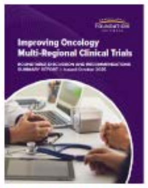
DETAILED CROSSWALK

Recent HHS/FDA Initiatives and Relevant Report Recommendations

	 **Improving Oncology Multi-Regional Clinical Trials** *Issued October 2025*	 **Developing Treatments for Rare Diseases** *Issued March 2026*	 **Enhancing Early-Stage Drug Development** *Issued June 2026*
OPERATION TRIALBLAZER			
Leverage NIH-Supported Networks	Rec #1 Unlock the potential of network approaches		
Phase 1 CMC Requirements			Rec #4 Update and Streamline Chemistry, Manufacturing, and Controls (CMC) Requirements
Risk-Based Nonclinical / Reduced Animal Testing			Rec #3 Modernize Nonclinical Requirements and Practices
Clarify 'Required' vs. 'Presumed-Required' IND Data			Rec #5 Clarify "Required" Versus "Presumed-Required" IND Data
Rolling / Staged IND Submission			Rec #2 Advance Rolling IND Submissions
Pre-IND Reform & Iterative Engagement		Rec #5 Establish Stakeholder/FDA Consultations for Rare Disease Endpoint Development Rec #17 Enable Early Identification and Resolution of Issues for Novel Endpoints and Trial Designs	Rec #11 Enhance Pre-IND Meeting and IND Review Best Practices Rec #13 Incentivize Fit-for-Purpose IND Submissions and Engagements
Fewer Protocol Amendments; Adaptive & Master-Protocol Designs		Rec #18 Enable Rare Disease Clinical Trials to Learn and Adapt More Effectively	Rec #8 Enable Use of Innovative Phase 1 Clinical Designs
Single-IRB Reform & Site Activation			Rec #16 Streamline Institutional Review Board (IRB) and Site Activation Processes

	ONCOLOGY MRCTS	RARE DISEASES	EARLY-STAGE DEVELOPMENT
Leverage Real-World Data, Natural History, and Registries		Rec #13 Advance Best Practices for Responsible Rare Disease Data Sharing Rec #14 Create Tiered Approaches for Natural History and Registry Data Acceptability Rec #15 Clarify Evidentiary Requirements for Utilizing Legacy Registry Data	
Trial Access, Clinician Incentives & Patient Financial Burden	Rec #2 Advance Patient-Centric, not Trial-Centric, Approaches; Reduce Financial Burdens		Rec #16 Streamline Institutional Review Board (IRB) and Site Activation Processes
National Coordination & Infrastructure; Technology Deployment			Rec #14 Build and Fund a Dedicated Network of Phase 1-Capable Clinical Trial Sites Rec #15 Create a National Phase 1 Coordinating Strategy
Master Trial Agreements; Contract / Budget Negotiation	Rec #3 Explore common budget and contract processes for U.S. trial sites		
Demonstrating Substantial Evidence of Effectiveness		Rec #2 Establish Fit-for-Purpose Tiered Patient-Relevant Endpoint and Biomarker Qualifications Rec #6 Align Evidentiary Thresholds for Slowly Progressive Diseases Rec #16 Promote Shared Understandings of Scientific Principles Supporting Flexible Evidentiary Strategies	
Improving Transparency of Regulatory Reasoning		Rec #16 Promote Shared Understandings of Scientific Principles Supporting Flexible Evidentiary Strategies	Rec #4 Update and Streamline Chemistry, Manufacturing, and Controls (CMC) Requirements Rec #5 Clarify “Required” Versus “Presumed-Required” IND Data

	ONCOLOGY MRCTS	RARE DISEASES	EARLY-STAGE DEVELOPMENT
FY 2027 HHS/FDA BUDGET INITIATIVES			
Artificial Intelligence / Machine Learning		Rec #12 Create Function-Based, Domain-Driven Endpoint Libraries Rec #20 Build a Cross-Stakeholder, AI-Enabled, Rare Disease Knowledge Management System	Rec #10 Develop Artificial Intelligence (AI)-Enabled Sponsor-Facing Decision Support Tools
Rare Disease Innovation Hub Strategic Agenda & Rare Disease Evidence Principles		Rec #2 Establish Fit-for-Purpose Tiered Patient-Relevant Endpoint and Biomarker Qualifications Rec #16 Promote Shared Understandings of Scientific Principles Supporting Flexible Evidentiary Strategies	Rec #9 Increase Inclusion of Patient Perspectives in Early-Stage Drug Development
Expedited IND / Clinical Trial Notification Pathway			Rec #2 Advance Rolling IND Submissions Rec #7 Enable a Phase 1 Clinical Trial Notification Pathway
New Approach Methodologies / Alternatives to Animal Testing R&D			Rec #3 Modernize Nonclinical Requirements and Practices
Advanced Pharmaceutical Manufacturing & CMC Streamlining			Rec #4 Update and Streamline Chemistry, Manufacturing, and Controls (CMC) Requirements
Post-Market Surveillance, Real-World Evidence & Alternative Testing Models	Rec #2 Advance Patient-Centric, not Trial-Centric, Approaches; Reduce Financial Burdens		

	ONCOLOGY MRCTS	RARE DISEASES	EARLY-STAGE DEVELOPMENT
2026 UNIFIED AGENDA			
Single IRBs	Rec #1 Unlock the potential of network approaches	Rec #5 Establish Stakeholder/FDA Consultations for Rare Disease Endpoint Development	Rec #16 Streamline Institutional Review Board (IRB) and Site Activation Processes
Expedited INDs for Phase 1 Clinical Trial Reform		Rec #5 Establish Stakeholder/FDA Consultations for Rare Disease Endpoint Development Rec #17 Enable Early Identification and Resolution of Issues for Novel Endpoints and Trial Designs	Rec #1 Adopt Risk-Proportionate IND Submission Requirements and Triage Review Processes Rec #2 Advance Rolling IND Submissions Rec #7 Enable a Phase 1 Clinical Trial Notification Pathway
cGMP: Advanced Manufacturing, Distributed, and Point of Care Manufacturing			Rec #4 Update and Streamline Chemistry, Manufacturing, and Controls (CMC) Requirements
Biologics Regulation Modernization			Rec #4 Update and Streamline Chemistry, Manufacturing, and Controls (CMC) Requirements
GLP for Nonclinical Laboratory Studies			Rec #3 Modernize Nonclinical Requirements and Practices
Nonclinical Testing Methodology			Rec #3 Modernize Nonclinical Requirements and Practices
Rabbit Pyrogen Testing			Rec #3 Modernize Nonclinical Requirements and Practices

	ONCOLOGY MRCTS	RARE DISEASES	EARLY-STAGE DEVELOPMENT
Responsibilities of Sponsors and Investigators		Rec #17 Enable Early Identification and Resolution of Issues for Novel Endpoints and Trial Designs	Rec #6 Improve “Safe-to-Proceed” and “Clinical Hold” Communications Rec #11 Enhance Pre-IND Meeting and IND Review Best Practices Rec #1 Adopt Risk-Proportionate IND Submission Requirements and Triage Review Processes
Promote Electronic Submission		Rec #2 Establish Fit-for-Purpose Tiered Patient-Relevant Endpoint and Biomarker Qualifications Rec #12 Create Function-Based, Domain-Driven Endpoint Libraries	
Proactive Disclosure of Complete Response Letters		Rec #16 Promote Shared Understandings of Scientific Principles Supporting Flexible Evidentiary Strategies	

	ONCOLOGY MRCTS	RARE DISEASES	EARLY-STAGE DEVELOPMENT
RECENT GUIDANCE DOCUMENTS (FINAL AND DRAFT)			
Cancer Clinical Trial Eligibility Criteria (three separate guidance documents)	Rec #2 Advance Patient-Centric, not Trial-Centric, Approaches; Reduce Financial Burdens		
Chemistry, Manufacturing, and Controls Flexibilities for Developing Human Cellular and Gene Therapy Products for a Biologics License Application			Rec #4 Update and Streamline Chemistry, Manufacturing, and Controls (CMC) Requirements Rec #1 Adopt Risk-Proportionate IND Submission Requirements and Triage Review Processes Rec #3 Modernize Nonclinical Requirements and Practices
Expedited IND Pilot Program; Request for Information			Rec #2 Advance Rolling IND Submissions Rec #1 Adopt Risk-Proportionate IND Submission Requirements and Triage Review Processes Rec #6 Improve “Safe-to-Proceed” and “Clinical Hold” Communications Rec #13 Incentivize Fit-for-Purpose IND Submissions and Engagements Rec #14 Build and Fund a Dedicated Network of Phase 1-Capable Clinical Trial Sites Rec #16 Streamline Institutional Review Board (IRB) and Site Activation Processes

ABBREVIATIONS

AI = artificial intelligence
cGMP = current Good Manufacturing Practices
CMC = Chemistry, Manufacturing, and Controls
CTN = Clinical Trial Notification
FDA = Food and Drug Administration
FIH = first-in-human
GLP = Good Laboratory Practices
GMP = Good Manufacturing Practices
HHS = Health and Human Services
IND = Investigational New Drug
IRB = Institutional Review Board
NAM = Novel Approach Methodologies
R&D = research and development
RWD = real-world data