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REPORT

Trustworthy Artificial Intelligence (TAI) for Patient-Centered Outcomes Research (PCOR)

Prepared for
The Office of the Assistant Secretary for Planning and Evaluation (ASPE)
at the U.S. Department of Health and Human Services

by
NORC at the University of Chicago

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Office Of The Assistant Secretary For Planning And Evaluation

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Executive Summary

Background. The rise of artificial intelligence (AI) in health care and health care research has stimulated discourse on AI's trustworthiness and its potential to cause harm. To provide guidance for U.S. Department of Health and Human Services (HHS) agencies on how to manage AI at all stages of the technology's lifecycle, the Office of the Chief AI Officer published the Trustworthy AI (TAI) Playbook in September 2021. The Playbook defined TAI as the "design, development, acquisition, and use of AI in a manner that fosters public trust and confidence while protecting privacy, civil rights, civil liberties, and American values, consistent with applicable laws." The Playbook also outlined six TAI principles: 1) fair/impartial, 2) transparent/explainable, 3) responsible/accountable, 4) robust/reliable, 5) privacy, and 6) safe/secure.

Considerations for implementing TAI principles for health care research, and patient-centered outcomes research (PCOR) in particular, are not explicitly addressed in the Playbook. Such considerations would be especially helpful for PCOR that the Office of the Secretary Patient-Centered Outcomes Research Trust Fund (OS-PCORTF) supports through data infrastructure capacity building.

Project Purpose. One goal of the 2020–2029 OS-PCORTF Strategic Plan is "to leverage leading technology solutions to improve data capacity for patient-centered outcomes and comparative clinical effectiveness research." Leading technology solutions include use of AI tools and methods. Under this goal, the HHS Office of the Assistant Secretary for Planning and Evaluation (ASPE) commissioned NORC at the University of Chicago (NORC) to develop a report to inform a better understanding about how the Playbook's TAI principles can be applied to OS-PCORTF projects. The TAI Playbook is a foundation to describe and understand the TAI principles. We used an adapted version of the National Library of Medicine (NLM) research lifecycle to highlight the connection between TAI principles and PCOR.

Methods. We used two approaches to gather the information summarized in this report: 1) an environmental scan of gray and peer-reviewed literature; and 2) eleven key informant discussions with federal and non-federal stakeholder experts in AI who validated findings synthesized from the environmental scan. We adapted the NLM's research lifecycle and mapped the findings to the six phases of the lifecycle to contextualize the considerations for the OS-PCORTF community and PCOR researchers.

Results. Our findings are organized into three categories to inform how OS-PCORTF projects can adhere to the HHS Playbook's six TAI principles:

- ***Key Informant Reflections on Implementing the Six HHS TAI Principles***

  Key informant discussions noted that the six HHS TAI principles cover all salient ethical areas for consideration when using AI in PCOR, yet some principles are more difficult to implement and interpret than others. There was consensus that the privacy principle is the most intuitive and easiest to implement. Key informants described the transparent/explainable principle as difficult to implement for "black box" AI models, where the decision-making process may not be explained. Nearly all key informants agreed that the fair/impartial principle is the most difficult to conceptualize and to implement. Key informants also reacted to the Playbook's definition of the safe/secure principle, noting that there should be more emphasis on protecting the safety and security of individuals from harm that may result from use of AI in research.

- ***Considerations for the OS-PCORTF Community and PCOR Researchers in Adhering to TAI Principles***

  This report describes 15 considerations for OS-PCORTF project adherence to the six TAI principles. We identified these considerations through the environmental scan of gray and peer-reviewed literature, refined and validated them through key informant discussions, and organized them by each of the six research lifecycle phases. Considerations that apply to all phases include ensuring patient privacy and safety are protected, evaluating tradeoffs between principles, and iteratively examining principles in every phase. We also identified TAI considerations for researchers specific to each research lifecycle phase. When planning a research project, considerations include determining the use case for the AI algorithm and establishing proper structures and procedures. During data acquisition, researchers can consider determining the appropriate volume, quality, and representativeness of the data. When preparing data for AI, considerations include augmenting the data and reducing errors that occurred during data collection. When analyzing data and maintaining AI models, researchers should test and evaluate models continuously for performance and for risk of bias or adverse events. Finally, when sharing results or reusing the AI algorithm, researchers can consider promoting transparency in their reporting.

- ***Opportunities for the OS-PCORTF to Support Work that Promotes Adherence to TAI Principles***

  To adhere to the HHS TAI principles, OS-PCORTF may consider 14 opportunities to support improvements to tools, resources, and methods/techniques. We used the environmental scan of gray and peer-reviewed literature to identify the opportunities and refined them through key informant discussions with federal and non-federal informants involved in AI-enabled research. We identified one opportunity related to governance, which describes updating documents that the OS-PCORTF has produced to address ethical considerations around using AI algorithms or methods. Five identified opportunities related to data, including development and use of standardized data sets, methods to augment training data, synthetic data modules, federated data models, and foundation models. Finally, we identified eight opportunities related to developing tools and resources, such as implementation guides, evaluation methods and metrics guidance, curated repositories of tools addressing bias and transparency, inventories of AI-related efforts, core resources for researchers using AI, and forums to discuss tools and resources.

Conclusion. Our findings highlight that the TAI principles outlined in the HHS TAI Playbook are important to implement when using AI for PCOR, but that implementation is complex and use case dependent. As the OS-PCORTF portfolio expands its projects that leverage AI, our report can be used as resource by the OS-PCORTF community, policymakers, PCOR researchers and others to inform application of the HHS TAI principles.

1. Introduction

The rapid evolution and expansion of artificial intelligence (AI) has led researchers to develop dozens of guidelines, frameworks, and tools to foster ethical AI. However, there is little concrete guidance on how to implement ethics principles in practice.[1] This gap in guidance, along with the inherently subjective interpretation of ethics principles, poses a challenge for organizations trying to implement and assess trustworthy AI (TAI).[2]

In March 2021, the U.S. Department of Health and Human Services (HHS) established the Office of the Chief AI Officer (OCAIO) to create processes supporting TAI development across HHS agencies. In 2021, the HHS OCAIO published a TAI Playbook outlining six core TAI principles and identifying actions to advance TAI for different types of AI solutions.[3]

The federal definition of TAI is the "design, development, acquisition, and use of AI in a manner that fosters public trust and confidence while protecting privacy, civil rights, civil liberties, and American values, consistent with applicable laws."[4] Although a large body of literature has been developed on AI ethics in *health care delivery*, far fewer publications focus on AI ethics in *health care research*, particularly patient-centered outcomes research (PCOR).[5] PCOR's focus on helping patients and caregivers "communicate and make informed health care decisions, allowing their voices to be heard in assessing the value of health care options" makes it critical for PCOR researchers using AI methods to understand and apply TAI principles throughout their research.[6]

Effective application of TAI principles in PCOR is relevant to the HHS Office of the Assistant Secretary for Planning and Evaluation (ASPE). Under delegation of authority by the Secretary of HHS and through the administration of the Office of the Secretary Patient-Centered Outcomes Research Trust Fund (OS-PCORTF), ASPE coordinates across relevant federal health programs to build data capacity for PCOR. The OS-PCORTF's strategic vision is "better data for patient-centered outcomes research to improve evidence generation, decision-making, and health outcomes for all Americans."[7]

Artificial intelligence (AI) "enables computer systems to perform tasks normally requiring human intelligence."[8]

Machine learning (ML), a type of AI, is "the use and development of computer systems that are able to learn and adapt without following explicit instructions, by using algorithms and statistical models to analyze and draw inferences from patterns in data."[9]

Predictive AI includes ML, statistical modeling, and data mining techniques that can support predictive analytics.[10]

The OS-PCORTF's Strategic Plan (2020 – 2029)[11] charts a course for strengthening data capacity for PCOR. The Plan's third goal is to leverage advanced technology solutions to improve the use of large volumes of data, as well as the variety and timeliness of data available for PCOR.[11] Such technology solutions include AI tools and machine learning (ML) techniques, which several OS-PCORTF-funded projects explore and use to improve the richness and robustness of evidence generated.[12, 13, 14] It is critical for ASPE to identify ways to ensure that future OS-PCORTF work using AI abides by TAI principles.

This report presents the findings of an environmental scan and key informant discussions conducted to better understand how TAI principles can be applied in the use of predictive AI in OS-PCORTF and PCOR projects. In the report, we do not address generative AI, which consists of deep learning models that can generate text, images, data, and other content.[15]

2. Background

In recent years, AI has become an important tool in precision medicine and biomedical research to leverage and analyze growing volumes of health care data, with important early successes in medical imaging research.[16] There are a variety of AI methods used for health care data, including ML and natural language processing (NLP).[3] AI can be used to mine and analyze large-scale data repositories—including data from electronic health record (EHR) systems, claims data, clinical registries, and genomics data—and to interpret outputs for clinical decision-making and population health.[17, 18] In addition, AI can be valuable for conducting clinical trials[19] and for engaging patient stakeholders in research.[20] Although not the focus of this report, generative AI tools such as ChatGPT can be used to improve efficiency in research, for example, by assisting in identifying relevant literature or code or scripts for ML models. We expect that as the field of AI evolves, applications of AI in health care research will continue to expand.

Illustrative applications of AI in health care research:[21]

- Developing matched cohorts for clinical trials, especially in oncology research.[22]
- Developing health information technology tools to aid in preventing medication errors and to improve patient safety.[23]
- Collecting health data using conversational agents, such as chatbots.[24]

The rise of AI in health care and health care research has sparked discussion about the trustworthiness of AI and its potential to cause harm, whether through breaches of patient privacy or by delivering systematically biased results. Researchers, clinical professional societies, and government agencies have all acknowledged that the widespread and increasing use of AI in health care and health care research may perpetuate inequities and needs oversight.[25] Increasingly, federal agencies and other organizations (listed below) are developing tools and guidance to mitigate potential harm due to AI by promoting TAI:

- The White House has made responsible AI research, development, and deployment a priority in the national agenda and has developed resources, such as the Blueprint for an AI Bill of Rights, to manage risks to national security.[26]

- The National Institute of Standards and Technology (NIST) developed an AI Risk Management Framework (AI RMF 1.0) in 2023 to help individuals and organizations better manage risks associated with AI; NIST has also released a playbook, roadmap, crosswalk, and explainer video to supplement the framework.[27]

- The Coalition for Health AI (CHAI), led by the MITRE Corporation, aims to develop "guidelines and guardrails" through a consensus-driven framework for health AI systems; CHAI has developed a draft blueprint for TAI implementation guidance.[28]

- The National Academy of Medicine (NAM) has initiated the Artificial Intelligence Code of Conduct project, which aims to provide a guiding framework to ensure AI algorithms used in health care and health care research perform "accurately, safely, reliably, and ethically in the service of better health for all." The project involves national multidisciplinary leaders in its efforts to advance TAI.[29]

3. Overview of HHS TAI Principles

The HHS TAI Playbook published in 2021 supports TAI development across HHS, outlining six core TAI principles and help to identify actions to advance TAI for different types of AI solutions.[3] Exhibit 1 lists

the definition for each principle, together with potential consequences of not aligning with the principles.

Exhibit 1. The Six TAI Principles from the HHS TAI Playbook and Potential Consequences of Nonalignment[3]

TAI Principle and Description[3]	Consequences of Nonalignment[30]
Fair/Impartial AI applications should include checks from internal and external stakeholders to help ensure equitable application across all participants.	Algorithms based on data that are inherently biased can result in research conclusions that perpetuate health inequities and that produce or reinforce negative health outcomes that disproportionately impact one group over another.
Transparent/Explainable All relevant individuals should understand how their data is being used and how AI systems make decisions; algorithms, attributes, and correlations should be open to inspection.	Lack of transparency can result in algorithmic systems that are hard to control, monitor, and correct (that is, the "black box" issue) and will result in lack of trust from key stakeholders and the public.
Responsible/Accountable Policies should outline governance and who is held responsible for all aspects of the AI solution (for example, initiation, development, outputs, decommissioning).	If responsibility for algorithmic systems is unclear, and if harm results from use of the algorithms, it will be difficult to know who to hold responsible for addressing and preventing further harm.
Robust/Reliable AI systems should have the ability to learn from humans and other systems and produce accurate and reliable outputs consistent with the original design.	Algorithms that are unreliable and/or inaccurate have a higher chance of producing research conclusions that are incorrect, which may harm patients and result in negative health outcomes, further eroding stakeholder and public trust.
Privacy The privacy of individuals, groups, or entities should be respected, and their data should not be used beyond its intended and stated use; data used has been approved by the data owner or steward.	If patients feel that their privacy was violated, they are unlikely to participate in research and may mistrust the health care system.
Safe/Secure AI systems should be protected from risks (including cyber) that may directly or indirectly cause physical and/or digital harm to any individual, group, or entity.	If access to protected patient information is compromised, information may be exploited by unauthorized entities; as a result, the organization using the AI system may lose credibility.

4. Report Purpose

The HHS TAI Playbook supports leaders across HHS in applying TAI principles for developing and deploying AI solutions; however, the principles must be described in the context of research, specifically PCOR. This report presents key considerations on how the TAI principles can be applied in the context of OS-PCORTF projects and PCOR more broadly. We use the TAI Playbook as a foundation, mapping to an adapted National Library of Medicine (NLM) research lifecycle construct to offer context for the principles. The report focuses on how to apply TAI principles when using predictive AI models for PCOR.

5. Methods

We gathered information for this report through: 1) an environmental scan of gray and peer-reviewed literature, and 2) key informant discussions with AI and PCOR experts to validate findings from the environmental scan.

Environmental scan. We used three overarching questions to guide our environmental scan:

1. What are the special considerations for applying TAI principles for OS-PCORTF/PCOR projects?
2. What strategies have been used to review TAI principles within AI solutions for improving PCOR data infrastructure and PCOR more broadly?
3. How have other agencies and research organizations applied and used trustworthy principles in their AI-focused PCOR/health care research work?

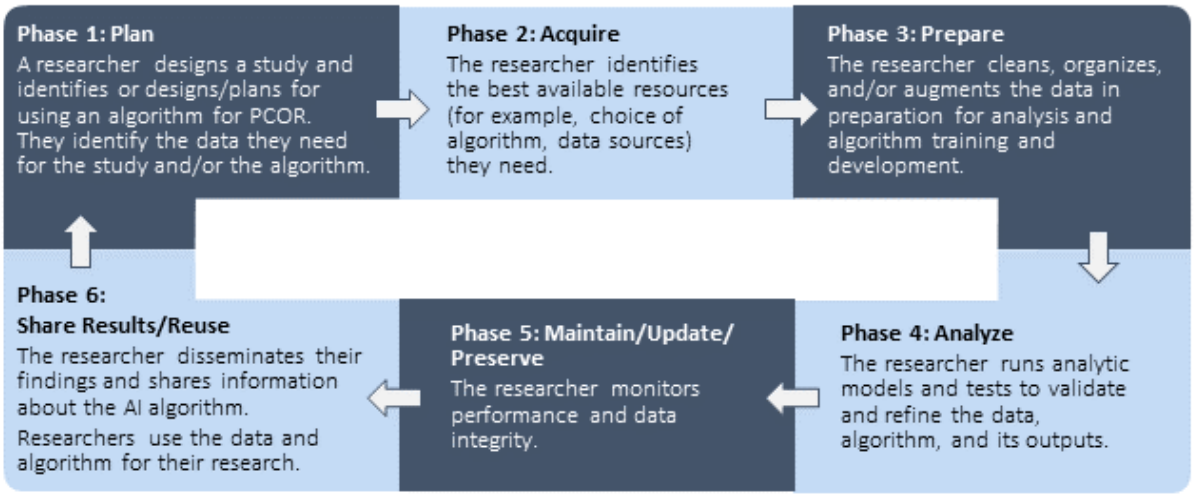
First, we used pre-specified search terms to search PubMed for peer-reviewed articles related to AI in PCOR and health care research more broadly, as well as to the six principles; see Exhibit A1 in Appendix A for search terms and Exhibit A3 for specific search strings. Next, we screened articles using a two-step process that involved a title/abstract review, followed by a full text review of the articles retained according to pre-specified inclusion/exclusion criteria; see Exhibit A2 in Appendix A. We then conducted supplemental targeted searches for topics or specific concepts recommended to us by subject matter experts (SMEs) or key informants. Finally, we searched backward through the reference list of selected articles to add any additional relevant articles.

Exhibit A4 in Appendix A shows the article selection process. The initial PubMed search resulted in 331 articles for review, of which we removed 108 duplicates. We included an additional 63 resources at this step per recommendation of subject matter experts (for example, peer-reviewed articles, reports, tools, organizational updates on websites, and blogs from trusted sources). A total of 286 articles underwent the titles/abstracts review step. Upon applying our inclusion/exclusion criteria on the title/abstract, we identified a total of 170 articles for the full text review, including 34 articles we identified through backwards searching of references. Lastly, after reviewing the full text of the 170 articles, a final total of 132 articles were included.

Key informant discussions. We conducted 11 virtual, one-hour semi-structured key informant discussions with 13 experts in the field of AI, including individuals from federal agencies, academic research centers, and the private sector. The SMEs and key informants commented on our initial environmental scan findings, and we incorporated their feedback into our final synthesis. See Appendix B for the detailed protocol used to guide each discussion.

Analytic approach. We organized and synthesized findings by mapping considerations relevant for PCOR researchers to six distinct phases of the NLM research lifecycle construct that were applicable to an AI-enabled research lifecycle; see Exhibit 2.[31]

Exhibit 2. Six Phases of the AI-Enabled Research Lifecycle



6. Findings

We organized the findings of the report into three categories: 1) key informant reflections on implementing the TAI principles; 2) important considerations for PCOR researchers and the OS-PCORTF community to take into account when using the HHS TAI principles; and 3) potential opportunities for the OS-PCORTF to support project alignment with TAI principles.

6.1 Key Informant Reflections on Implementing the Six HHS TAI Principles

The TAI Playbook emphasizes the importance of all six principles to ensure TAI; however, the Playbook also acknowledges the challenges and tradeoffs related to implementing each principle. Key informants remarked that although TAI principles cover all the salient ethical areas, fully implementing each principle in a given project is typically a challenge.

Key informants noted that the **privacy** principle is the most intuitive and easiest to implement. According to both the literature and key informants, there are established, vetted tools and methods for protecting patient privacy in health care research already in use.[27, 32, 33] The tools and methods can be used for maintaining the privacy of data used in research that leverages AI. Key informants described the **transparent/explainable** principle as difficult to implement for black box AI models, where the decision-making process cannot always be explained. However, researchers can facilitate transparency by using tools and resources to document how the AI model was created; documentation should describe and characterize data sources, algorithm and parameter choices in model development and summarize performance validation in a way that a general audience can understand.

Nearly all key informants agreed that the **fair/impartial** principle is the most difficult to conceptualize and to implement. Implementing fairness in AI requires addressing the human factors that introduce bias in data and mitigating bias within existing data sets used for algorithm development. If there is underlying bias in the data used to train predictive AI algorithms, the resulting conclusions or predictions may further exacerbate existing inequities.[25] Several key informants also described a general lack of guidance regarding the definition of fairness and how to apply measurements for fairness. A lack of guidance stems from the inherent difficulty in defining and measuring fairness, as perceptions of fairness may vary with different cultural and institutional contexts.

> "'Fairness and impartiality' would be the most difficult because it is not intrinsic to building models… the idea of fairness and impartiality [is] not intrinsic or intuitive because society is complex, therefore the environment where models are deployed will be complex."
>
> **-Federal Key Informant**

Key informants reacted to the TAI Playbook's definition of the **safe/secure** principle, noting that there should be more emphasis on protecting the safety of individuals from potential harm caused by AI use,[34, 35] rather than focusing on the security of the AI system itself (for example, from malicious attacks).

Additionally, key informants noted there are tradeoffs with implementing the TAI principles.[36, 37, 38] The TAI Playbook emphasizes that "TAI principles are not mutually exclusive, and tradeoffs often exist when applying them."[3] Often a focus on one principle may require less adherence to another principle.[37] For example, when developing an AI-enabled health care tool, researchers often must select a cutoff point for action.[39] Selection of this cutoff point requires researchers to weigh maximizing *sensitivity*—identifying patients who would benefit from an intervention, aligning with the **fair/impartial** principle – against maximizing *specificity* – ensuring patients are not unnecessarily placed at risk by the intervention, aligning with the **safe/secure** principle.[39]

Recognizing that health care research is at an inflection point regarding the use of AI, informants noted that it is not feasible to stop AI use in the health care research context. Rather researchers must remain vigilant in building trust in AI solutions by being transparent about strengths, weaknesses, and limitations.

6.2 Considerations for OS-PCORTF Projects in Adhering to TAI Principles Across the Research Lifecycle

Below, we describe considerations that the OS-PCORTF community and PCOR researchers should take into account to align with the TAI principles; see Exhibit 3 for a summary of the considerations. We have organized the findings by the NLM's six research lifecycle phases (as shown in Exhibit 2), plus an initial overarching category that applies throughout the research lifecycle. Each consideration is tagged with the TAI principle(s) it addresses.

Exhibit 3. Considerations to Adhere to TAI Principles Across the Six Research Lifecycle Phases

Overarching Considerations
• **<u>Consideration 1:</u> Develop clear and effective protocols for data management and stewardship to ensure privacy and security are protected when developing, training, validating, and implementing AI models. (Transparent/Explainable; Responsible/Accountable; Privacy; Safe/Secure)**

Exhibit 3. Considerations to Adhere to TAI Principles Across the Six Research Lifecycle Phases
• Consideration 2: Consider the tradeoffs involved in taking action to improve one or more TAI principles within a project, and document decisions regarding tradeoffs throughout the research lifecycle. (Fair/Impartial; Transparent/Explainable; Responsible/Accountable; Robust/Reliable; Privacy; Safe/Secure)
• Consideration 3: Address and reassess AI solutions for trustworthiness in every phase of the research lifecycle. (Fair/Impartial; Transparent/Explainable; Responsible/Accountable; Robust/Reliable; Privacy; Safe/Secure)
Phase 1: Plan
• Consideration 4: Determine whether AI is appropriate for the research questions you are trying to answer, before beginning the project. (Fair/Impartial; Responsible/Accountable)
• Consideration 5: Develop a Steering Committee or Technical Expert Panel when leveraging AI solutions. The Committee or Panel should comprise experts in AI, data management, and information technology, as well as representatives of the patients and/or communities affected by the work. Where possible, consider the inclusion of experts that are also members of the affected communities. (Fair/Impartial; Transparent/Explainable; Responsible/Accountable; Robust/Reliable; Privacy; Safe/Secure)
• Consideration 6. Enhance transparency and protect privacy by implementing clear, thorough, data consent procedures that explicitly address use of patient data in AI models. (Transparent/Explainable; Responsible/Accountable; Privacy)
Phase 2: Acquire
• Consideration 7: Determine the appropriate volume and quality of data to support the identified problem and AI application, when identifying data sets. (Fair/Impartial; Robust/Reliable)
• Consideration 8: Assess whether the selected data sets represent the population being studied, when leveraging secondary data sets such as clinical registries, claims, or EHR data. (Fair/Impartial)
• Consideration 9: Explore the use of multiple, diverse, and high-quality data sources that support the identified use case for the AI model, including validation and training data sets. (Fair/Impartial; Transparent/Explainable; Responsible/Accountable; Robust/Reliable; Privacy)
Phase 3: Prepare
• Consideration 10: Consider techniques and methods that augment the data used when leveraging AI, especially in situations where multiple, diverse data sets cannot be acquired, or the amount of data needs to be artificially increased. (Fair/Impartial; Transparent/Explainable; Robust/Reliable; Privacy)
• Consideration 11: Consider instituting processes and protocols to reduce measurement error, missing data, and selection bias, any or all of which may occur during data collection. (Fair/Impartial; Robust/Reliable)

health cost. However, what this approach ignored was that Black patients have lower health expenditures than White patients, despite having higher morbidity and mortality rates. As a result, this cost-based algorithm would perpetuate the health care utilization resource bias observed in the data when it was used to direct health care resources.

Consideration 5. Develop a Steering Committee or Technical Expert Panel when leveraging AI solutions. The Committee or Panel should comprise experts in AI, data management, and information technology, as well as representatives of the patients and/or communities impacted by the work. Where possible, consider the inclusion of experts that are also members of the affected communities. (Fair/Impartial; Transparent/Explainable; Responsible/Accountable; Robust/Reliable; Privacy; Safe/Secure)

Establishing a clear advisory body or governance structure at the start of the research process facilitates adherence to TAI principles in all phases of the research lifecycle. Steering committees or technical expert panels could advise on the creation of research questions, the identification and review of appropriate data sets, analytic methods and tools, and clear, detailed data protection plans.

For the advisory function, our environmental scan identified the need for close collaboration with cross-disciplinary stakeholders, including those with expertise in areas such as mitigating bias, statistical or ML techniques, making data "AI ready," risk mitigation, privacy, security, and health system strengthening.[50, 20, 38] However, several key informants noted that building a bench of experts in the predictive AI field, as in any emergent field, is an ongoing enterprise-wide challenge. Additional workforce development and training will be required to help ensure that AI is used effectively, responsibly, and appropriately in research.

> "When you're starting to plan the program or plan the work that you're going to do as a researcher, having representatives and a steering committee that are from the communities of interest is critical. They see things that we don't see."
>
> **-Federal Key Informant**

Researchers should consider the perspectives of the community, patients, health system leaders, and end-users such as clinicians affected by AI use, not only to identify potential biases in an AI tool but also to promote trust. Several key informants emphasized this point, particularly in the context of PCOR research. Patients can be engaged in steering committees, advisory boards, focus groups, or other governance structures. In a community governance model, for example, patients or research participants can be consulted on topics such as assessing the risks of data usage, identifying methods to minimize potential harms, and ensuring the priority population benefits from the results of the research.[42] The National Institutes of Health (NIH) Artificial Intelligence/Machine Learning Consortium to Advance Health Equity and Researcher Diversity (AIM-AHEAD) program provides a good model for increasing community engagement in research that leverages AI.[51]

Consideration 6. Enhance transparency and protect privacy by implementing clear, thorough data consent procedures that explicitly address the use of patient data in AI models. (Transparent/Explainable; Responsible/Accountable; Privacy)

Researchers involved in AI development, and who have access to patients whose data are being leveraged, should communicate with patients about how AI tools work in general and how their data may be used in training AI tools to make decisions. Patients have the right to a plain-language explanation about how their data will be used in an AI-enabled research project, potential harms that could result, and their right to withdraw their data.[52]

Appendix A. Additional Detail on Methods

Exhibit A1. Environmental Scan PubMed Search Terms

Search Term Category	Example Terms*
Artificial Intelligence	Artificial intelligence [MeSH Major Topic]
TAI Principles	Trust, trustworthy, bioethics, ethical, ethics, principles, responsible **fair**, impartial, unbiased, nondiscrimination, equity **transparent**, explainable, disclosure, understandable, open-source **responsible**, accountable, governance, monitored **safe**, secure, risk management, resilient **privacy**, confidential, protections, sensitive, consent **robust**, reliable, accurate, effective, quality, consistent
Implement	Implementation, application, translation, intervention, algorithm
Evaluation	Assess, evaluate, review, audit, measure, checklist, tools, metrics
Patient-Centered Outcomes Research	Patient-centered care [MeSH Major Topic]

*Bolded terms are the six principles in the HHS TAI Playbook, with related terms on the same line.

Exhibit A2. Environmental Scan Inclusion and Exclusion Criteria

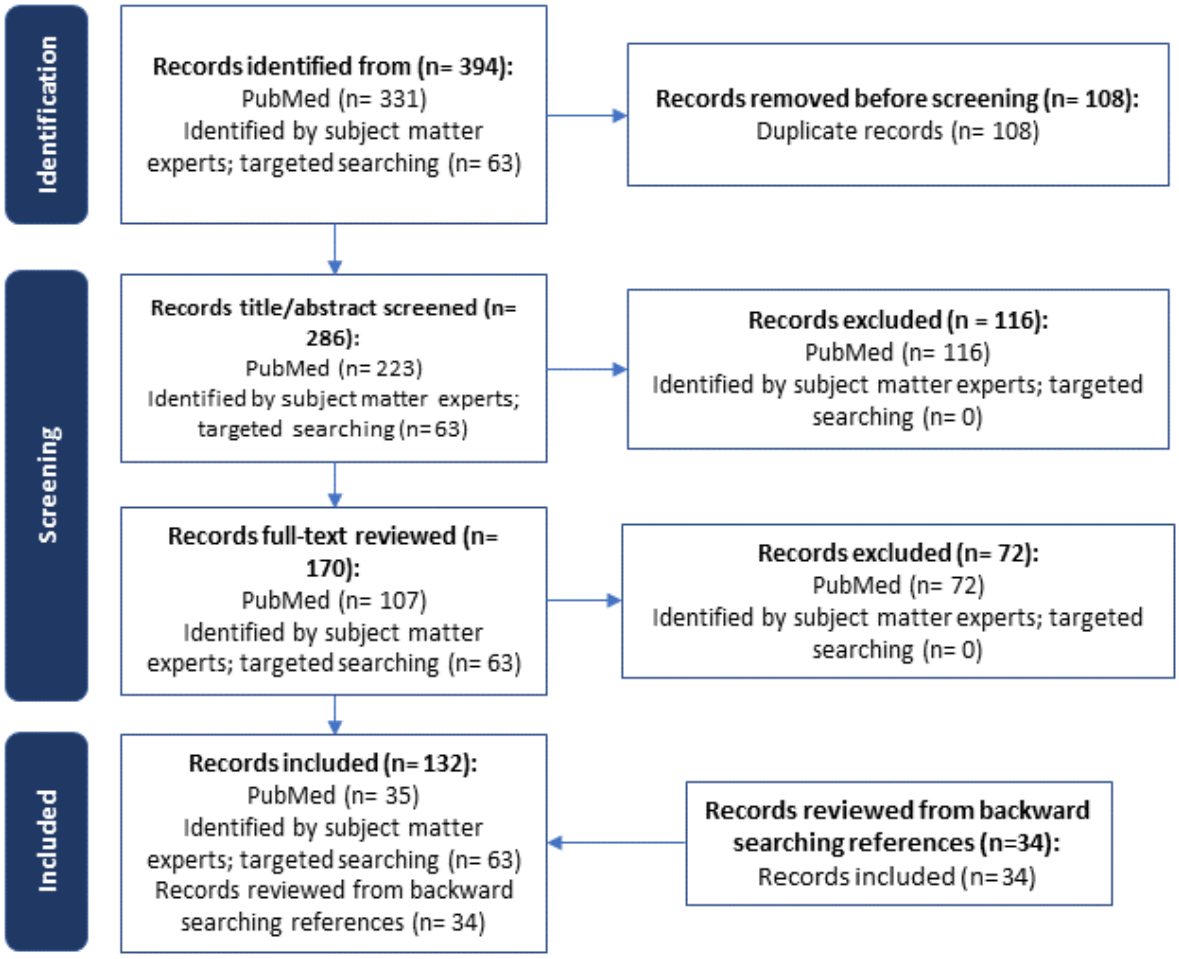
Category	Inclusion Criteria	Exclusion Criteria
Publication Year	2018 - present (last 5 years)	Prior to 2018
Document Type	**Gray literature**: Reports, evaluations, white papers, conference proceedings, case studies, fact sheets, issue briefs, blog if from a reputable expert **Peer review**: Theoretical articles, primary and secondary data analyses, scoping review, meta-analyses/systematic reviews	**Gray literature**: Opinion pieces
Sources	Academic, expert, evaluator	News outlet
Focus	Discusses consideration of or strategies for reviewing TAI principles in the context of PCOR or health care research	No discussion of reviewing TAI principles General discussion of TAI in relation to other sectors

Exhibit A3. Peer-Reviewed Literature Searches Conducted on PubMed

Search	Targeted Principle/ Focus	Search String	Filters Applied
1	Fair	("artificial intelligence"[MeSH Major Topic] AND ("trust"[Title/Abstract] OR "trustworthy"[Title/Abstract] OR "bioethics"[Title/Abstract] OR "responsible"[Title/Abstract] OR "ethical"[Title/Abstract] OR "ethics"[Title/Abstract] OR "governance"[Title/Abstract] OR "principles" [Title/Abstract]) AND ("implementation" OR "algorithm" OR "application" OR "translation" OR "intervention") AND ("assess" OR "evaluate" OR "review" OR "audit" OR "measure" OR "checklist") AND ("fair" OR "impartial" OR "unbiased" OR "nondiscrimination" OR "equity"))	2018-2023 English
2	Transparent	("artificial intelligence"[MeSH Major Topic] AND ("trust"[Title/Abstract] OR "trustworthy"[Title/Abstract] OR "bioethics"[Title/Abstract] OR "responsible"[Title/Abstract] OR "ethical"[Title/Abstract] OR "ethics"[Title/Abstract] OR "governance"[Title/Abstract]) AND ("implementation" OR "algorithm" OR "application" OR "translation" OR "intervention") AND ("assess" OR "evaluate" OR "review" OR "audit" OR "measure" OR "checklist") AND ("transparent" OR "explainable" OR "disclosure" OR "understandable" OR "open source"))	2018-2023 English
3	Responsible	("artificial intelligence"[MeSH Major Topic] AND ("trust"[Title/Abstract] OR "trustworthy"[Title/Abstract] OR "bioethics"[Title/Abstract] OR "responsible"[Title/Abstract] OR "ethical"[Title/Abstract] OR "ethics"[Title/Abstract] OR "governance"[Title/Abstract]) AND ("implementation" OR "algorithm" OR "application" OR "translation" OR "intervention") AND ("assess" OR "evaluate" OR "review" OR "audit" OR "measure" OR "checklist") AND ("responsible" OR "accountable" OR "traceable" OR "monitored" OR "governance"))	2018-2023 English
4	Safe	("artificial intelligence"[MeSH Major Topic] AND ("trust"[Title/Abstract] OR "trustworthy"[Title/Abstract] OR "bioethics"[Title/Abstract] OR "responsible"[Title/Abstract] OR "ethical"[Title/Abstract] OR "ethics"[Title/Abstract] OR "governance"[Title/Abstract]) AND ("implementation" OR "algorithm" OR "application" OR "translation" OR "intervention") AND ("assess" OR "evaluate" OR "review" OR "audit" OR "measure" OR "checklist") AND ("safe" OR "secure" OR "risk management" OR "resilient"))	2018-2023 English
5	Privacy	("artificial intelligence"[MeSH Major Topic] AND ("trust"[Title/Abstract] OR "trustworthy"[Title/Abstract] OR "bioethics"[Title/Abstract] OR "responsible"[Title/Abstract] OR "ethical"[Title/Abstract] OR "ethics"[Title/Abstract] OR "governance"[Title/Abstract] OR "principles"[Title/Abstract]) AND ("implementation" OR "algorithm" OR "application" OR "translation" OR "intervention") AND ("assess" OR "evaluate" OR "review" OR "audit" OR "measure" OR "checklist") AND ("privacy" OR "protections" OR "sensitive" OR "confidential" OR "consent"))	2018-2023 English

Search	Targeted Principle/ Focus	Search String	Filters Applied
6	Robust	("artificial intelligence"[MeSH Major Topic] AND ("trust"[Title/Abstract] OR "trustworthy"[Title/Abstract] OR "bioethics"[Title/Abstract] OR "responsible"[Title/Abstract] OR "ethical"[Title/Abstract] OR "ethics"[Title/Abstract] OR "governance"[Title/Abstract]) AND ("implementation" OR "algorithm" OR "application" OR "translation" OR "intervention") AND ("assess" OR "evaluate" OR "review" OR "audit" OR "measure" OR "checklist") AND ("robust" OR "reliable" OR "purposeful" OR "performance-driven" OR "accurate" OR "effective" OR "quality" OR "consistent"))	2018-2023 English
7	PCOR & AI	(patient centered care[MeSH Major Topic]) AND (artificial intelligence[MeSH Major Topic])	2018-2023 English

Exhibit A4. Article Selection Process



Appendix B. Key Informant Discussion Protocol

Introduction

1. I want to start by having you do a brief introduction of yourself. Can you please introduce yourself and briefly tell us about your work related to using AI in research?
2. Did you have the chance to review the information sheet? Do you have questions?

   As a brief overview, in September 2021 HHS published a Trustworthy AI (TAI) Playbook to provide guidance for HHS agencies on how to manage AI at all stages of the technology's lifecycle. The six TAI principles are fair/impartial, transparent/explainable, responsible/accountable, safe/secure, privacy, and robust/reliable.

3. [*For informants involved in research*] In what ways have TAI principles impacted how you conduct research?

Domain 1: Reactions to the List of Opportunities for OS-PCORTF to Support Alignment to TAI Principles

We'd like to first ask for your thoughts on the list of opportunities for OS-PCORTF in the information sheet that we shared with you before the call. These are potential ways to support PCOR researchers in aligning to HHS TAI principles. As a reminder, patient-centered outcomes research aims to generate high-quality evidence about the effectiveness of treatments, services, and other health care interventions on the full range of outcomes that patients, caregivers, clinicians, policymakers, and other stakeholders have identified as important.

4. Did any of the opportunities stand out to you as especially important? Why?
5. Of the opportunities described, which do you think would be important to focus on in the near-term (1-3 years) for improving alignment to TAI principles for patient-centered outcomes research?
6. Of the opportunities described, which do you think would be important to focus on in the long-term for improving alignment to TAI principles for patient-centered outcomes research?

   a. Why do you think this a long-term opportunity? Are there steps that can be taken in the short-term to help us achieve this opportunity?

7. After reading this list, are there other opportunities for activities or projects that OS-PCORTF could support related to implementing TAI in patient-centered outcomes research that you would add to the list?

   a. What TAI principle(s) would this opportunity address? How would this support use of TAI in patient-centered outcomes research?

Domain 2: Reactions to the List of Considerations for Project Teams Carrying Out OS-PCORTF Projects or PCOR Research

I would now like to turn to ask you about the list of considerations we provided for OS-PCORTF projects or PCOR researchers to align to trustworthy principles when using AI in their work. As a reminder, OS-PCORT projects focus on building data capacity for conducting patient-centered outcomes research (PCOR). One example of a project utilizing AI solutions to build data capacity is using machine learning to enable health information exchange for PCOR focused on COVID-19. The OS-PCORTF has also funded the creation of high-quality training data sets for machine learning for two use cases: kidney disease and drug resistance in patients infected with tuberculosis.

8. Are there any particular tools or resources that have been helpful in your work to align to the TAI principles?

    a. Are there any specific to evaluating or assessing PCOR or research projects for TAI principles?

9. In your AI-related work, which of the six principles have you found to be most challenging to adhere to and why?

    a. What types of resources would make it easier for you to adhere to these principles?

10. Are there any particular tools or resources for applying TAI principles that you have tried to use but faced barriers in their application? If so, please describe.
11. Are there considerations that you think are particularly relevant for the OS-PCORTF community (e.g., HHS partners) or PCOR researchers? Why?
12. Based on your experience, are there other considerations that we did not include that could be implemented by OS-PCORTF projects or PCOR researchers?

Conclusion

13. What future work do you think the OS-PCORTF can support in the area of TAI?
14. Is there anything else you would like to share about implementing or assessing trustworthy principles in PCOR?

Those are all the questions that we had for you today. Thank you again for your time and insights. Please do not hesitate to reach out if you have further questions about this project.

Appendix C. Reporting Checklists

Exhibit C1. Available Reporting Checklists and Protocols

Name	Description	Use
Transparent Reporting of Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD)[106]	TRIPOD is a 22-item checklist that includes items essential to the transparent and accurate reporting of **studies that develop or validate multivariable clinical prediction models**. TRIPOD-AI is an extension of the TRIPOD statement that was developed specifically for use with prediction model studies that leverage AI and machine learning techniques.	TRIPOD-AI provides researchers leveraging AI with guidelines to help them report details that will be needed for other researchers to evaluate their study's quality and interpret findings.
Prediction model Risk of Bias Assessment Tool (PROBAST)[106]	PROBAST works **to assess the risk of bias in and improve reporting of machine learning-based on multivariable prediction model studies for diagnosis and prognosis**. It uses 20 questions organized across four domains (participants, predictors, outcomes, and analysis) as the basis of its standardized tool for bias evaluation.	It serves as a tool for researchers to appraise, conduct, and analyze machine learning-based prediction model studies.
Standards for Reporting of Diagnostic Accuracy Standards (STARD)-AI[111]	First formulated in 2000, this protocol was designed to standardize **comparative studies of new or alternative diagnostic tests against an established reference standard** and was updated in 2021 to address key considerations for AI interventions. Some of the topics covered in the checklist include data processing methods, AI index test development methods, fairness metrics, explainability, and human-AI index tests. The goal is to generate a list of minimal essential items that should be reported in all AI diagnostic test accuracy studies.	STARD-AI supports researchers in appraising the quality and comparing the diagnostic test accuracy of AI models reported in scientific studies. **Note:** If the study is focusing on multivariable prediction models (for example, time to event predictions), the TRIPOD-AI may be more appropriate.
Consolidated Standards of Reporting Trials-Artificial Intelligence (CONSORT-AI)[112] **Extension**	Among the earliest of such protocols, introduced in 1996 (with further updates in 2001 and 2010), CONSORT aimed to specify reporting guidelines for parallel group randomized controlled trials (RCTs). The CONSORT-AI extension is a new reporting guideline **for clinical trial reports of interventions with an AI component**. It includes 14 new items with an AI focus, to be routinely reported in addition to the CONSORT 2010 items.	It supports researchers, editors, and peer reviewers in understanding, interpreting, and critically appraising the quality of clinical trial design and risk of bias in the reported outcomes.
Consolidated Standards of Reporting Trials of Electronic and mobile Health Applications and Online Telehealth (CONSORT-EHEALTH)[113]	The CONSORT-EHEALTH extension aims to capture the unique challenges of **reporting eHealth and mHealth RCTs**, particularly related to details that support reproducibility, theory-building, and implementation in other settings. The checklist includes 17 items that are considered "essential" and 35 subitems considered "highly recommended." Authors must address each of the items on the checklist.	This is useful for researchers of eHealth and mHealth interventions as well as researchers who use web-based recruitment or data collection methods. Many elements can be applied to evaluation reports, not just RCTs.

Name	Description	Use
Transparent Reporting of Evaluations with Nonrandomized Designs (TREND) Statement[114]	This is a 22-item checklist to guide **transparency in the reporting of non-RCTs**. The checklist complements CONSORT (described above). Designed for behavioral and public health intervention evaluations, the checklist focuses on the description of the intervention, description of the comparison condition, reporting of outcomes, and design information to assess possible biases.	Researchers, funding agencies, journal editors, and reviewers can use the statement as a guide when designing evaluation studies, reporting evaluation results, and reviewing manuscripts.
Standard Protocol Items: Recommendations for Intervention Trials-Artificial Intelligence (SPIRIT)-AI Extension[115]	SPIRIT was developed in 2013 to improve the completeness of clinical trial protocol reporting. Recognizing that AI interventions must undergo rigorous evaluations, researchers developed the SPIRIT-AI extension in tandem with CONSORT-AI to serve as a **reporting guideline for clinical trial protocols evaluating interventions with an AI component**.	SPIRIT-AI supports editors and peer reviewers to understand, interpret, and critically appraise the design and risk of bias for a planned clinical trial.

Appendix D. Table of Acronyms

Acronym	Description
AI	Artificial intelligence
AIM-AHEAD	Artificial Intelligence/Machine Learning Consortium to Advance Health Equity and Researcher Diversity
ASPE	Assistant Secretary for Planning and Evaluation
CDC	Centers for Disease Control and Prevention
CHAI	Coalition for Health Artificial Intelligence
CONSORT-AI	Consolidated Standards of Reporting Trials-Artificial Intelligence
DQA	Data Quality Assessment
EHR	Electronic health record
FAIR	Findable, Accessible, Interoperable, and Reusable
HHS	Health and Human Services
HIE	Health information exchange
ML	Machine learning
NAM	National Academy of Medicine
NIH	National Institutes of Health
NIST	National Institute of Standards and Technology
NLM	National Library of Medicine
NLP	Natural language processing
NORC	NORC at the University of Chicago
OCAIO	Office of the Chief AI Officer
OS-PCORTF	Office of the Assistant Secretary Patient-Centered Outcomes Research Trust Fund
PCOR	Patient-Centered Outcomes Research
PET	Privacy-enhancing technologies
RCT	Randomized controlled trials
SRE	Security Requirements Engineering
TAI	Trustworthy artificial intelligence
TREND	Transparent Reporting of Evaluations with Nonrandomized Designs
TRIPOD	Transparent Reporting of Multivariable Prediction Model for Individual Prognosis or Diagnosis
XAI	Explainable artificial intelligence

Appendix E. Glossary of Terms

Artificial Intelligence: The capability of computer systems to "perform tasks normally requiring human intelligence."[8]

Algorithm: A process or set of instructions that "will help calculate an answer to a problem," especially when given to a computer.[116]

Algorithmovigilance: The science related to the "evaluation, monitoring, understanding, and prevention of adverse effects of algorithms in health care."[79]

Bias: An error that can occur in an artificial intelligence model if the model's results are systematically prejudiced by its training data.[117]

"Black Box" Algorithms: Algorithms that "humans cannot survey," since they typically "do not follow well-defined rules" and are comprised of "opaque systems that no human or group of humans can closely examine."[118]

Contestable Artificial Intelligence: Artificial intelligence systems that are "open and responsive to human intervention throughout their lifecycle, not only after an automated decision has been made, but also during its design and development."[119]

Data Augmentation: A series of techniques that address the problem of limited data by "artificially increasing the amount of data by generating new data points from existing data," which can involve making changes to existing data or leveraging deep learning models to produce new data models.[120]

Data Set: A collection of separate but related sets of information that can be manipulated as a single unit by a computer.[121]

Deep Learning: A type of machine learning that leverages multilayered neural networks to simulate how the human brain behaves. These layers allow an algorithm to "learn from large amounts of data" and strengthen the algorithm's accuracy.[122]

Explainable AI (XAI): A set of frameworks, tools, processes, and methods that allow users to understand and trust the results created by machine learning algorithms. XAI can be used to describe an AI model, its anticipated impact, and potential bias.[83]

Foundation Model: A model that is trained on broad, unlabeled data that can be adapted to a wide range of tasks. Types of foundation models include generative AI (see definition below) and large language models.[100]

Generative AI: Deep learning models that are able to generate text, images, video, and other content by "identifying patterns in large quantities of training data, and then creating original material that has similar characteristics."[117] The popular AI model ChatGPT is an example of a generative AI tool.

Hyperparameter: The parameters whose values control the learning process of the algorithm. Hyperparameters are set before training a model so that the model cannot change its values during learning/training.[123]

Machine Learning: A sub-field of artificial intelligence that involves "the use and development of computer systems that are able to learn and adapt without following explicit instructions by using algorithms and statistical models to analyze and draw inferences from patterns in data."[9]

Metadata: Information describing the "characteristics of data."[124] It can include information about the content and context of a data set and information used to manage data.[125]

Natural Language Processing: A sub-field of artificial intelligence that works to "enable computers to process human language in the form of text or voice data and to 'understand' its full meaning."[126]

Overfitting: A modeling error that occurs when a statistical model fits exactly against a minimal set of training data. This makes the model "unable to perform accurately against unseen data, defeating its purpose."[127]

Privacy-Enhancing Technologies: Digital tools that "allow information to be collected, processed, analyzed, and shared while protecting data confidentiality and privacy."[128]

Representative Data: Data that includes accurate information on the communities that it may impact, which is critical for ensuring the effectiveness of AI algorithms.[129]

Synthetic Data: Computer-generated information that is used to "augment or replace real data to test and train artificial intelligence models."[130]

Testing Data: Data that is used after a machine learning model is built to "evaluate the performance and progress of [the] algorithms' training and adjust or optimize it for improved results."[131]

Training Data: An initial, large data set that is used to teach a machine learning model to "recognize patterns or perform your criteria."[131]

Trustworthy AI: The "design, development, acquisition, and use of AI in a manner that fosters public trust and confidence while protecting privacy, civil rights, civil liberties, and American values, consistent with applicable laws."[3]

Underfitting: An error in that occurs when a data model is overly simple or requires additional training time, which causes the model to be "unable to capture the relationship between the input and output variables accurately, generating a high error rate on both the training data set and unseen data."[132]

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