors or variables that significantly contribute to the model's predictions. This analysis helps explain the clinical relevance of the model's outputs and provides transparency in the decision-making process.
- **Documentation of Model Architecture and Specifications**: Transparency is ensured by thoroughly documenting the AI/ML model's architecture, algorithms, input/output specifications, and any supporting evidence or reasoning for the model's outputs. This documentation helps stakeholders understand the inner workings of the model and evaluate its transparency.
- **Input from Regulatory Authorities and External Experts**: Seeking input from regulatory authorities and external experts familiar with AI/ML models in the trial context can provide valuable insights and evaluations of transparency and explainability. Their expertise helps ensure that the models meet regulatory standards and provide sufficient transparency to enable effective decision-making.

ACRO believes that the totality of evidence or interpretability of the model are better guidelines for good and sound model performance. Given the tradeoffs, ACRO recommends a risk-based approach to focus on outcomes and results rather than requiring detailed explainability of AI/ML tools.

16. What factors are considered when selecting open-source AI software for AI/ML model development in clinical trials?

Regarding the selection of open-source AI software for model development in clinical trials, the following factors are considered:

- **Reputation and Community Support**: The reputation and community support of the open-source software are important factors. Established and widely used software with an active community of developers and contributors often indicates a higher level of reliability, support, and ongoing improvement.
- **Regulatory Compliance and Standards:** The software should comply with relevant regulatory requirements and standards, such as data privacy and security regulations, Good Clinical Practice (GCP) guidelines, and industry best practices for clinical trials.
- **Stability, Reliability, and Scalability**: The software's stability, reliability, and scalability are critical considerations, particularly for large-scale clinical trials. It should be capable of handling large volumes of data and perform consistently under different operational conditions.
- **Documentation, Support, and Updates**: The availability of comprehensive documentation, user support, and regular updates is important. This ensures that users have access to resources and assistance when using the software and that security vulnerabilities are promptly addressed through software updates.
- **Compatibility with Existing Infrastructure**: Compatibility with existing IT infrastructure and data management systems used in clinical trials is crucial for seamless integration and efficient workflow.

By considering these factors, organizations can select open-source AI software that aligns with their specific needs and requirements for model development in clinical trials.

17. How is real-world data (RWD) utilized to monitor AI/ML models in clinical trials?

RWD plays a crucial role in monitoring AI/ML models in clinical trials through the following processes:

- **Integration of RWD Sources**: RWD from sources such as electronic health records, product registries, and wearables are integrated to monitor the real-world performance and safety of AI/ML models. These data sources provide valuable insights into the model's performance in diverse patient populations and real-world settings.
- **Post-Market Surveillance**: RWD is utilized for post-market surveillance to assess the performance of AI/ML models after they are deployed in real-world clinical settings. By analyzing RWD, researchers can evaluate how the model performs in practice and identify any potential issues or discrepancies.
- **Continuous Monitoring**: Continuous monitoring of AI/ML outputs is conducted using RWD to compare the model's predictions with actual trial outcomes. This allows

researchers to detect any discrepancies or drift and take appropriate corrective measures if necessary.

- **Informing Adaptive Trial Designs and Safety Monitoring**: RWD is leveraged to inform adaptive trial designs, patient stratification, and safety monitoring protocols. By analyzing RWD, researchers can identify patterns, trends, and potential safety concerns that can inform the refinement and optimization of AI/ML models in clinical trials.
- **Privacy Considerations:** RWD sources should be vetted appropriately for privacy considerations.

By utilizing RWD in these processes, researchers and trial sponsors can gain valuable insights into the real-world performance, safety, and effectiveness of AI/ML models in clinical trials. This integration of RWD enhances the monitoring and evaluation of these models, enabling continuous improvement and optimization throughout the trial lifecycle.

18. What documentation is used to inform and record data source selection and inclusion/exclusion criteria in AI/ML model development for clinical trials?

In AI/ML model development for clinical trials, the following documentation is commonly used to inform and record data source selection and inclusion/exclusion criteria:

- **Rationale and Criteria for Data Source Selection**: Documentation includes a clear description of the rationale and criteria used for selecting data sources. This ensures that the chosen data sources are representative and relevant to the specific objectives of the clinical trial. It outlines considerations such as data availability, quality, diversity, and compatibility with the AI/ML model.
- **Inclusion/Exclusion Criteria**: Documentation includes the explicit inclusion and exclusion criteria used to identify eligible patient populations, study endpoints, or specific data variables. This information ensures transparency in the selection process and helps to establish the population characteristics or data elements that align with the trial objectives.
- **Data Preprocessing Step**s: Detailed records are maintained regarding any data preprocessing steps performed during model development. This includes documentation of cleaning, normalization, or imputation techniques applied to address missing values or data inconsistencies. These steps ensure the quality and reliability of the data used in the AI/ML model.
- **Ethical and Regulatory Considerations**: Documentation covers the ethical considerations and regulatory compliance measures associated with data collection and usage. It includes information on data privacy, informed consent, institutional review board (IRB) approvals, and compliance with relevant regulations and guidelines to ensure the ethical handling and protection of patient data.

By maintaining comprehensive documentation of data source selection and inclusion/exclusion criteria, researchers and trial sponsors can ensure transparency, reproducibility, and compliance *throughout the AI/ML model development process. These records contribute to the overall integrity and reliability of the clinical trial data and the AI/ML models derived from it.*

19. How are stakeholders addressing explainability and balancing performance/explainability in AI/ML models used in clinical trials?

Stakeholders in the clinical trial community recognize the importance of explainability and strive to strike a balance between performance and explainability in AI/ML models. The following approaches are commonly employed:

- **Multidisciplinary Collaborations**: Stakeholders engage in multidisciplinary collaborations involving experts from various domains, including AI/ML, clinical research, ethics, and regulatory affairs. This collaboration ensures adequate human oversight, interpretability, and ethical considerations throughout the AI/ML model lifecycle.
- **Sensitivity Analyses and External Validations**: Stakeholders conduct sensitivity analyses and external validations to assess the robustness, generalizability, and explainability of AI/ML models. These evaluations help identify the impact of different variables and assess the model's behavior in various scenarios, contributing to transparency and understanding.
- **Transparent Reporting and Documentation**: Stakeholders emphasize transparent reporting and documentation of AI/ML models' development, performance, and limitations. Clear documentation of the model's architecture, algorithms, input/output specifications, and any supporting evidence or reasoning helps facilitate external scrutiny and enhances trust in the model's outcomes.

By employing these approaches, stakeholders in the clinical trial community aim to ensure that AI/ML models used in clinical trials are not only high-performing but also explainable. This allows for a better understanding of the decision-making process and facilitates trust among regulators, trial sponsors, healthcare professionals, and patients.

20. What approaches are used to document uncertainty in model predictions in the context of clinical trials?

In clinical trials, stakeholders employ various approaches to document uncertainty in model predictions, ensuring transparency and informed decision-making. These approaches include:

- **Probabilistic Modeling Techniques**: Stakeholders utilize probabilistic modeling techniques to quantify and communicate uncertainty in model predictions. These techniques allow for the estimation of uncertainty intervals or confidence levels associated with the model's outputs, providing valuable insights into the range of possible outcomes.
- **Sensitivity Analyses**: Stakeholders conduct sensitivity analyses to assess the impact of varying input data or assumptions on model predictions. By systematically exploring

different scenarios or parameter values, sensitivity analyses help identify sources of uncertainty and their influence on the model's outputs.

- **Documentation of Uncertainty Sources and Assumptions**: Stakeholders document any sources of uncertainty, limitations, and assumptions that are inherent in the model development process. This includes capturing uncertainties related to data quality, model assumptions, and potential biases, ensuring transparency and facilitating a better understanding of the model's reliability.
- **Explanation of Uncertainty Metrics**: Stakeholders provide clear explanations of uncertainty metrics or indicators as part of the model documentation and reporting. This involves describing the meaning and interpretation of uncertainty measures, enabling stakeholders to make informed decisions based on a comprehensive understanding of the model's predictive capabilities.

By employing these approaches, stakeholders in the clinical trial community aim to document and communicate uncertainty associated with model predictions. This enhances transparency, facilitates risk assessment, and helps stakeholders interpret and contextualize the results of AI/ML models in the clinical trial setting.