Welcome to the 2025 CTSI FDA Symposium

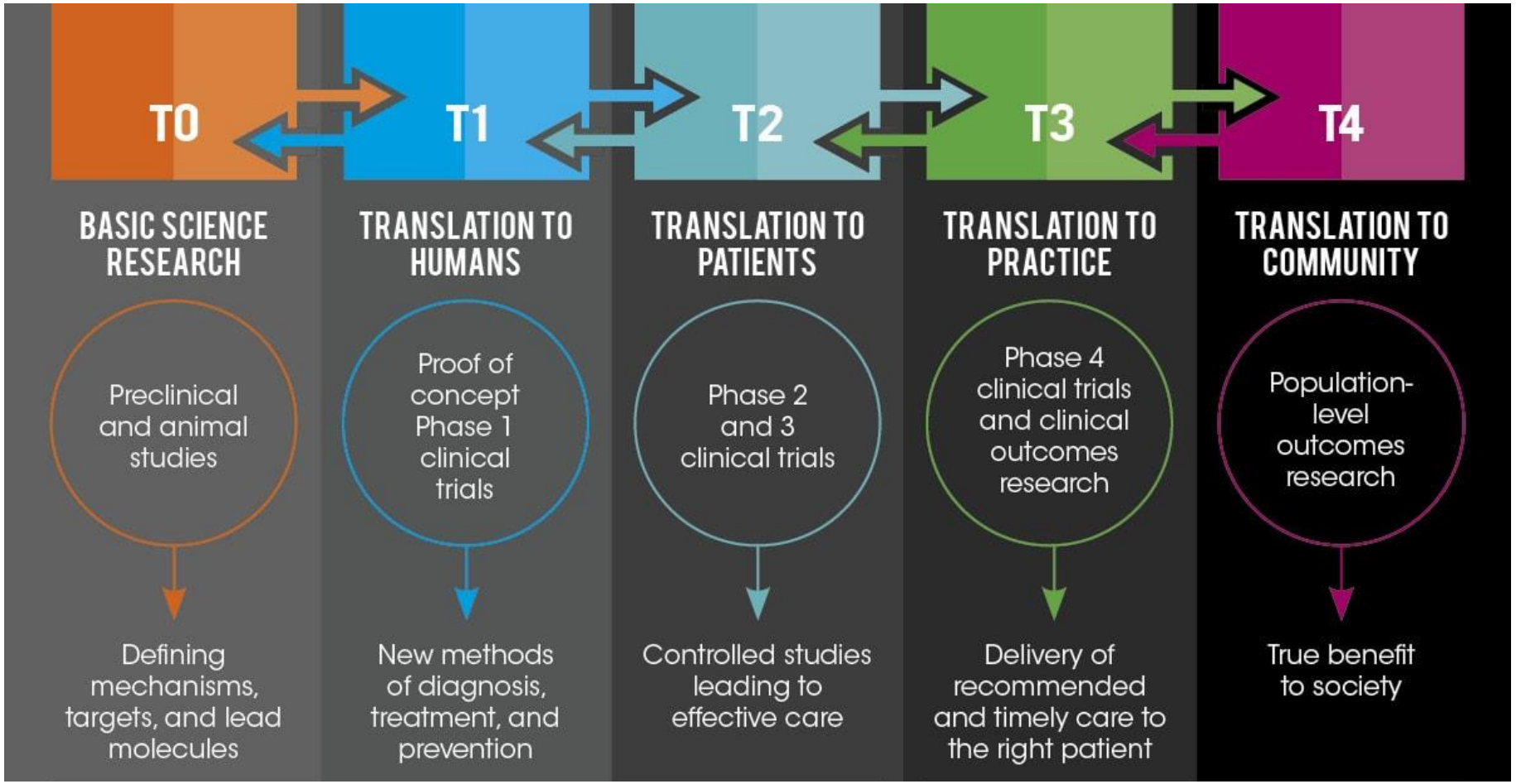
CTSI Introduction

Julie Johnson, PharmD

Director of the Clinical and Translational Science Institute

Principal Investigator of the Clinical and Translational Science Award

What is translational research?



T5: Full dissemination and implementation in the community

NIH CTSA awards

- 65 CTSA hubs nationally
  - Most are multi-institution
  - Some are state-wide or multi-state
- Ohio State CTSA hub is a collaboration between Ohio State and Nationwide Children's Hospital

Ohio State CTSI seeks to speed translation of discoveries to practice to improve health for all

- CTSA awards broadly intended to:
  - create institutional resources to reduce barriers to clinical and translational research (in the institution and that can be broadly adopted)
  - Identify approaches in research that can streamline translation to practice
  - create training opportunities for clinical and translational scientists

Clinical and Translational Science Institute Strategy Map 2025 – 2030

Our Vision: To Advance Today's Discoveries to Improve Health for All

Ambition: The Clinical and Translational Science Institute aims to be a national leader and model CTSA hub in advancing impactful clinical and translational research at The Ohio State University and Nationwide Children's Hospital.

Domains and Goals

Clinical and Translational Research

Innovate, cultivate and support clinical and translational research and science

Workforce

Develop and support a community of clinical and translational scientists and research professionals for current and future success

Data Science

Enable clinical and translational science advances through data resources, biomedical informatics and data science

Community Partnerships

Enrich community research partnerships and facilitate dissemination and implementation of research findings in communities

Interdisciplinary Collaboration

Enabling interdisciplinary collaboration that leverages depth and breadth of institutional expertise

Thanks to:

- Meeting planners: Karen Carter, April Green, Jessica Fritter, Carolynn Jones
- CTSI staff for multiple types of support
- College of Nursing
- Program speakers

Device Development

Subinoy Das, MD, FACS

U.S. Institute for Advance Sinus Care and Research

Text questions/comments to 919-810-4373

Financial Disclosures/COI

- Co-Founder, Zotarix, LLC

- Chief Medical Officer, Investor for Soundtrace, Inc

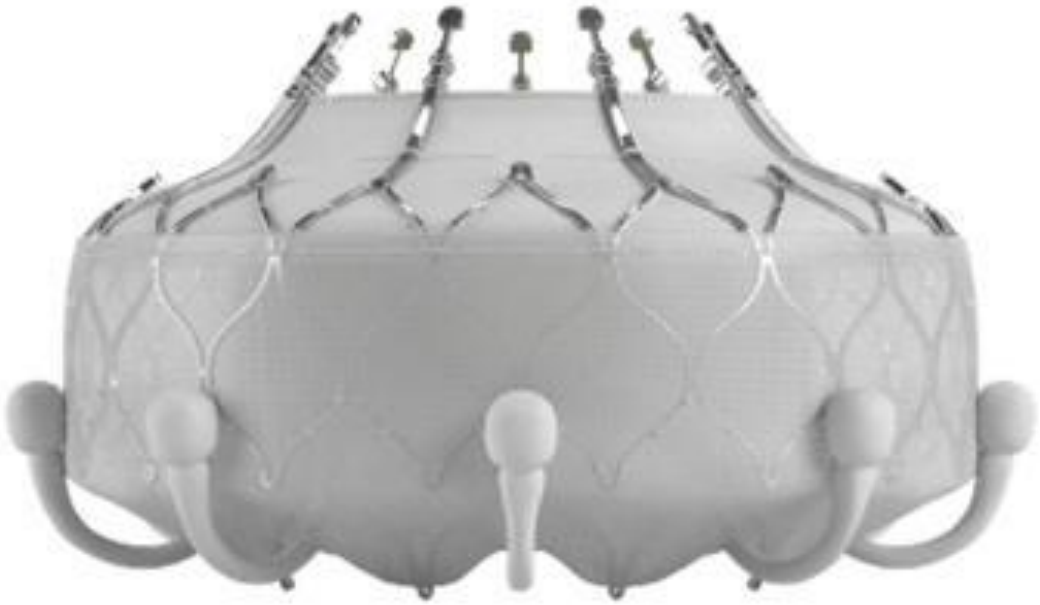
- External Advisory Board - Ohio State University Clinical and Translational Science Institute

- Licensing Agreements & Patent Assignments with OSU, Nationwide Children's Hospital

Text questions/comments to 919-810-4373

Development Overview

- IP/Company Development
- Regulatory Approval
- Manufacturing/Scaling
- Marketing/Sales

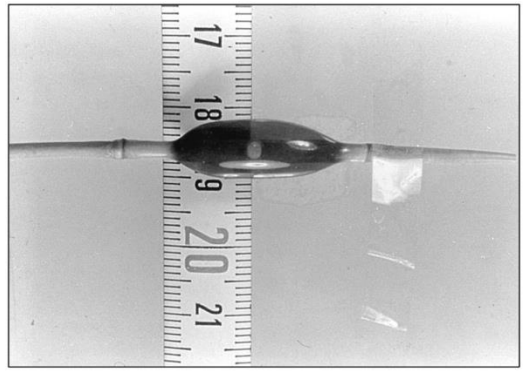


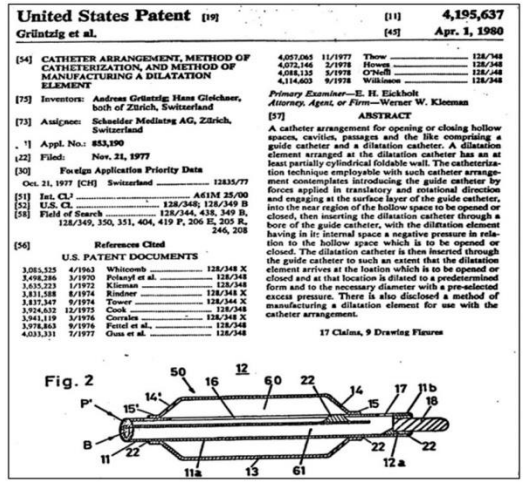
Edwards Transcatheter Aortic Valve Replacement

Text questions/comments to 919-810-4373

IP Development

- Provides Exclusivity/Limits Competition
- Hidden purpose of clinical trials





United States Patent [19]
Grüntzig et al.

[11] 4,195,637
[45] Apr. 1, 1980

[54] CATHETER ARRANGEMENT, METHOD OF CATHETERIZATION, AND METHOD OF MANUFACTURING A DILATATION ELEMENT

[75] Inventors: Andreas Grüntzig; Hans Gleichner, both of Zürich, Switzerland

[73] Assignee: Schneider Medintag AG, Zürich, Switzerland

[21] Appl. No.: 853,190

[22] Filed: Nov. 21, 1977

[30] Foreign Application Priority Data
Oct. 21, 1977 [CH] Switzerland 12835/77

[51] Int. Cl.² A61M 25/00
[52] U.S. Cl. ..... 128/348; 128/349 B
[58] Field of Search ..... 128/344, 438, 349 B, 128/349, 350, 351, 404, 419 P, 206 E, 205 R, 246, 208

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Primary Examiner—E. H. Eickholt
Attorney, Agent, or Firm—Werner W. Kleeman

[57] ABSTRACT

A catheter arrangement for opening or closing hollow spaces, cavities, passages and the like comprising a guide catheter and a dilatation catheter. A dilatation element arranged at the dilatation catheter has an at least partially cylindrical foldable wall. The catheterization technique employable with such catheter arrangement contemplates introducing the guide catheter by forces applied in translatory and rotational direction and engaging at the surface layer of the guide catheter, into the near region of the hollow space to be opened or closed, then inserting the dilatation catheter through a bore of the guide catheter, with the dilatation element having in its internal space a negative pressure in relation to the hollow space which is to be opened or closed. The dilatation catheter is then inserted through the guide catheter to such an extent that the dilatation element arrives at the location which is to be opened or closed and at that location is dilated to a predetermined form and to the necessary diameter with a pre-selected excess pressure. There is also disclosed a method of manufacturing a dilatation element for use with the catheter arrangement.

17 Claims, 9 Drawing Figures

Fig. 2

1980 Patent from Andreas Gruntzig, Father of modern coronary angioplasty

Text questions/comments to 919-810-4373

Company Development

- Raise 5-10 million dollars for average 510k with a predicate device

- Raise through several rounds
- 500k Friends and Family round
- 1-2 M Series A round
- 2-5 M Series B round; etc, etc.

Text questions/comments to 919-810-4373

Regulatory Compliance

- 83,000 deaths over last ten years due to medical devices

- FDA Class 1 - Registration
- FDA Class 2 – Clearance
- FDA Class 3 – (Pre-) Market Approval

- CE Mark (European equivalent)

2024 Transcatheter tricuspid valve heart repair system, Abbott Medical

Text questions/comments to 919-810-4373

Manufacturing/Scaling

- Inevitably there will be new versions; design changes

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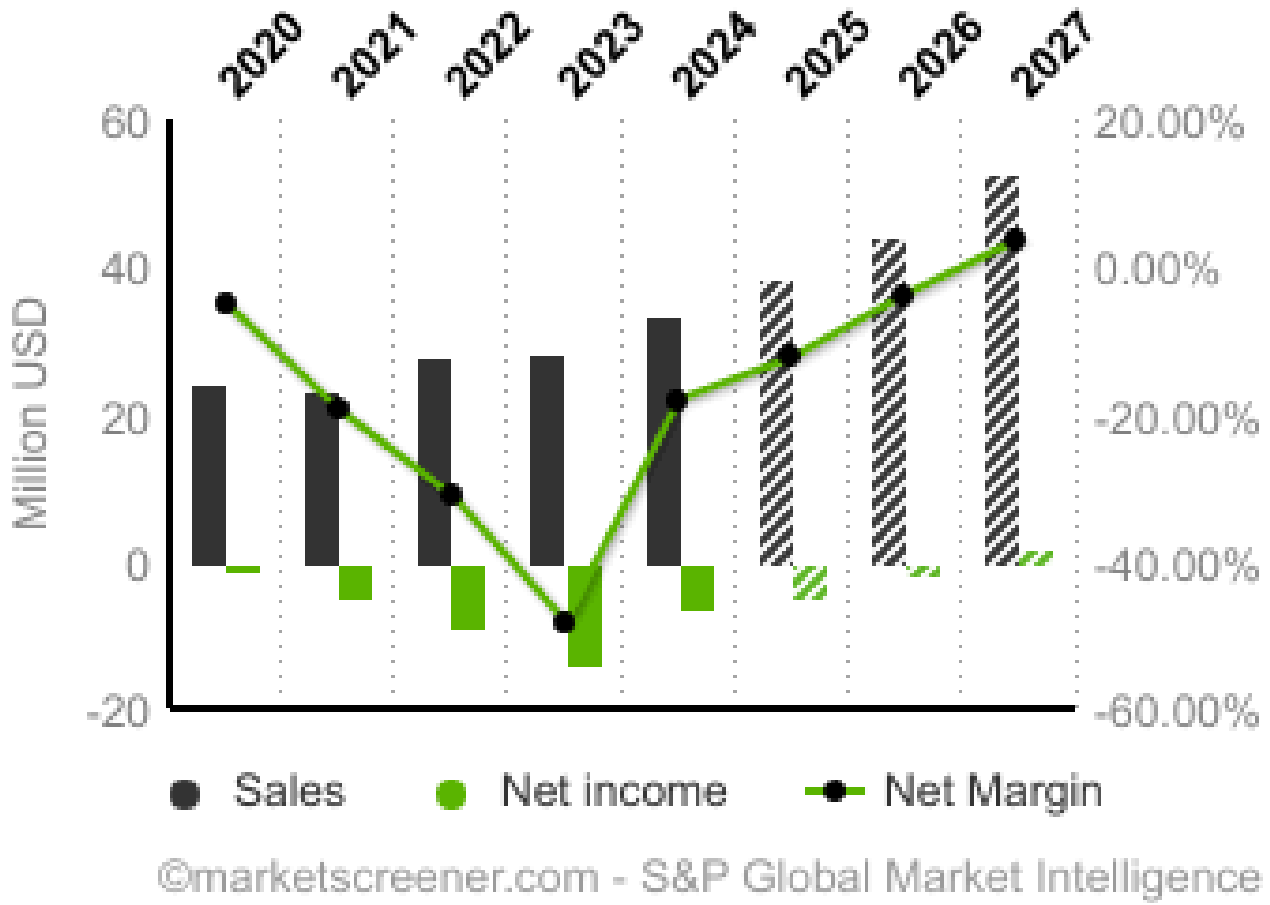
Marketing/Sales



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FDA REQUIREMENTS

- Class 1, 2, and 3 Devices

- Learn the most dangerous products in each class.

510K with SE to predicate!!!

De novo 510k doubles cost and adds 12 months

Why the Device Sponsors are Crazy!

- About to go broke
- Need the data to support future funding
- If the FDA rejects their submission, company likely bankrupt
- They have known dates of when they can’t make payroll

Usability Engineering

- Recent Emphasis at the FDA
- Complicated instructions no longer a solution; need it for each user who interacts with device
- Need hard data from end-users

Text questions/comments to 919-810-4373

Learn the Regulations!

- European Standard 62366 - Human Factors and Usability
- QSR (231 CFR Part 820) – Quality System Requirements
- ISO 13485 – Foundation for QMS Compliance
- ISO 10993 - Biocompatibility Risk Mitigation
- ISO 14971 – Risk Management
- IEC 62304 – Software and Cybersecurity

Challenge #1

- Find the 510k numbers for the 2 Predicate Devices we used to develop our Tivic ClearUP System

- Hint #1: Google FDA registration lookup

- Type in Tivic under company name

- Click on submission; Click on K number; Click on Summary
- Read Summary and find the K numbers of the 2 predicates

Challenge #2

- Who was the Principal Investigator of the Clinical Trial to support the
- 510k applilcation of ClearUP; What institution?

- Hint #1: Click on Clinical Trial link in the listing

- Click on clinical trial summary link

Text questions/comments to 919-810-4373

Pearls

- Less is More!
- Startups need speed, efficiency, and communication like no other
- The work has been done before; no need to reinvent the wheel
- Understand the needs of your sponsor

Text questions/comments to 919-810-4373

Thank You!

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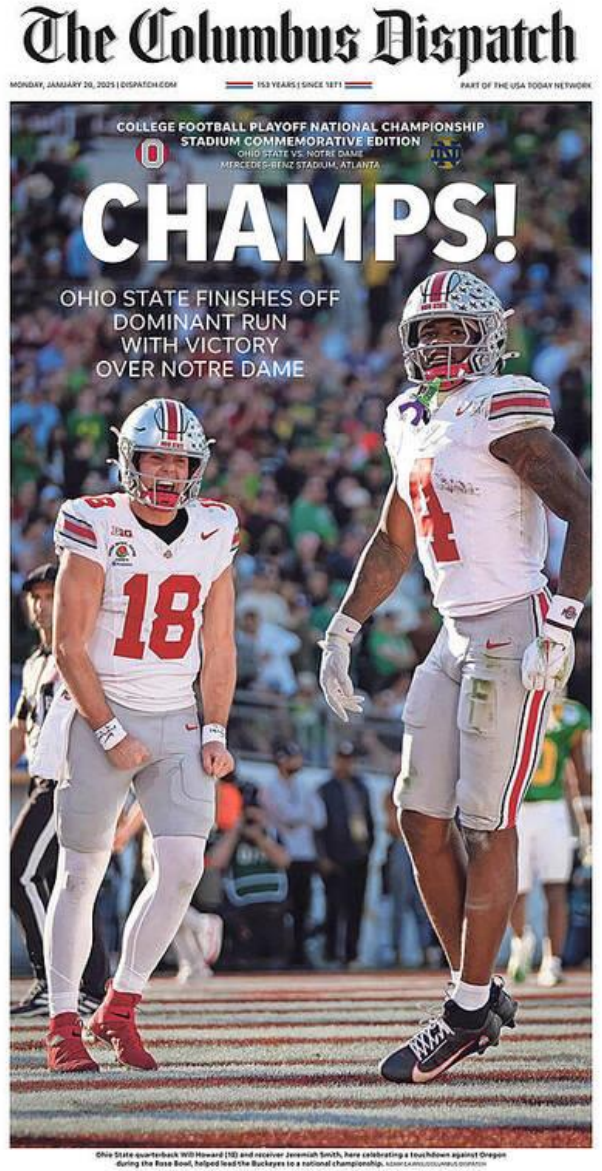


Decentralized Trials

Grace Maynard-Wentzel, CCRP, CHRC

Deputy Director, State of Ohio Adversity and Resilience (SOAR)

Department of Psychiatry and Behavioral Health

The Ohio State University

The presenter for this session is:

Grace Wentzel

I have no relevant financial relationship(s) in connection with this educational activity.

- Grace.Maynard-Wentzel@osumc.edu

Topics

- DCT Benefits and Challenges
- SOAR
- Financials
- Regulatory
- Operations
  - Study Team
  - Assessments
  - Safety Labs
  - Investigational Product
  - Adverse Event Monitoring
  - Monitoring Visits
- Maximize the chance for Success

Decentralized Clinical Trials (DCTs)

a trial that includes decentralized elements where trial-related activities occur at locations other than traditional clinical trial sites

Benefits

- Participant Convenience
- Reduced burden on caregivers
- Possible access to more representative population (rural, limited mobility)
- May improve recruitment, enrollment and retention rates

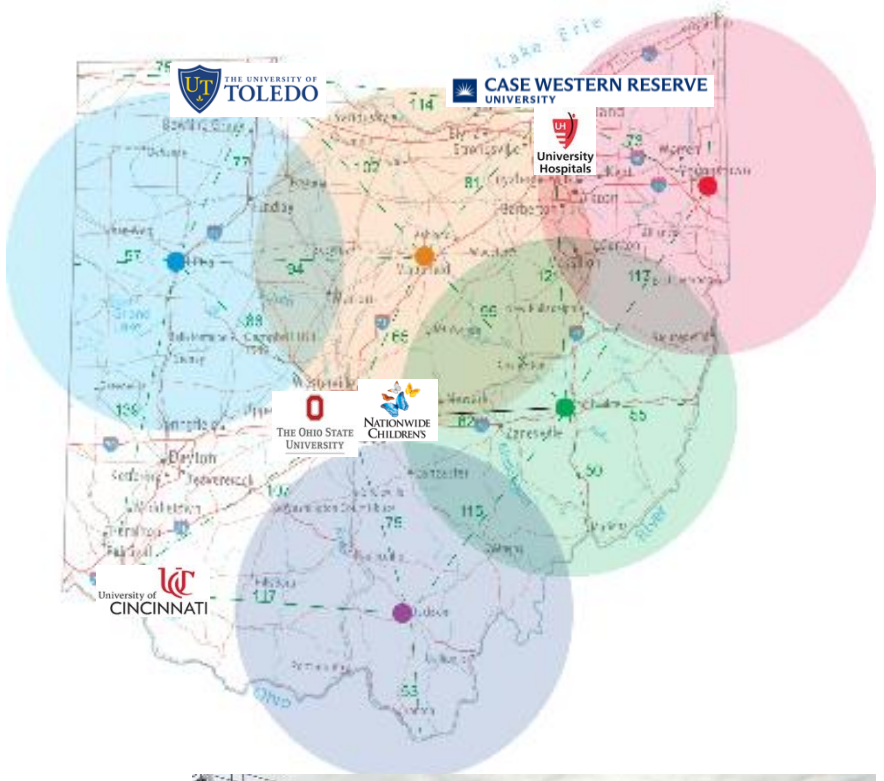
Challenges

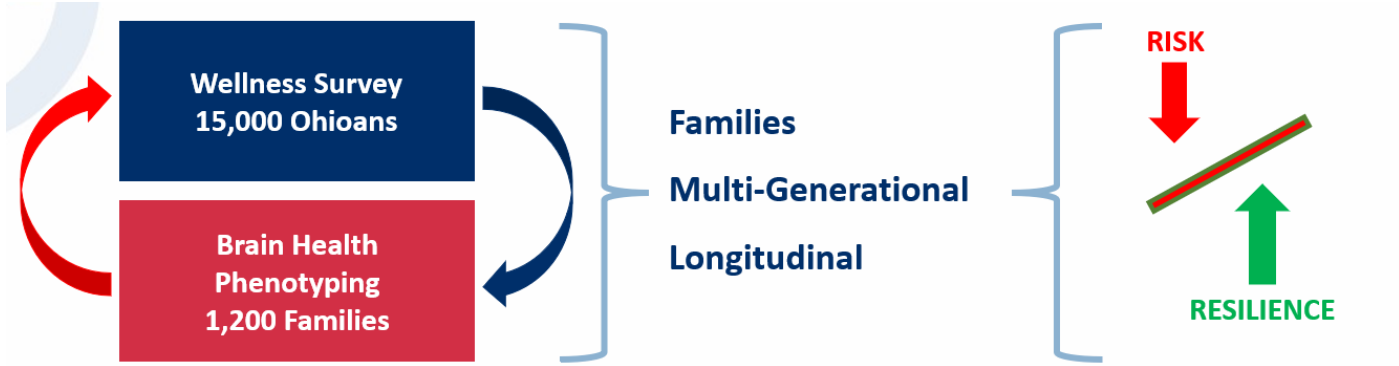
- Participant access to reliable technology
- Management of AE/SAE
- Hybrid models
  - Clear lines of accountability
  - Potential variability in data collection
  - Research knowledge of partner locations
  - Consistency of equipment

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/conducting-clinical-trials-decentralized-elements

SOAR Studies

- **Vision: Identify ways to improve care and treatment**
- Discover modifiable (and not modifiable) risk and resilience factors for
  - Mental health
  - Addiction
  - Suicide
  - Overdose
  - Persistent Distress





Financials

- Lab costs at non-research facilities
- Will study pay for technology services and/or equipment for participants?
  - Will your site have to obtain these through IT?
- Travel cost for study team?
- Remote monitoring
  - Labor intensive, scanning, uploading, organizing
  - Potentially more time to resolve questions
- Investigational product shipping costs
- Study team responsibilities even though the visit is remote
- May need multiple “arms” of the budget if using a Clinical Trials Management System
  - Increased time and resources to set up complex budgets

Regulatory & IRB

This is more complicated than most people think

- Use of Homecare
  - Whose 1572 are they on?
  - Training/Accountability
  - Where do protocol violations get reported?
- Investigational Product
  - Able to ship across state lines?
  - State licensure requirements
- Local facility labs and procedures
  - Training/Accountability
  - Information exchange, amendments?
  - What documentation is required on the 1572?
  - Billing compliance
- Clinical providers licensure
- Data acquisition for sites
- Data management for sponsors

Study Team

CHALLENGES

- Were they hired with the expectation of home visits?
  - Non-judgement
  - Cultural sensitivity
  - Comfortable
- Most organizations have HR requirements related to expectations in job descriptions
  - If not in job description and employee is harmed, is there a liability to the institution?
- Institutional policies and procedures for training, safety and security
  - Should it include a pre-visit review for firearms, aggressive pets, etc.?

POSSIBLE SOLUTIONS

- Candidates informed about possibility of home visits
- Job descriptions updated to include this responsibility
- Required training for managing participant interactions in a kind, respectful, non-judgmental way
- Home Visit policies and procedures for
  - Pre-visit assessment
  - Safety
  - Security
  - Emergency situation management
    - Should there always be 2 study staff members?
- Role play, mock visits case scenarios

Assessments

CHALLENGES

- Physical Exams
- Vital Signs
- Injection site reactions
- Studies requiring photographic or visual inspection of condition
  - Dermatology studies
  - Hemangiomas
- Assessments requiring special equipment
  - Imaging specs
  - Physical Therapy
  - Developmental

POSSIBLE SOLUTIONS

- Obtain physical at PCP, share data with study
- Apple Watch, FitBit, Garmin
- Participant takes a picture, sends it securely
- Telehealth options
  - Institutional platform requirements
  - Participant must download ahead of time, cost
  - Can it be recorded?
- Identify what can/cannot be done virtually
  - Some developmental assessments must be in person
  - Documentation of equipment used in CRF so it is known during data analyses
  - Ship equipment to participants' home

Safety Labs

CHALLENGES

- Pediatric sample collection
- Special tubes
- Specific processing instructions
- Lab normal range variations
- Results
  - Timeliness
  - Receipt mechanism
  - Include in EMR?
- Billing compliance
  - Labs will collect insurance information

POSSIBLE SOLUTIONS

- Identify facilities with pediatric expertise
- Send supplies to participant
- Lab kits including processing
- No easy solution
  - database will need revised or too many queries will be generated
- Identify primary contact for issues
  - Determine ahead of time if labs need to be part of EMR?
- Identify labs close to participants home during screening
  - Can sponsor contract directly with a national lab company?
  - Card to participant with study & billing information
  - Communicate to participant that account must be set up as self-pay
    - Reimburse participant via ClinCard

Investigational Product

CHALLENGES

- State licensure requirements
- Stability during shipment
- Storage in participants' home
- Requires mixing or some other special preparation
- IP accountability
  - Lost, misused product

POSSIBLE SOLUTIONS

- Can sponsor work with central IP service provider?
  - Can sponsor ship direct to participant?
  - Will study budget cover additional licensures for pharmacy staff? Willingness?
- IP Manual must include detailed stability information
  - Identify courier or shipping company prior to study start
- Ensure storage instructions are provided and confirmed prior to initial shipment
  - Provide extra resources, references for participants
- Telehealth, videos, detailed instructions
- As above, should be done frequently
  - Clear protocol guidelines for adherence, lack of accountability, withdrawal of participant

Adverse Event Monitoring

CHALLENGES

- Unexpected, study related determination
- Contract and Consent Language
- Required study data
- Billing compliance, cost recovery

POSSIBLE SOLUTIONS

- May be more difficult over zoom, may need more tests, time
- Clear definition of study related injury
  - Congruency in contract and consent
- Need record release signed
  - Most are institution specific
  - Ability to get all details to meet expedited and follow up reporting requirements
- Clear, detailed Processes
  - Provide document participant can carry in wallet
  - System in place to capture events so they can be billed for

Monitoring “Visits”

CHALLENGES

- Inability to access systems
  - Not user friendly
- In person allows for real-time review and resolution
  - Lost in translation
- Time intensive on the site

POSSIBLE SOLUTIONS

- Organizational process for external access to records
  - Limit by date and/or individual
  - Technology solution for record organization
- Schedule virtual meetings
  - Minimize emails
  - Clear, detailed eCRF guidelines
- Create secure portal
  - Consistent organization, naming convention
  - Additional resource with this primary responsibility

Maximize the Chance for Success

- Thorough protocol review PRIOR to accepting the study
- Establish a robust feasibility process that includes key stakeholders for the following considerations:
  - Participant Experience
  - Budgetary
  - Operational
  - Regulatory & IRB
- Understand your institutional requirements for usage of technology solutions
- Develop and implement detailed, comprehensive Manuals of Procedures/Standard Operating Procedures to maximize data integrity
- Establish training and processes to facilitate fully decentralized and hybrid clinical trials
  - Every study should be viewed through a “what if COVID?” lens

Summary

Fully decentralized or hybrid clinical trials

- Reduce barriers for people to participate
- Are complex
- Require people, processes and systems to ensure their success

If the science is excellent, the operational challenges can be overcome!

Revision to ICH E6 (R3)

Jessica Fritter, DHSc, MACPR, ACRP-CP

The Ohio State University

Overview

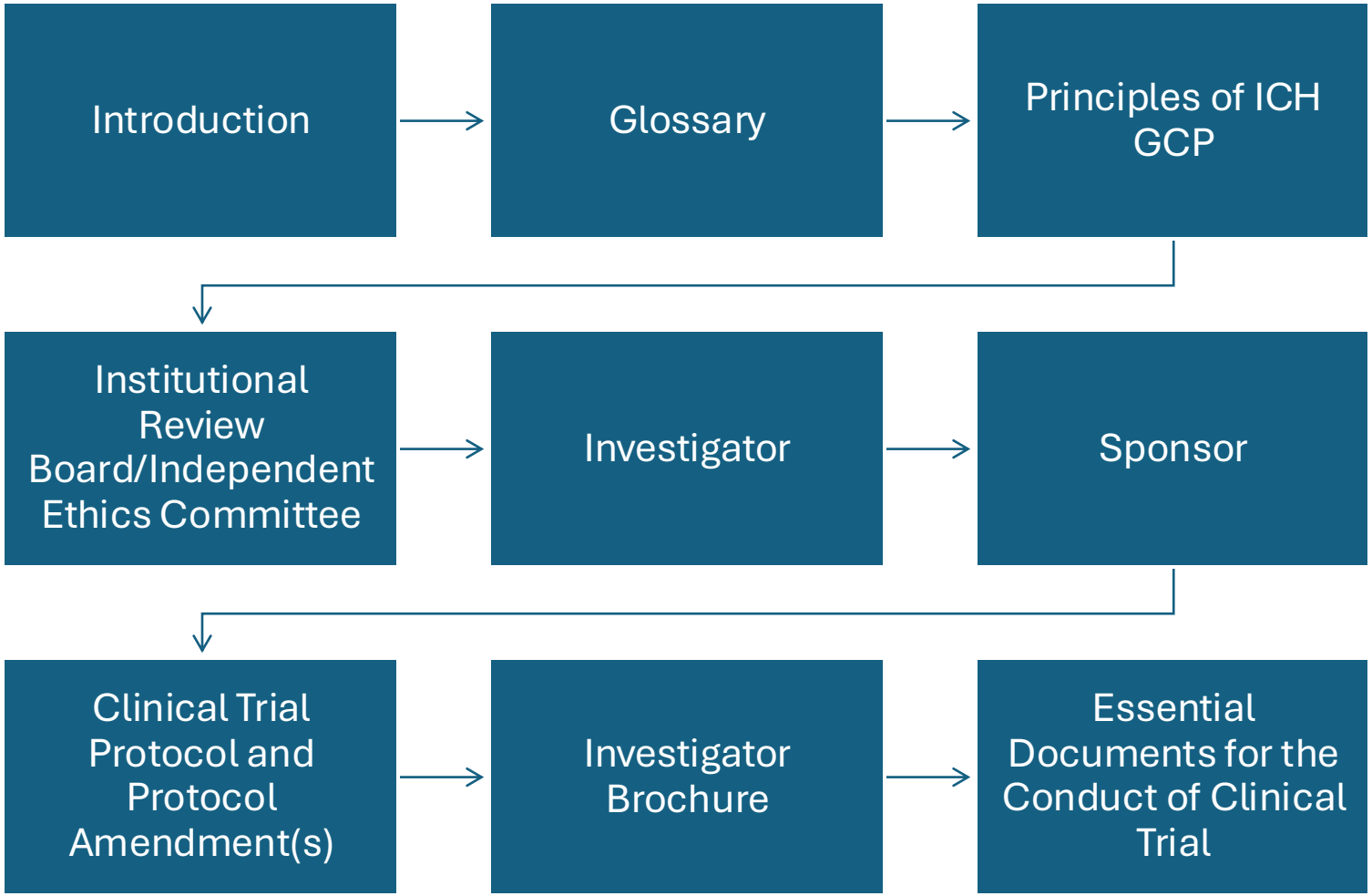
- New Structure
- Glossary Changes
- ICH E6(R3) Principles
- Key Changes
  - Principles
  - IRB/IEC
  - Investigator
  - Sponsor
- Timeline of changes

[adobestock/Worawut]

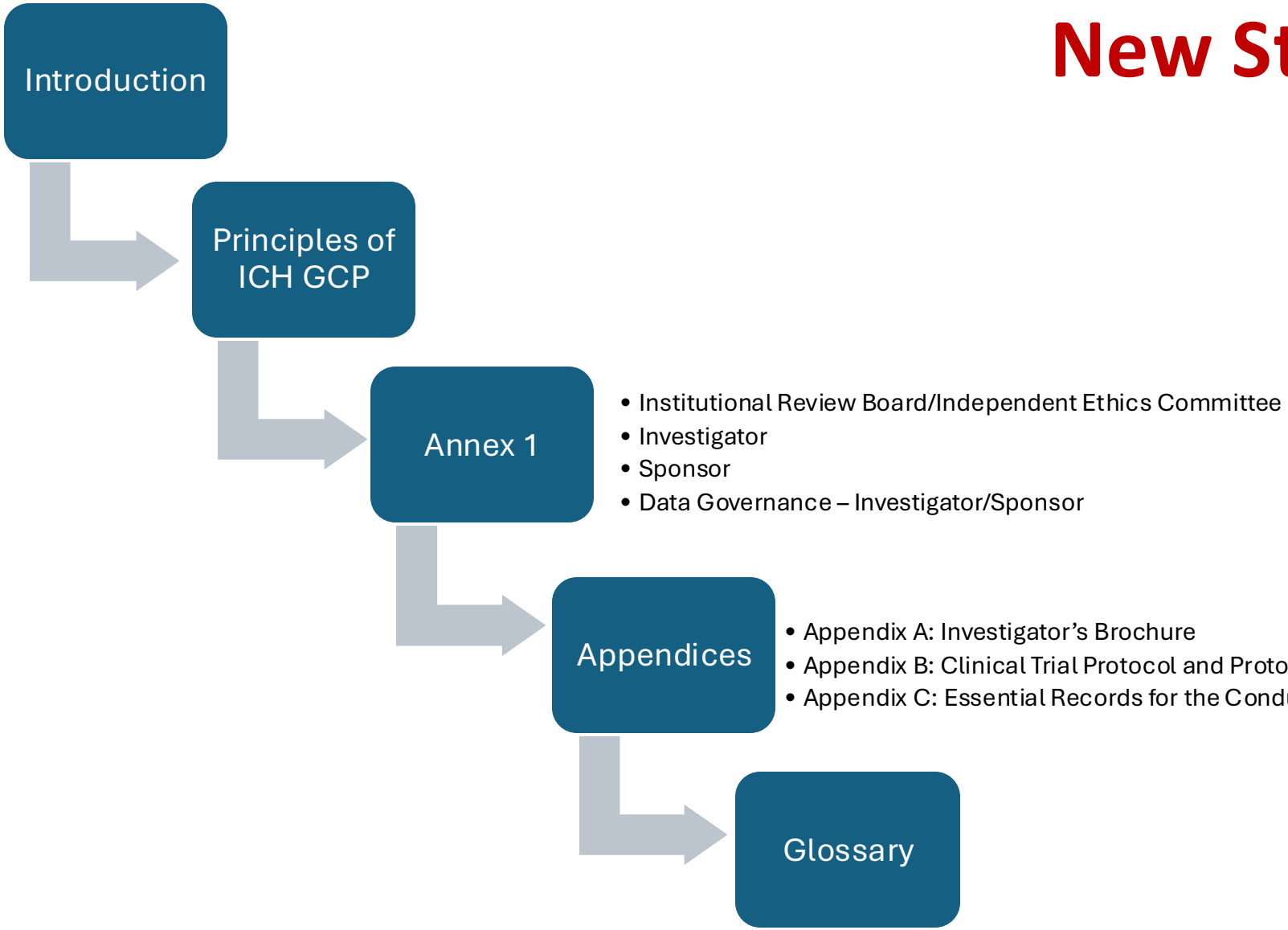
Motivators for Transformation

- Need for improved clarity & readability
- Move from ‘one-size-fits-all’ to ‘fit-for-purpose’
  - Emphasis on risk-based approaches and quality factors
- Evolving trial designs
- Lessons learned from the COVID-19 pandemic
- Heighten the informed consent process
- Data governance & digital enhancements

ICH E6 R2 Guidance - Structure



ICH E6 R3 – New Structure



- Institutional Review Board/Independent Ethics Committee
- Investigator
- Sponsor
- Data Governance – Investigator/Sponsor

- Appendix A: Investigator's Brochure
- Appendix B: Clinical Trial Protocol and Protocol Amendment(s)
- Appendix C: Essential Records for the Conduct of a Clinical Trial

Glossary Changes

- Definition of Good Clinical Practice:
  - A standard for the planning, initiating, performing, recording, oversight, evaluation, analysis, and reporting of clinical trials that provides assurance that the data and reported results are reliable and that the rights, safety, and well-being of trial participants are protected.

Glossary Changes

New Terms

- Assent
- Computerized Systems
- Validation
- Data Acquisition Tool
- Data Integrity
- Metadata
- Reference Safety Information
- Service Provider
- Signature
- Suspected Unexpected Serious Adverse Reaction (SUSAR)

Revised Terms

- Agreement (was Contract)
- Adverse Events & Adverse Reaction
- Essential Records (was Essential Documents)
- IRB/IEC
- Investigator
- Investigator Site (was Trial Site)
- Source Records (was Source Data)
- Sponsor
- Trial Participant (was Subject/Trial Subject)
- Among others…

Principles of ICH E6 (R3)

Ethical Principles

Informed Consent

IRB/IEC Review

Science

Qualified Individuals

Quality

Risk Proportionality

Protocol

Reliable Results

Roles & Responsibilities

Investigational Products

[adobestock/SewcreamStudio; Verin; Bussakon; pressmaster; Andrii Yalanskyi; Prostock-studio; Jo Panuwat D; Supatman; spyrakot; Cagkan; VK Studio]

New Principles

7. Risk Proportionality

Clinical trial processes, measures and approaches should be implemented in a way that is proportionate to the risks to participants and to the importance of the data collected and that **avoids unnecessary burden on participants and investigators.**

- Proportionate risk inherent to the trial
- Focus on risk associated with trial participation
- Risk management
- Operationally feasible, avoiding unnecessary complexity, procedures, and data collection

10. Roles and Responsibilities

Roles and responsibilities in clinical trials should be clear and documented appropriately.

- Sponsor may transfer or investigator may delegate their tasks, duties etc. but they retain overall responsibility for their activities.
- Agreements should clearly define the roles, activities and responsibilities for the clinical trial and be documented appropriately.
- Sponsor or investigator should maintain appropriate oversight.

Key Changes - Principles

Ethical Principles

- Ensuring to not exclude participant populations

Informed Consent

- Consider relevant aspects of the trial
- Include technology sources

IRB/IEC Review

- Periodic review per regulatory requirements

Science

- Periodic scientific review to determine if modifications to the trial are needed

Qualified Individuals

- Need for individuals with different expertise and training across all phases

Quality

- Fit for purpose & quality by design

Protocol

- Well designed protocol (protection of participants and for reliable results)
- Operational feasibility of protocol

Reliable Results

- Data quality, data integrity
- Transparency of clinical trials – registration on publicly accessible databases and the public posting of results

Investigational Products

- Retain its quality & IP managed to align with treatment and maintain blinding

Key Changes – IRB/IEC

CONSENT TO INCLUDE DIGITIZATION AMONG OTHER APPROACHES

REASONABLE REIMBURSEMENT FOR PARTICIPANT COMPENSATION IS NOT CONSIDERED COERCIVE

RETAIN ALL RELEVANT RECORDS IN ACCORDANCE WITH APPLICABLE REGULATORY REQUIREMENTS

Key Changes – Investigator

2.3 Responsibilities

- Qualifications & oversight extend beyond site staff (includes service providers)
- Sponsor can help in identifying service providers, but investigator is responsible for selection
- Delegation documentation may not be required for routine clinical care

2.9 End of Participation in a Clinical Trial

- Guidance on management of collected data from withdrawn or discontinued participants
- Address participants' concerns and try to determine the reason for the participant withdrawing without applying undue influence
- Transparency with sharing trial results and treatment details

[adobestock/BartPhoto]

Key Changes – Sponsor

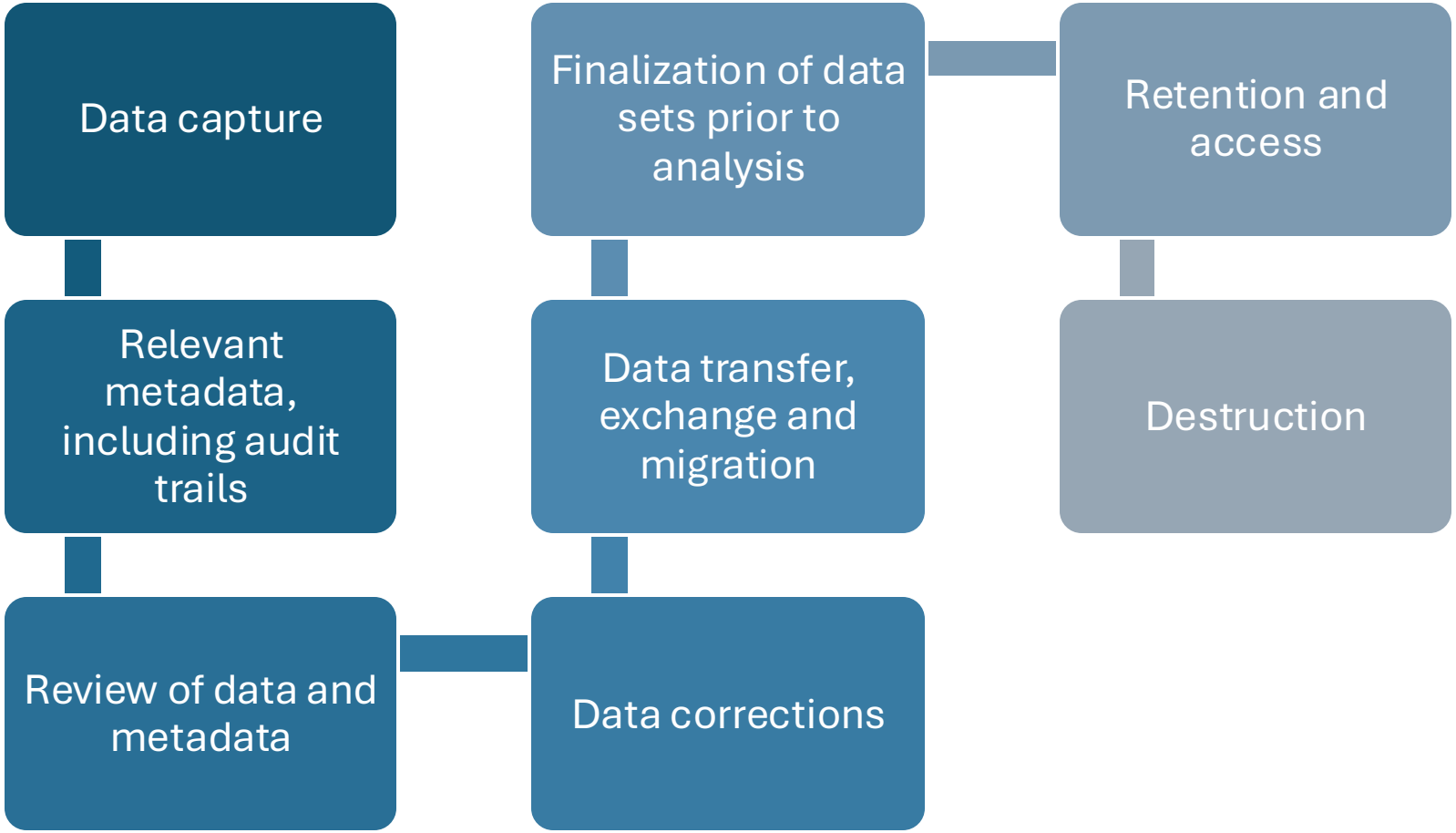
- 3.2 Resources
- 3.4 Qualification & Training
- 3.6 Agreements
- 3.9 Sponsor Oversight

[adobestock/BartPhoto]

Key Changes – Data Governance

- Shared responsibility between sponsor and investigator
- Key items to be addressed throughout the full data life cycle:
  - Data protection
  - Management of computerized systems
  - Essential elements (randomization, dose adjustments, blinding)
  - Process to support key decision making (data finalization, unblinding etc.)
- Computerized systems should be fit for purpose and validated
- Described the elements of data life cycle

Data Life Cycle

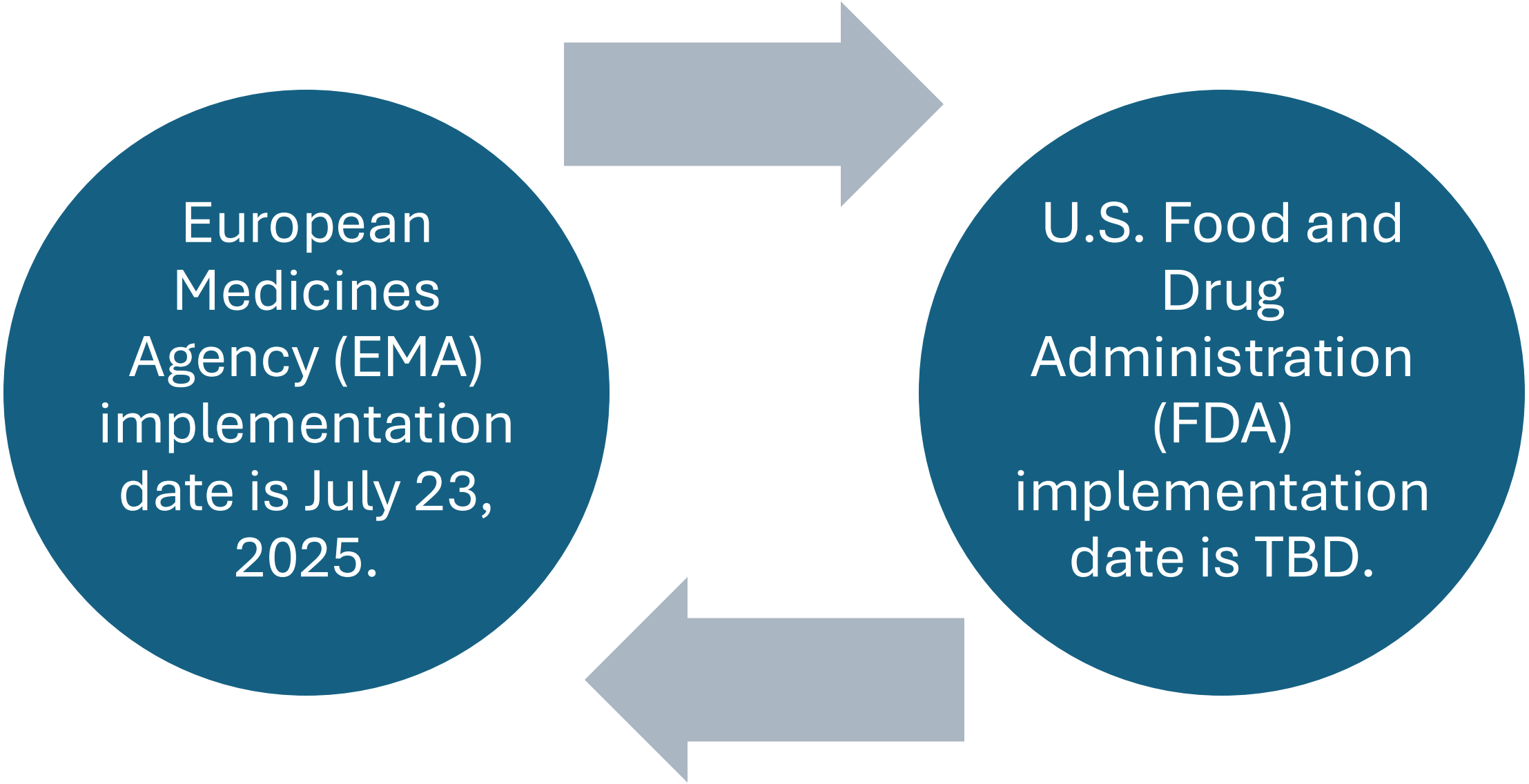


Replicated from ICH document:
https://database.ich.org/sites/default/files/ICH_E6%28R3%29_Step%204_Presentation_2025_0123.pdf

Key Changes – Appendices

- Investigator's Brochure
  - Must list expected adverse reactions and the IB template was removed
- Protocol
  - Flexibility in protocol and schedule of events required
- Essential Records
  - *Not documents* and need to include a risk-based assessment

Timeline


European Medicines Agency (EMA) implementation date is July 23, 2025.
U.S. Food and Drug Administration (FDA) implementation date is TBD.

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21 CFR 11 – REDCap Black

Timothy Huerta, PhD, MS, CRIO

Associate Dean for Research Information Technology (RIT)

What is 21 CFR Part 11?

- Sets U.S. FDA standards for electronic records and electronic signatures and is required when:
  - Conducting FDA-regulated clinical research (e.g., drug or device trials)
  - Using electronic records as source data
  - Using electronic signatures for official documentation
  - Submitting data to FDA to support product approval
  - Also required if sponsor, contract, or IRB mandates it
- Purpose: ensuring data integrity, security, and auditability for regulated research
- Not required for non-regulated studies or when using paper source records and electronic transcription only

Institutional Responsibilities

System requirements

- System validation
- Build validation
- Secure access control
- Reliable audit trails
- Accurate record reproduction and retention
- Enable logging and user roles

Study requirements

- Build validation
- Secure access control
- Reliable audit trails
- Use secure login credentials

Study Team Responsibilities

- Before data collection:
  - Determine whether Part 11 applies
  - Request
  - Submit project for validation if needed
- During study:
  - Maintain audit readiness
  - Follow institutional standard operating procedures
- After study:
  - Retain records in accordance with sponsor, IRB, and regulatory requirements

Data in FDA Regulated Clinical Trials using REDCap Black

Heather Lansky
Assoc. Dir., Enterprise Applications Management
Dept. of Research Information Technology

Jason Lones
Applications Development Senior Consultant
Dept. of Research Information Technology

The Ohio State University
Clinical and Translational Science Institute

The Ohio State University
College of Medicine

REDCap Usage

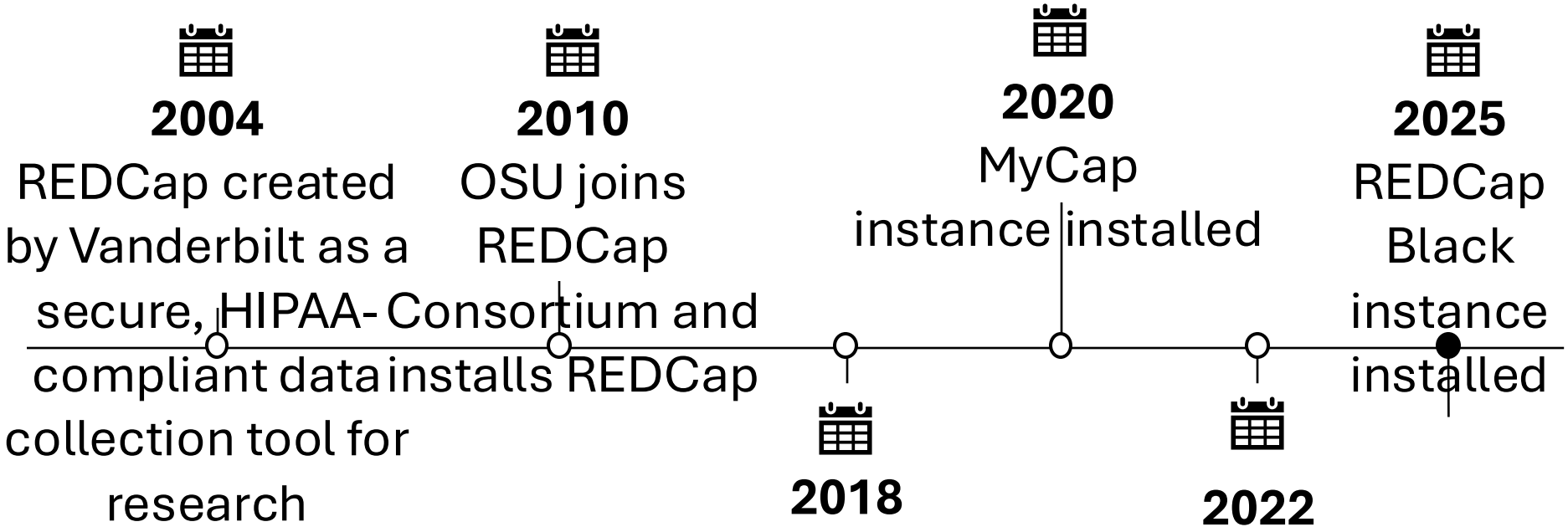
at OSU and Globally

5 REDCap instances at OSU	**13302** Users at OSU	**7274** Projects at OSU
7782 Institutions in the Consortium	**3.7M** Users globally	**2.3M** Projects globally

[1]Source: https://project-redcap.org/ April 23, 2025

REDCap History

15 Years of Research Support at OSU



Establishment of REDCap Black

- Created to address need for a **validated** system
- **Existing systems** difficult to retrofit to compliance requirements
- Installed “in the cloud” on Microsoft Azure to **leverage** Microsoft compliance documentation

REDCap Black will be the only instance suitable for FDA-regulated research, while REDCap Scarlet and Grey will remain available for non-FDA-regulated studies and other uses.

Key Stakeholders and Governance

Systems Workgroup

- Office of the Chief Research Information Officer (OCRIO)
- Department of Research Information Technology (RIT)
- Wexner Medical Center Information Technology (WMC-IT)

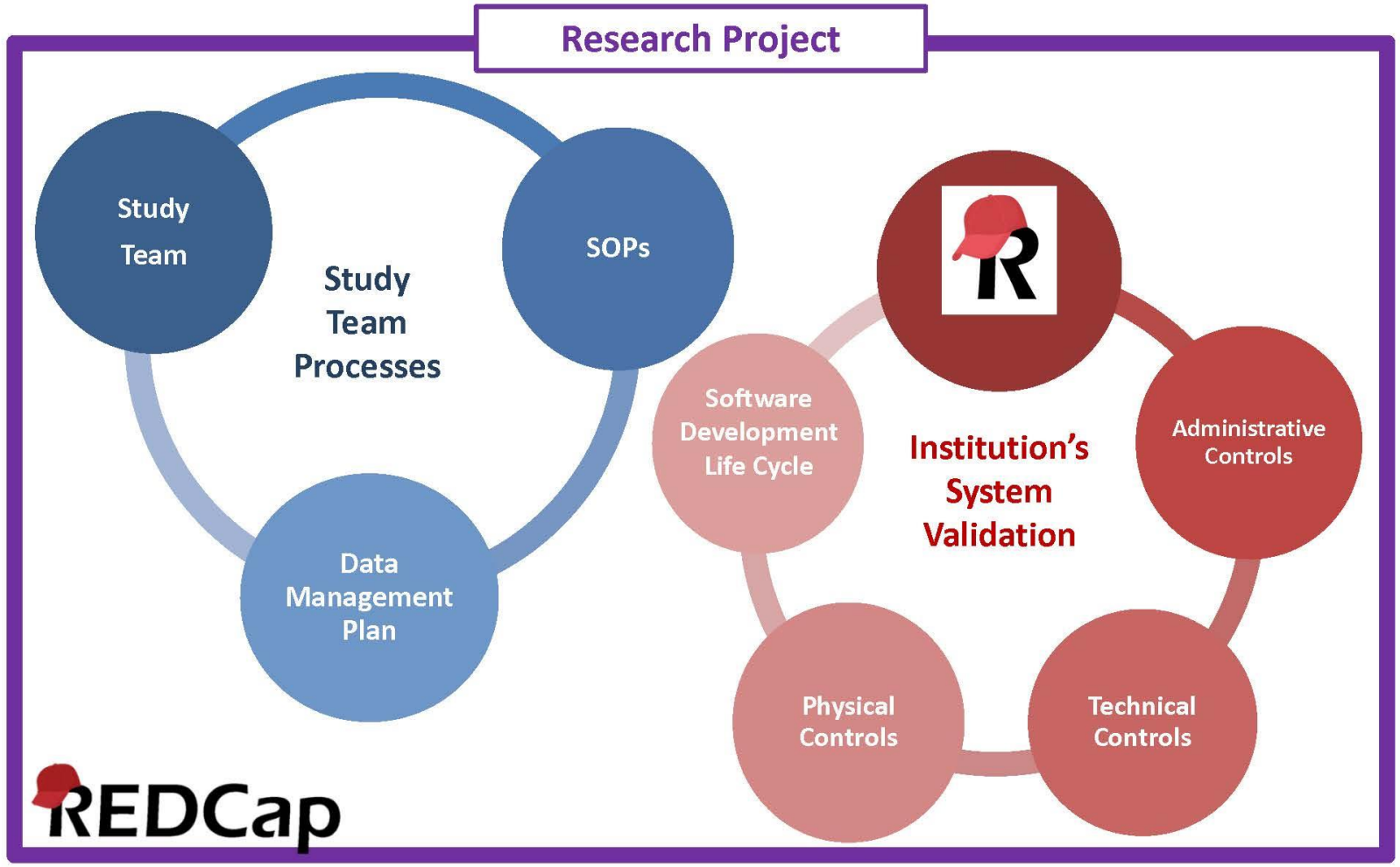
Operations Workgroup

- Office of the Chief Research Information Officer (OCRIO)
- Enterprise for Research, Innovation and Knowledge (ERIK) – Office of Research Compliance
- College of Medicine – Office of Research Compliance (COMOR-C)
- Clinical and Translational Science Institute (CTSI)
- Center for Clinical Research Management (CCRM)

Communications Workgroup

- OCRIO
- ERIK – Office of Research Compliance
- CTSI

Study + System = Part 11 Compliance



OSU's System Validation Effort

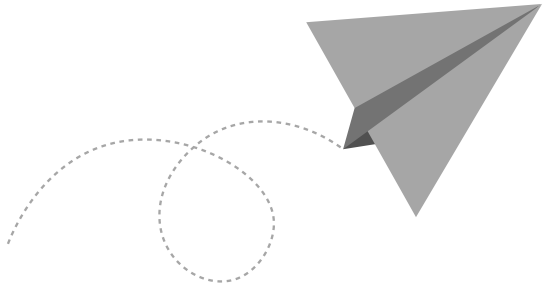
Validation Objectives

- Ensure REDCap meets requirements for electronic records & signatures
- Confirm data integrity, security, and audit trails

Validation Components

- System Requirements Specification (SRS)
  - Defines functional and regulatory requirements
- Installation Qualification (IQ)
  - Verifies proper installation of REDCap in a secure environment
- Operational Qualification (OQ)
  - Tests REDCap functions (e.g., user access, audit trail, form validation)
- Performance Qualification (PQ)
  - Confirms system performs reliably in a production-like setting

Pilot Phase - Timeline



- Operations Workgroup determined a pilot phase of one project onboarding per month

  Example cadence:

  - Project 1 – Onboarding in April, build in May
  - Project 2 – Onboarding in May, build in June
  - Project 3 – Onboarding in June, build in July
- Submissions accepted for onboarding in June (and beyond) for consideration by the Operations Workgroup
- Broad deployment anticipated later in 2025

Pilot Phase - Requirements

- Compliance with 21 CFR 11 required
- New study (no data collection started)
- No “DIY”
  - RIT-EDC does the build at hourly rate $124/hr
  - Pilots receive offset of cost from OCRIO and COM
- Single site
- REDCap Black must be used for the entire project build, not limited to only the consent portion
- No need for external modules or API functionality
- English language only

Next Steps

- Studies eligible for consideration for the pilot should contact rit-edc@osumc.edu and supply the following information:
  - Principal Investigator
  - College
  - Research stage (e.g., proposal submission, funded)
  - If funded, is the project ready for data collection, or is the start date pending?
  - Funding source (e.g., departmental, industry sponsor)

Thank You

rit-edc@osumc.edu

AI Predictive Analytics Model

Lang Li, PhD

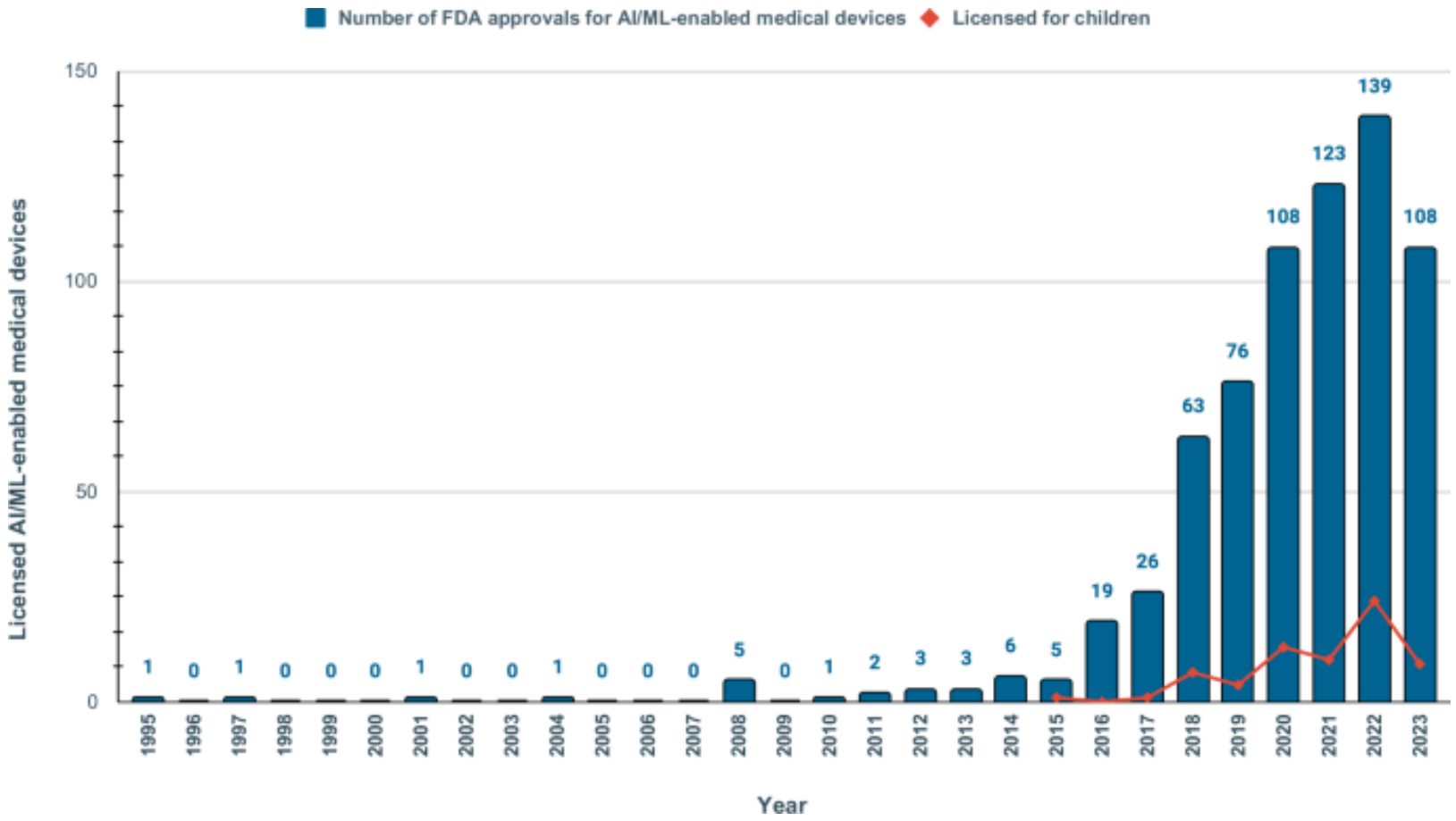
Chair, Biomedical Informatics, Department of Medicine,

The Ohio State University

Overview

- AI/ML: FDA Policies and Guidelines
- AI/ML implementation in clinical practice guidelines within The Ohio State University Medical Center
- Biomed-ML: a comprehensive knowledge portal for machine learning and artificial intelligent applications in biomedical research.

How many AI/ML devices have been approved by FDA?



To date, by 2024, the FDA has approved 950 medical devices driven by artificial intelligence and machine learning (AI/ML) for potential use in clinical settings.

AI/ML

FDA Policies and Guidelines

Food and Drug Administration – AI Regulatory Pathways

Software as a Medical Device (SaMD)

Class I (Low Risk)

Class II (Moderate Risk)

- OsteoDetect
- Adjunct tool, does not replace clinician's review

De Novo classification, premarket approval

Good Machine Learning Practice for Medical Device Development: Guiding Principles	
Multi-Disciplinary Expertise Is Leveraged Throughout the Total Product Life Cycle	Good Software Engineering and Security Practices Are Implemented
Clinical Study Participants and Data Sets Are Representative of the Intended Patient Population	Training Data Sets Are Independent of Test Sets
Selected Reference Datasets Are Based Upon Best Available Methods	Model Design Is Tailored to the Available Data and Reflects the Intended Use of the Device
Focus Is Placed on the Performance of the Human-AI Team	Testing Demonstrates Device Performance During Clinically Relevant Conditions
Users Are Provided Clear, Essential Information	Deployed Models Are Monitored for Performance and Re-training Risks are Managed

- A randomized clinical trial is not required.
- Software usability studies are useful.

AI in Drug Discovery

- Regulatory – Still need clinical trials
- Intellectual Property

Challenges in ML/AL tool/device development in clinical setting

- "AI Chasm":
  - Ongoing challenges in crossing the translational gap from research to practice
  - Few published AI algorithms that have been shown to improve clinical outcomes in real-life settings

- Requires approval from multiple regulatory and compliance groups
  - IRB
  - Risk assessment
  - IT prioritization

- Requires coordination of multiple stakeholders for successful integration
  - Technical team
  - Clinical Team
  - Research Team

- There was no clear pathway to implementation of AI/ML tools, especially those created by OSU researchers

Policy Development

- Policy Subcommittee of the Research Information Systems Steering Team (RISST), was charged with creating a new policy for clinical implementation of AI/ML tools

- Policy subcommittee was created in December 2021
  - Request went out for volunteers
  - Researchers from Basic science, Clinical trials, Informatics

- In 2022 we were asked to develop a new AI/ML policy. General process:
  - Subcommittee:
    - determined scope, identified other related policies, reviewed literature
    - identified stakeholders/SMEs and invited them to create task force
  - Taskforce drafted policy and presented back to subcommittee for review
  - Presented to RISST

Policy details

- Objective: To outline a recommended process for deploying an artificial intelligence (AI), machine learning (ML), or predictive model into the clinical space. Appropriate implementation requires an interdisciplinary team and guidelines to ensure safe and excellent care for our patients.

- In scope:
  1. Models created through research that have yet to be widely adopted in clinical guidelines
  2. Models created for quality improvement (QI) or operations, excluding those developed by the Analytics Center of Excellence
  3. Models created through collaborations with outside vendors or other institutions

- Out of scope:
  1. Models that are currently evaluated through standard OSUWMC IT and clinical guidance

Policy details

- Establish standard of care (SOC) and workflow
  - Each team requires a clinical champion, a data science champion
  - Required to present a SOC model or benchmark dataset if one exists

- Predictive model selection
  - If research – should be published in peer-reviewed journal
  - If QI – should be peer evaluated by ACE
  - Model should be consistent with AMIA's standard principles for AI in healthcare (1)

- Statistical validation
  - If feasible, all models should be validated with clinical data derived from EHR data at OSUWMC using accepted statistical methods for validating models (e.g., AUC, AIC, precision, recall, F1-score).
  - must show superior performance compared to SOC model in retrospective validation.
  - must perform bias and fairness evaluation prior to implementation
  - If the model is designed to calculate from prospective/dynamic clinical data, it should be validated in a separate location from the clinical space (in the background)

(1)Solomonides AE, Koski E, Atabaki SM, Weinberg S, McGreevey JD, Kannry JL, Petersen C, Lehmann CU. Defining AMIA's artificial intelligence principles. J Am Med Inform Assoc. 2022 Mar 15;29(4):585-591. doi: 10.1093/jamia/ocac006. PMID: 35190824; PMCID: PMC8922174.

Policy details

- Clinical validation, requires:
  - Plan for how to interpret output (attached clinical practice guideline)
  - Workflow diagram
  - Clinical experts must approve via stakeholder committees

- Regulatory review
  - IRB approval will be obtained prior to submitting the request for IT resources.
  - The product owner or PI is responsible for assessing whether FDA review/approval is needed for the use of the model and/or tool as Software as a Medical Device
  - The model/implementation plan must be approved by the predictive analytics stakeholder group, Health System IT Prioritization, and reviewed by the Risk Assessment Team

Procedures

Prior to obtaining funding

- Establish clinical/data science champions
- Discuss feasibility with IT (consider LOS)
- Submit IRB

When ready to implement

- Submit a review request to appropriate stakeholder group.
- Be ready to present results of: retrospective validation, plan for prospective validation/study, evidence of peer evaluation, evidence for support in the targeted clinical space, workflow diagram, evaluation for bias,

Implementing

- Build
- Test
- Pilot
- Full roll out
- Regular monitoring

Biomed-ML: a comprehensive knowledge portal for ML/AI applications in biomedical research

Biomed-ML is automatically generated by BioBERT

- **49,627** papers focus on ML/AI applications to clinical science,
- **25,319** papers focus on basic science.

Classify ML/AI applications in biomedical Research (annotation guideline)

Clinical Science (c)

- Predicting clinical outcomes, such as disease diagnosis and prognosis, using patient data.
- Predicting therapy responses, including efficacy and adverse events, using patient data.
- Predicting healthcare facility usage based on population data.
- Predict public health outcomes using population data.
- Predict mobile health impacts.
- Predict clinical phenotypes using multi-omics data.
- Predict patient toxicity, unless specified as cyto-toxicity, which is categorized under Basic science.

Basic Science (b)

- Predicting gene or protein functions using multi-omics data in cell culture models or animal models.
- Predicting protein screening and drug screening outcomes.
- Predicting drug pharmacology properties.
- The abstract may mention clinical applications of these predictive models, but none are applied to patient-level data.

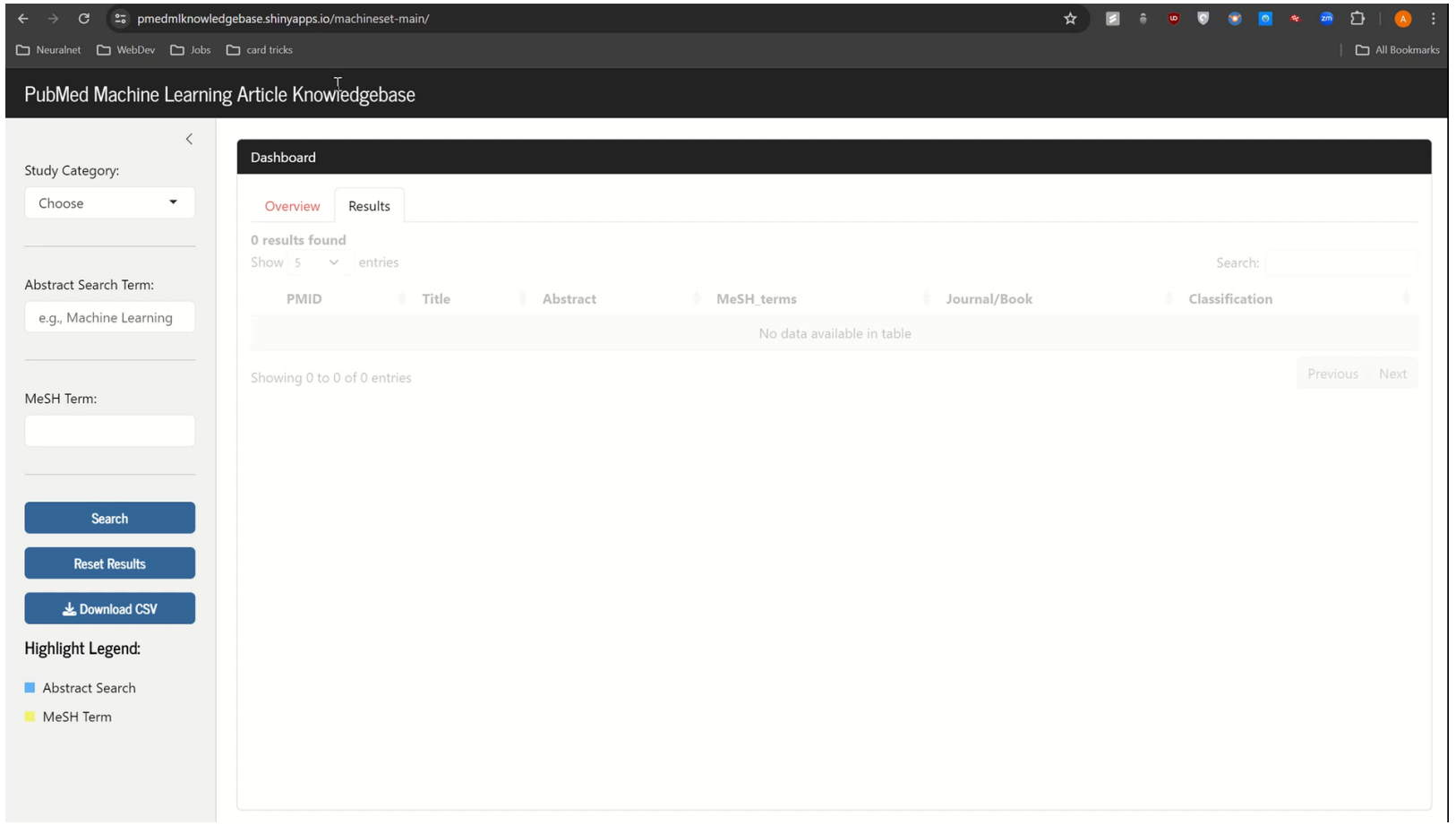
Review Articles (r)

- Covers review articles related to AI/ML applications in biomedical research.

Others (o)

- Predicting traffic problems.
- Predicting battery power.
- Predict environmental issues (e.g., air pollution, water pollution), unless related to disease or public health.
- Predicting farming or forest outcomes, including plant production and cattle production.
- Predict ecological issues unrelated to human health.
- Predict social or behavioral issues (not disease-related).
- Predict mobile network performance.
- Predict some biochemical properties unrelated to life science.

Biomed-ML Knowledgebase Demo



Acknowledgement

- Courtney Hebert, MD, Associate Professor, Department of Biomedical Informatics, Department of Internal Medicine, College of Medicine, The Ohio State University

- Andrew Hampton, PhD, Senior Licensing Officer, AI, ML and Digital Health, Office of Innovation and Economic Development, The Ohio State University.

- Aniruddha Sankoli, MS. Department of Electronic and Computing Engineering. College of Medicine, The Ohio State University.

Lunch

11:45 a.m. – 12:30 p.m.

Drug Development

Angel Cinco, MD, MPH

Nationwide Children's Hospital

Office of Research Regulatory Affairs

Office of Research Regulatory Affairs (ORRA)

Mission:

The Office of Research Regulatory Affairs plays a crucial role in guiding investigators through the complex processes of submission, review, and FDA approval for clinical trials. By providing a streamlined and uniform approach, we help ensure that trials are developed and implemented consistently. Our goal is to simplify the regulatory landscape for researchers, making it easier for them to focus on their innovative work.

Vision:

Our goal is to assist medical facilities in advancing new ideas to clinical trials by navigating the regulatory landscape. Our regulatory affairs team possesses extensive expertise to develop detailed strategies and support staff in achieving successful FDA reviews.

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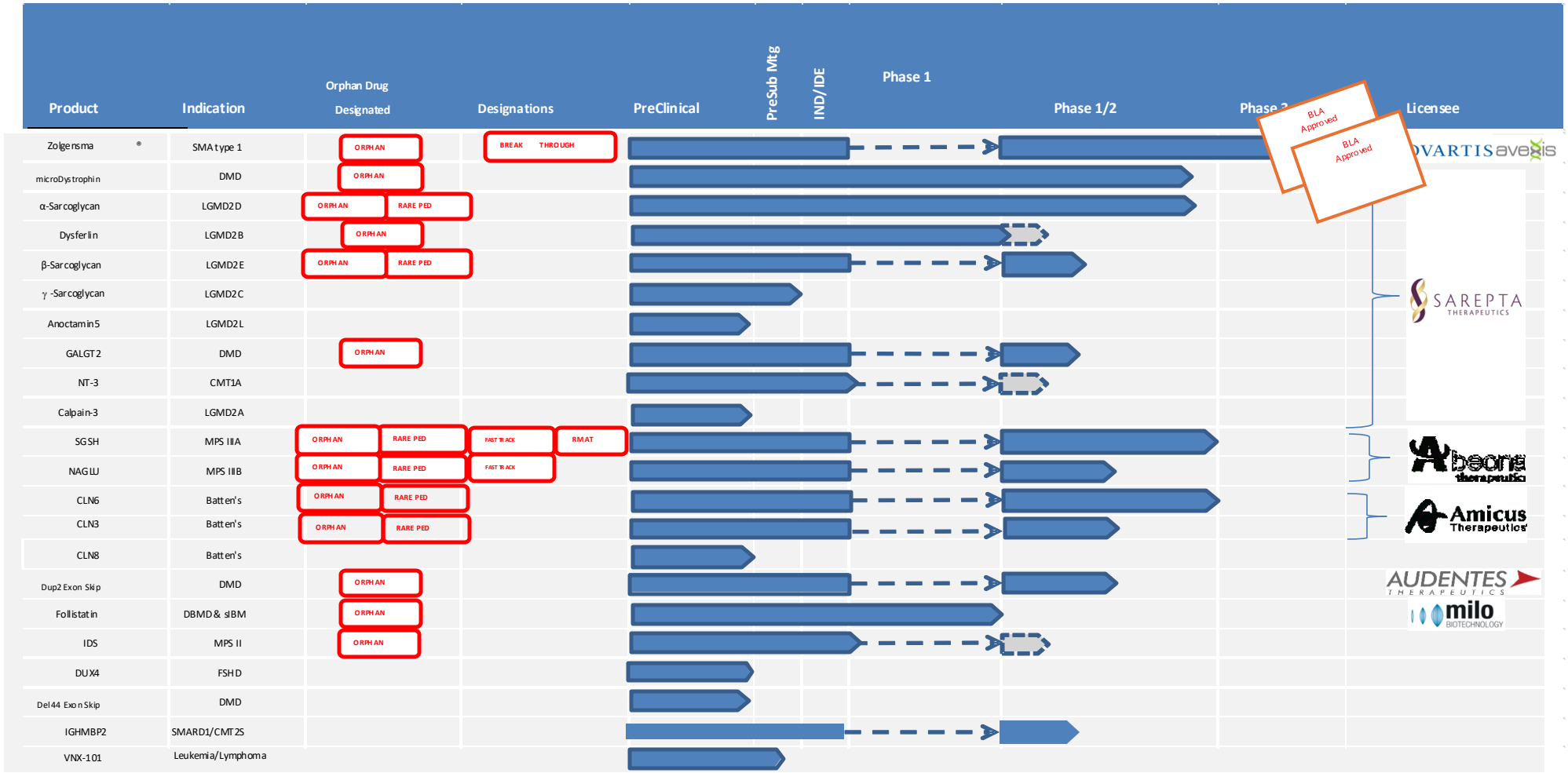
Role of ORRA

- Provide regulatory support from preclinical stage through clinical trial
- Communicate and interact with FDA regulators - including meeting requests, data packet submissions
- Oversee submission of IND application and provide maintenance of the IND (amendments, annual reports, etc.)
- Support for study records to be inspection ready
- Training for new sponsor-investigators and other individuals involved

Gene Therapy Pipeline



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Cell and Viral Therapy Pipeline

	Product	Indication	Organ Drug Designation	Fast Track or Breakthrough	Preclinical	Preliminary Meeting	IND/IDE	Phase 1	Phase 1/2	Licensee
Cell Therapy	Auto NK	Neuroblastoma								
	UD TGFβi NK	Neuroblastoma								
	UD TGFβi NK	Gliomas								
	Hapleuk	Hematologic malignancies and myelodysplasia								
	OTS NK	AML								
	UD TGFβi NK	Sarcoma								
	Universal NK	HSV								
	Universal NK	AML								
	CAR T	ALL								
	VSTs	Adenovirus								
	CAR NK	AML								
Tissue Engineering	Vascular Graft	Single ventricle cardiac anomalies		HUD, Breakthrough						GUNZE
Neurological Therapy	Northera (Droxidopa)	Dysautonomia in Menkes Disease Survivors								
Viral Therapy	HSV C134	Recurrent Malignant Glioma	Orphan							MUSTANGBIO
Radionuclide Therapy	Lutathera	CNS Tumors of Meningiomas								NOVARTIS
Intravitrial Therapy	Cerliponase alfa	Retinal Disease Progression	Orphan							BIOMARIN

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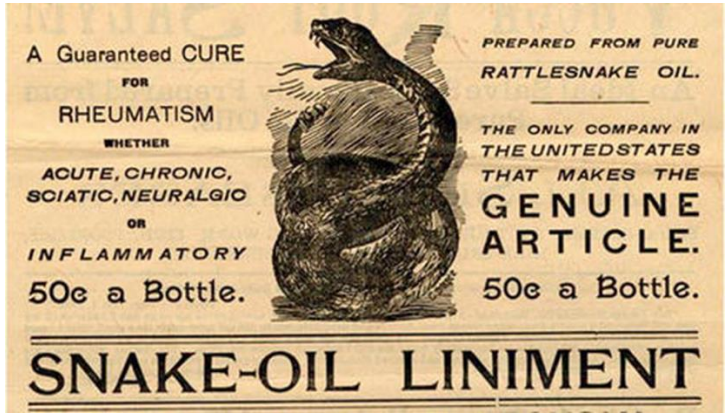
Investigational Drug

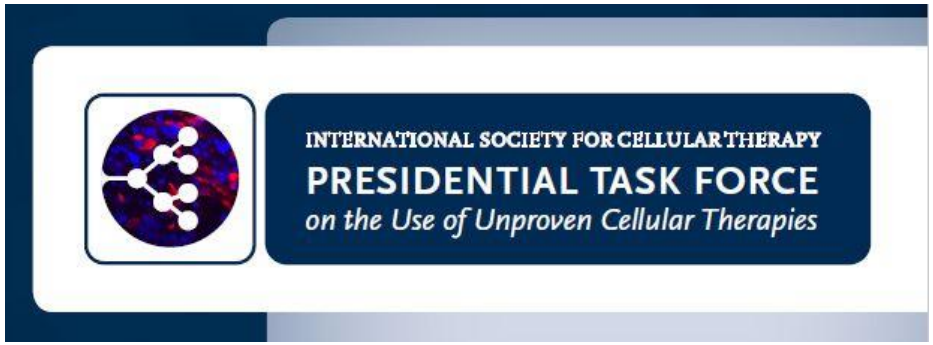
- An unapproved drug
- An FDA approved drug being used in a formal study for a new indication, route of administration, dosage level, subject population.

Pathway

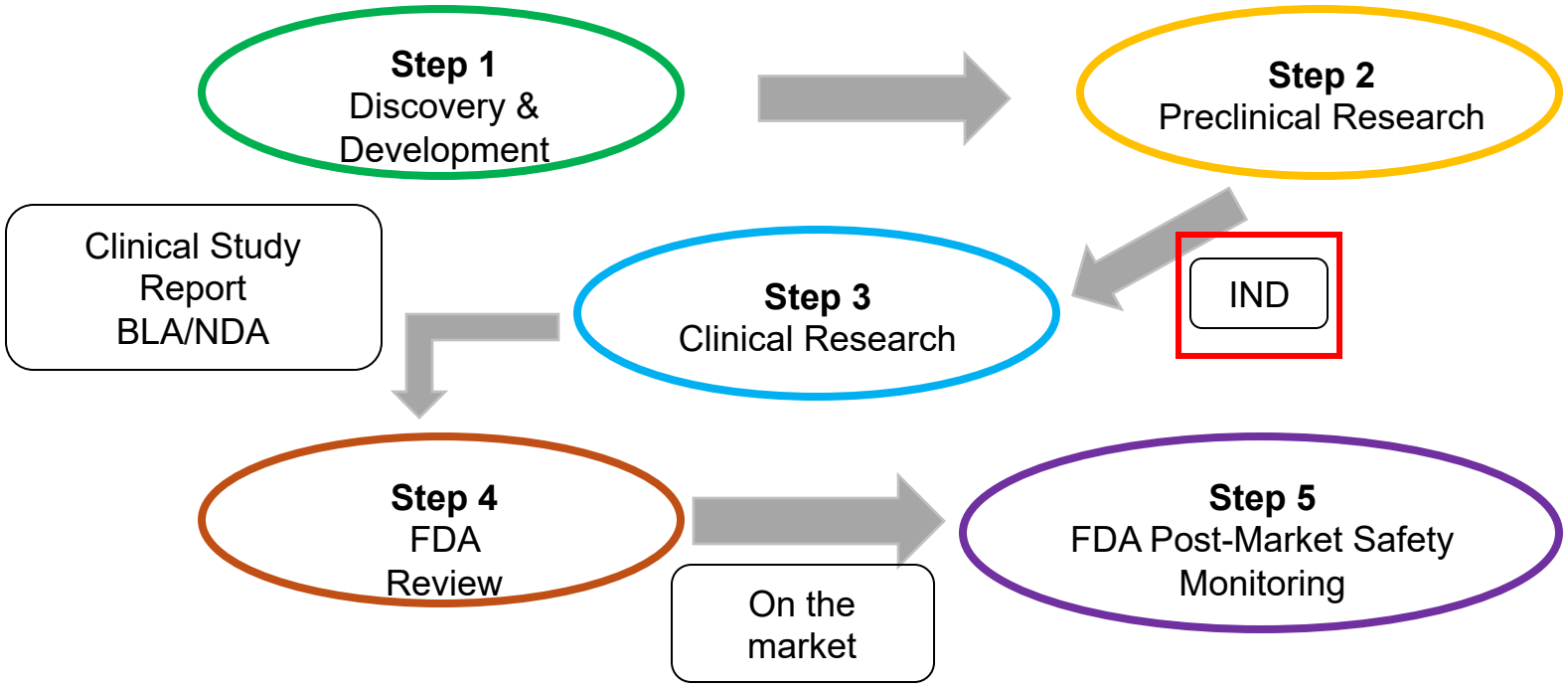
Federal Food, Drug, & Cosmetic Act 1938 (*FD&C Act*)

- Required safety testing before market
- Prohibit interstate commerce
- Established labeling rules





Drug Development



FDA Review Staff

- Comprised of several office
  - CDER, CBER
- Specialized Reviewers
  - Physicians, Pharmacologists, Biochemists

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What is an IND/IDE?

- Investigational New Drug
- Investigational Device Exemption
- Legal requirement
- *Originally* provided permission to ship investigational drugs/devices across state lines prior to market approval
- *Today* allows studies in humans of non-approved products under FDA and IRB approval
- FDA reviews for safety to unreasonable risk

What is an IND/IDE?

- It is a request for FDA authorization to administer an investigational new drug in humans

- Allows for the operation of a clinical trial to collect data on that drug and the drug's use

Purpose of the IND

- It affirms manufacturing, pharmacology, and toxicology for human testing
- Requires trials be performed in accordance with Good Clinical Practice (GCP)
- Provides FDA oversight

  - FDA's review focuses on safety of human subjects and ensuring that the studies will produce useful information to assess safety and efficacy of the test product.

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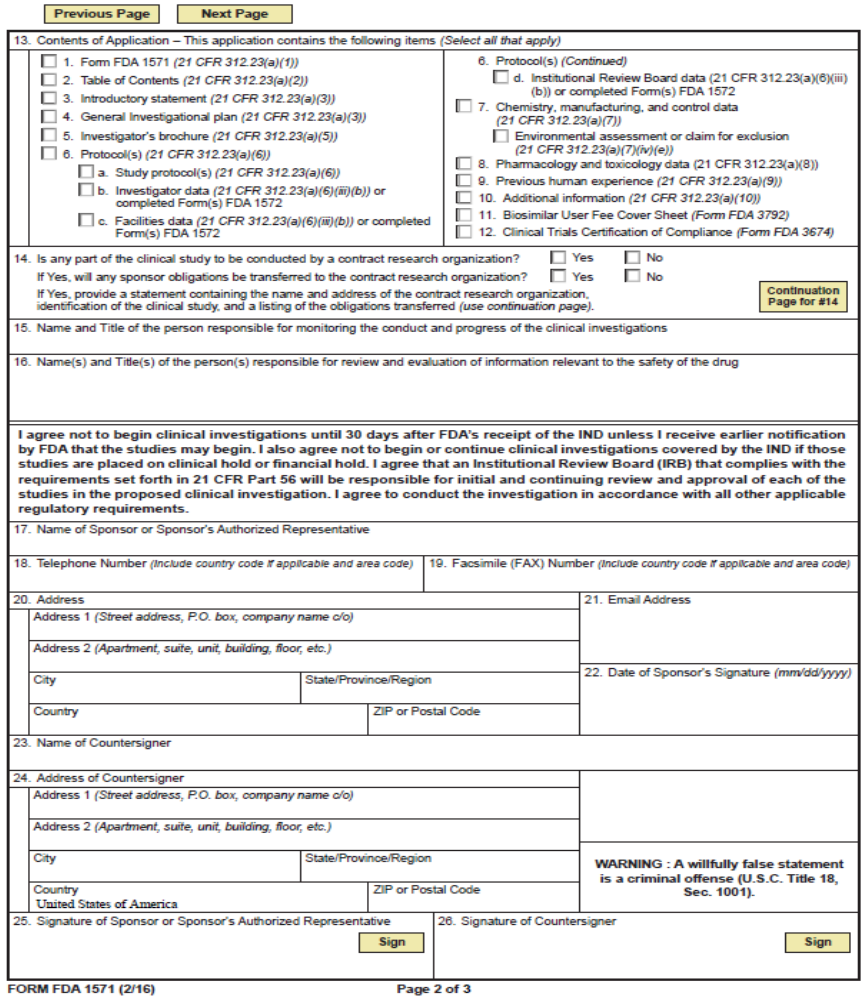
IND APPLICATION

1. FDA Forms 1571
2. Table of Contents
3. Introductory Statement
4. General Information
   - Intended indication and future development plan
5. Investigators' Brochure



Previous Page | Next Page

13. Contents of Application – This application contains the following items *(Select all that apply)*

- ☐ 1. Form FDA 1571 *(21 CFR 312.23(a)(1))*
- ☐ 2. Table of Contents *(21 CFR 312.23(a)(2))*
- ☐ 3. Introductory statement *(21 CFR 312.23(a)(3))*
- ☐ 4. General Investigational plan *(21 CFR 312.23(a)(3))*
- ☐ 5. Investigator's brochure *(21 CFR 312.23(a)(5))*
- ☐ 6. Protocol(s) *(21 CFR 312.23(a)(6))*
  - ☐ a. Study protocol(s) *(21 CFR 312.23(a)(6))*
  - ☐ b. Investigator data *(21 CFR 312.23(a)(6)(iii)(b))* or completed Form(s) FDA 1572
  - ☐ c. Facilities data *(21 CFR 312.23(a)(6)(iii)(b))* or completed Form(s) FDA 1572
- ☐ 6. Protocol(s) *(Continued)*
  - ☐ d. Institutional Review Board data (21 CFR 312.23(a)(6)(iii)(b)) or completed Form(s) FDA 1572
- ☐ 7. Chemistry, manufacturing, and control data *(21 CFR 312.23(a)(7))*
  - ☐ Environmental assessment or claim for exclusion *(21 CFR 312.23(a)(7)(iv)(e))*
- ☐ 8. Pharmacology and toxicology data (21 CFR 312.23(a)(8))
- ☐ 9. Previous human experience *(21 CFR 312.23(a)(9))*
- ☐ 10. Additional information *(21 CFR 312.23(a)(10))*
- ☐ 11. Biosimilar User Fee Cover Sheet *(Form FDA 3792)*
- ☐ 12. Clinical Trials Certification of Compliance *(Form FDA 3674)*

14. Is any part of the clinical study to be conducted by a contract research organization? ☐ Yes ☐ No
If Yes, will any sponsor obligations be transferred to the contract research organization? ☐ Yes ☐ No
If Yes, provide a statement containing the name and address of the contract research organization, identification of the clinical study, and a listing of the obligations transferred *(use continuation page)*. Continuation Page for #14

15. Name and Title of the person responsible for monitoring the conduct and progress of the clinical investigations

16. Name(s) and Title(s) of the person(s) responsible for review and evaluation of information relevant to the safety of the drug

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold or financial hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set forth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

17. Name of Sponsor or Sponsor's Authorized Representative

18. Telephone Number *(Include country code if applicable and area code)*

19. Facsimile (FAX) Number *(Include country code if applicable and area code)*

20. Address
- Address 1 *(Street address, P.O. box, company name c/o)*
- Address 2 *(Apartment, suite, unit, building, floor, etc.)*
- City | State/Province/Region
- Country | ZIP or Postal Code

21. Email Address

22. Date of Sponsor's Signature *(mm/dd/yyyy)*

23. Name of Countersigner

24. Address of Countersigner
- Address 1 *(Street address, P.O. box, company name c/o)*
- Address 2 *(Apartment, suite, unit, building, floor, etc.)*
- City | State/Province/Region
- Country: United States of America | ZIP or Postal Code

WARNING : A willfully false statement is a criminal offense (U.S.C. Title 18, Sec. 1001).

25. Signature of Sponsor or Sponsor's Authorized Representative — Sign

26. Signature of Countersigner — Sign

FORM FDA 1571 (2/16) Page 2 of 3

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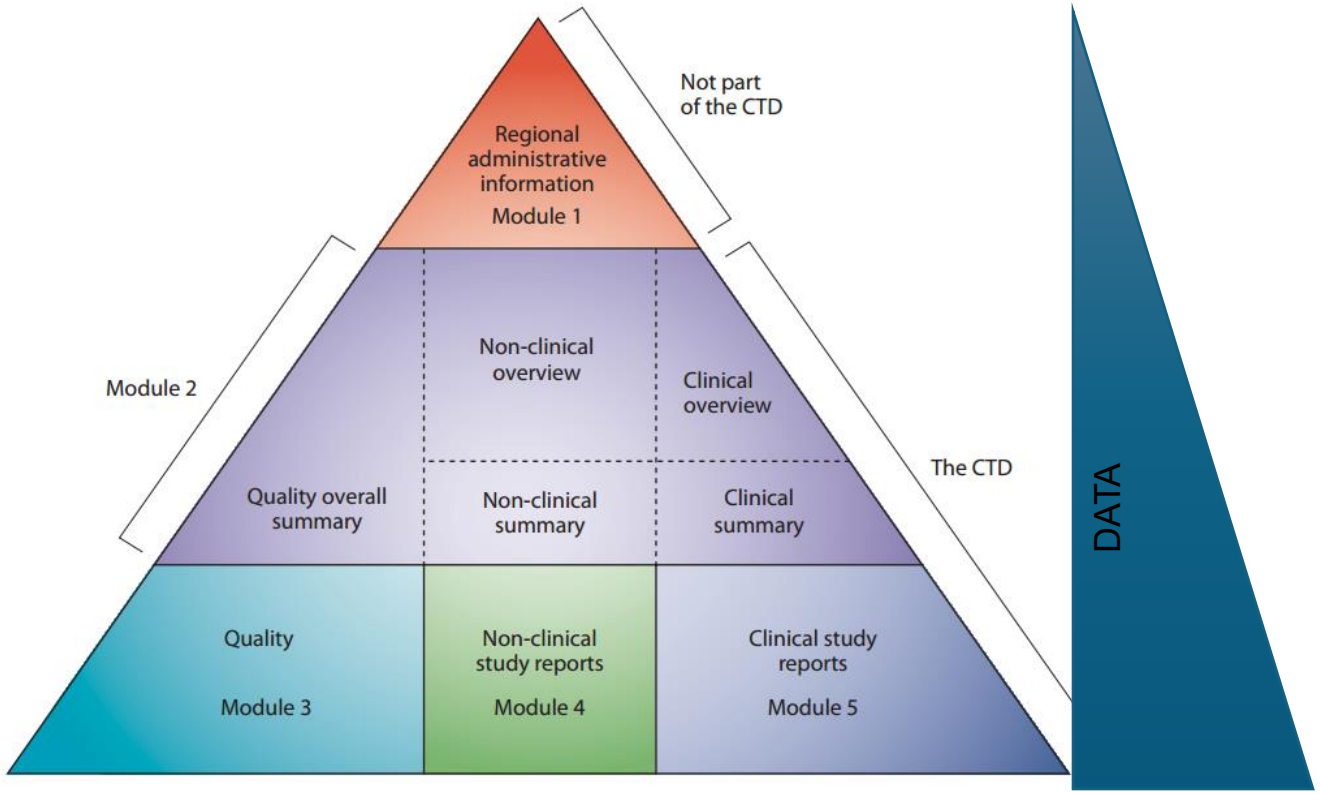
IND APPLICATION

6. Protocol
7. Chemistry, Manufacturing, and Control Data (CMC)
8. Pharmacology and Toxicology Information
9. Previous Human Experience
10. Additional Information

COMMON TECHNICAL DOCUMENT



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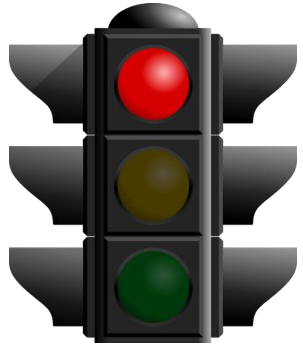
NCH Submits IND

- Dr. Mendell Submits IND to FDA
- Gene Therapy for Duchenne Muscular Dystrophy

FDA Review of IND

- FDA will issue decision within **30 days** following receipt of IND
- "May proceed" notice or "no news is good news," your IND is now Active
  - *INDs are not "approved"*
  - *IDEs are approved*
- "Clinical Hold" – order issued by FDA

to delay or suspending clinical investigation



Sponsor and Investigator Responsibilities

- Select qualified investigators
- Ensure proper monitoring, recording and reporting
  - FDA annual report, protocol updates, safety reports, other amendments
- Ensure FDA and all participating investigators are promptly informed of significant new adverse effects or risks

IND Maintenance

- You have an active IND, you have to maintain it

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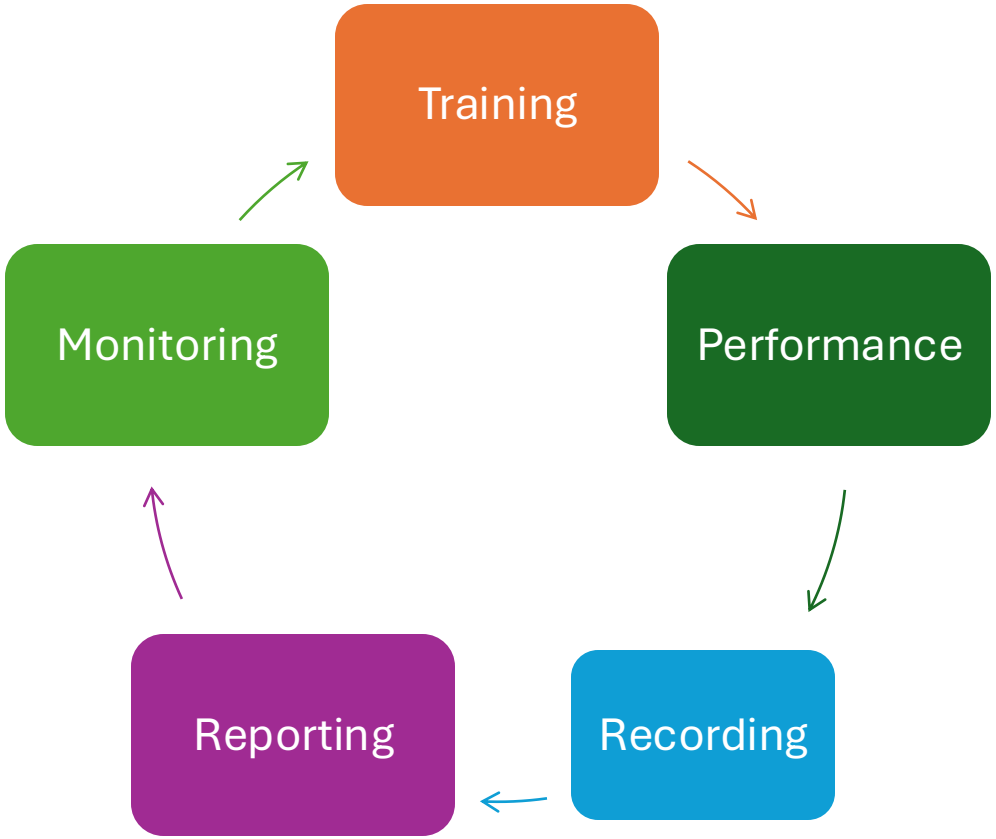
IND Maintenance



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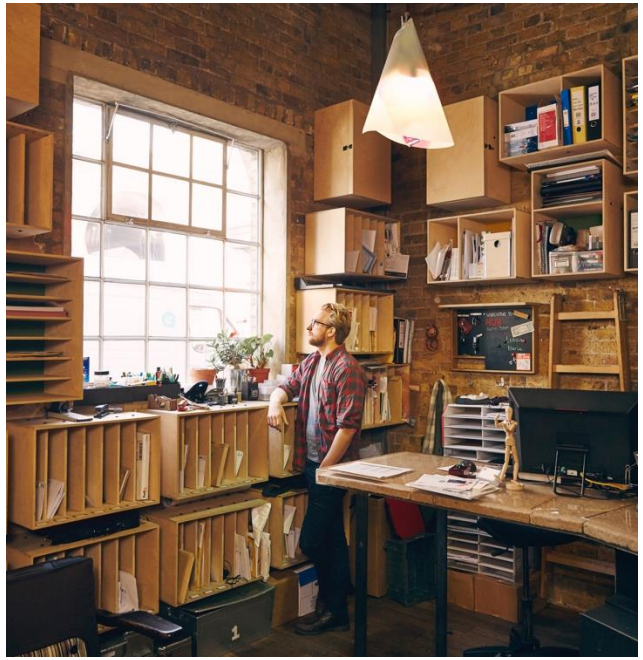
IND Maintenance

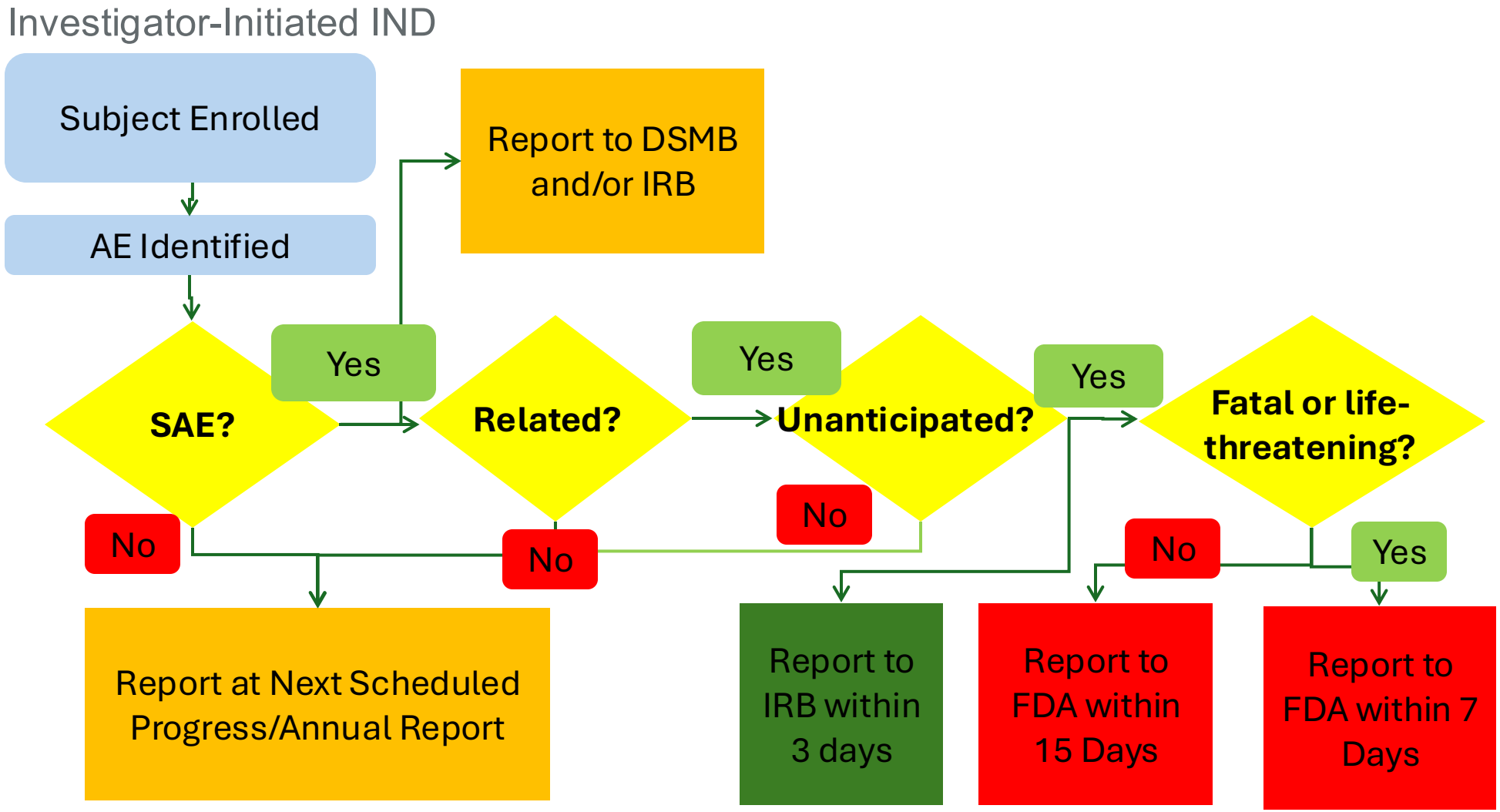
- Record Keeping
  - Disposition of the drug/device
  - Patient records (i.e. histories, ICF, diaries)



IND Maintenance

- Documentation
  - Proof that the investigational plan/protocol was adhered to
  - Proof of FDA and IRB compliance
  - In the Event of an Audit
    - Evidence of study performance
    - Who, what, when, where, why and how

Safety Reports



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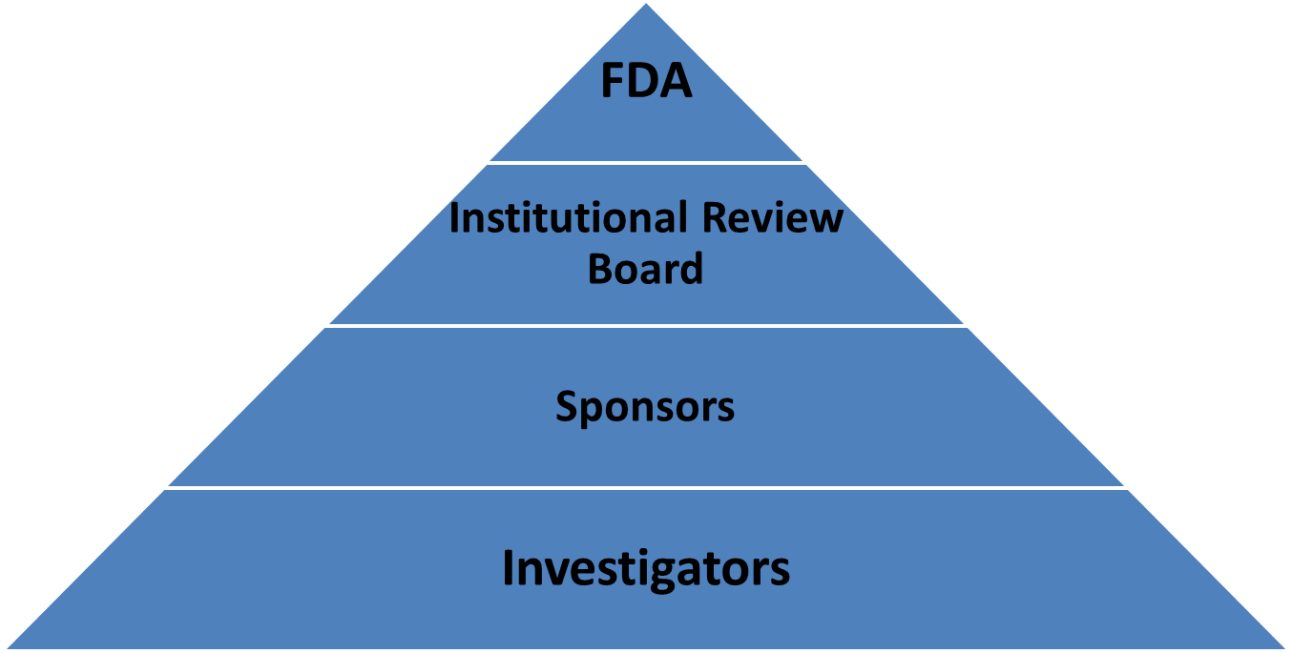
IND Annual Reports

(21 CFR 312.33)

- Brief description of study results
  - Most frequent and most serious adverse events
  - DSMB reports
- Updated information on:
  - General investigational plan
  - Investigator's brochure (if applicable)
  - Significant protocol updates
  - Foreign marketing developments
- Log of Outstanding Business with FDA

Reporting Hiearchy



IND Transferred to Sarepta

- IND was eventually transferred to Sarepta
- Sarepta was able to obtain FDA approval for marketing.

Marketing

- New Drug Application/Biologic License Application
- Approval Time: 6 to 10 Months

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Sarepta Elevidys

- FDA Approval
  - Full Approval based on Data from a Phase 3 EMBARK Clinical Trial
- Indications: Only approved gene therapy in patients with DMD

Post Market

- Continued Monitoring
- Label Changes
  - New Adverse Events
  - New INDs for New Indications
- Patents
- Generic Drugs

Sarepta and Elevidys

- Approval for non-ambulatory people under accelerated approval
- Based on a marker that is considered reasonably likely to predict a clinical benefit.
- Clinical trials showed an increase in a marker called ELEVIDYS microdystrophin

ct us

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The Office of Research Regulatory Affairs (ORRA)

Moving discoveries from bench to the best outcomes for children everywhere.

The Abigail Wexner Research Institute at Nationwide Children's Hospital enhances the health of children by engaging in high quality, cutting-edge research that results in better ways to prevent, screen for, diagnose and treat pediatric illness. With the guidance and support of the Office of Research Regulatory Affairs (ORRA) investigators, programs and medical faculty and staff are equipped to navigate the complex regulatory landscape, develop regulatory strategy and move new ideas into clinical trials.

The ORRA also services both Nationwide Children's Hospital and the Abigail Wexner Research Institute by:

- Providing guidance on emergent regulatory issues,
- Spearheading data quality and integrity programs for preclinical research, and
- Advising partners such as the Institutional Review Board, Institutional Animal Care and Use Committee, Legal Services, Office of Research Compliance and Integrity, Clinical Research

Contact Us

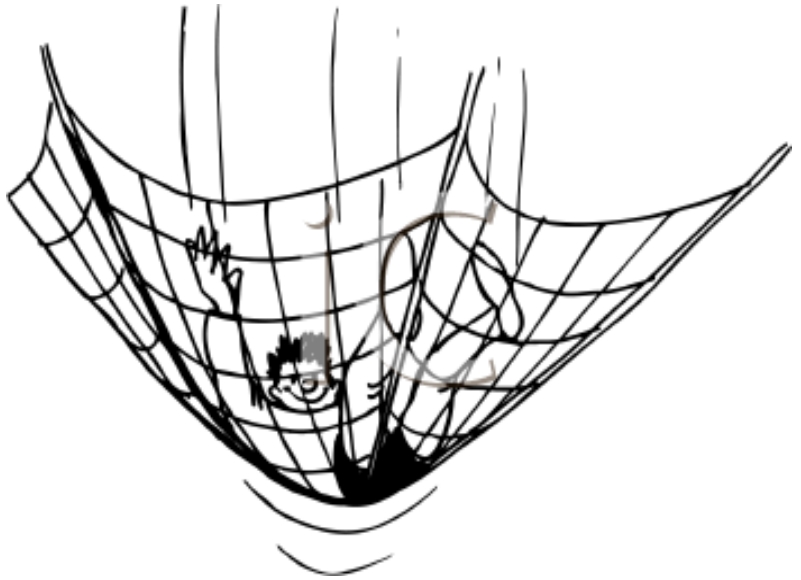
Kevin Bosse, PhD, RAC
Director, Office of Research Regulatory Affairs

Sue K. Marting, MBA
Program Coordinator, Office of Research Regulatory Affairs

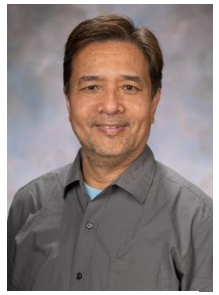
(614) 722-6962

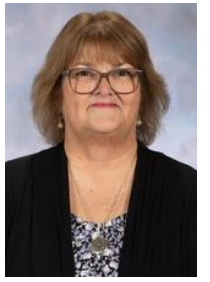
(614) 355-1593

Email Us







NATIONWIDE CHILDREN'S
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Contact Us

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  - Kevin.Bosse@NationwideChildrens.org
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- WWW.nationwidechildrens.org/ddd
- https://nationwidechildrens.sharepoint.com/sites/A10071/ORRA.

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Thank You

Questions?

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When your child needs a hospital, everything matters.℠

Protocol Development

April Green, MACPR, CCRC

Clinical and Translational Science Institute,

The Ohio State University

Protocol Development

Begin with the end in mind

Protocol Development

- Grant Application vs Research Protocol
  - Grant Application- scientific outline that is directed to scientific experts. May include multiple aims.
  - Research Protocol - is a technical and specific manual for a single project. *It guides the IRB reviews and the study execution.*

Protocol Development – Aims and Objectives

First determine:

- The research aims and objectives
  - **Aims:** overall intention or purpose for the research. Signals where you hope to be at the end. *Somewhat Broad*
  - **Objectives:** Provides the specific steps you will take to get to the end. *Very Specific, short-term, and measurable.*

Protocol Development – Research Type

Begin with determining:

- The research aims and objectives
- The type of research needed to obtain the data

Retrospective

- Chart Review
- Looks at data that already exists
- Exposures to risk or protection factors effect an outcome
- Often done without consent

Prospective

- Looks at future outcome
- Patients are consented and enrolled in the study

Prospective Types

- Observational
- Interventional
- Non-Interventional
- Therapeutic
- Non-Therapeutic

Protocol Development - Prospective

Begin with determining:

- The research objectives/aims
- The type of research needed to obtain the data

- **Observational –** A study that documents how a person reacts when they're confronted with a choice or situation. "Behavior"
- **Interventional Research** – A study where at least some of the participants are assigned to receive one or more intervention/treatment (drugs, device, biologics, education/training, diet, exercise, etc.)
- **Non-Interventional Research** – A study where no participants receive an intervention/treatment (Blood draws, observational, etc.)
- **Therapeutic Research** – A study that enrolls patients and provides specific treatment to patients to study the treatment's impact on the disease. Looking at cause and effect.
- **Non-Therapeutic Research** – A study designed to collect generalizable knowledge, that may benefit subjects with a similar condition in the future. No likelihood or intent of producing a diagnostic, preventive or therapeutic benefit to the current subjects.

Protocol Development – Phases/Stages

Begin with determining:

- The research objectives/aims
- The type of research needed to get the needed information
- Drug phase/device stage if applicable

Pharmaceuticals			Medical Devices		
Phase	**Subjects**	**Purpose**	**Stage**	**Subjects**	**Purpose**
0 Pilot / Exploratory	10 - 15	• Test a very small (subtherapeutic) dose of a new drug to study its effects & how it works in the human body. • Not all drugs will undergo this phase.	Pilot / Early Feasibility / First-in-Human	10 - 30	• Small study to collect preliminary safety & device performance data in humans. • Guides device modifications &/or future study design.
I Safety & Toxicity	10 - 100	• True first-in-human study to test safety & toxicity, usually in healthy humans.	Traditional Feasibility	20 - 30	• Assess safety & efficacy of the near-final or final device design in patients. • Guides the design of the pivotal study.
II Safety & Efficacy	100's	• Assess efficacy & safety in patients.			
III Clinical Effectiveness	100's – 1000's	• Confirm clinical efficacy, safety & adverse events. • Compare the new drug to standard care or a commonly used drug.	Pivotal	100's	• Large study to confirm clinical efficacy, safety & risks. • Statistically driven.
IV Post-Market / Surveillance	1000's	• Monitor long term effectiveness & safety in the general population.	Post-Market	1000's	• Monitor long term effectiveness, safety & usage in the general population.

Image obtained through GenesisResearchServices https://genesisresearchservices.com/clinical-trials-medical-device-trials/

Protocol Development – Biostatistician

Then contact your biostatistician to help with trial design:

- Randomized
- Blinding/Open Label
- Parallel/Cross-over
- Stopping Requirements
- Target Accrual Numbers
- Statistical Significance

email: biostatistics@osumc.edu

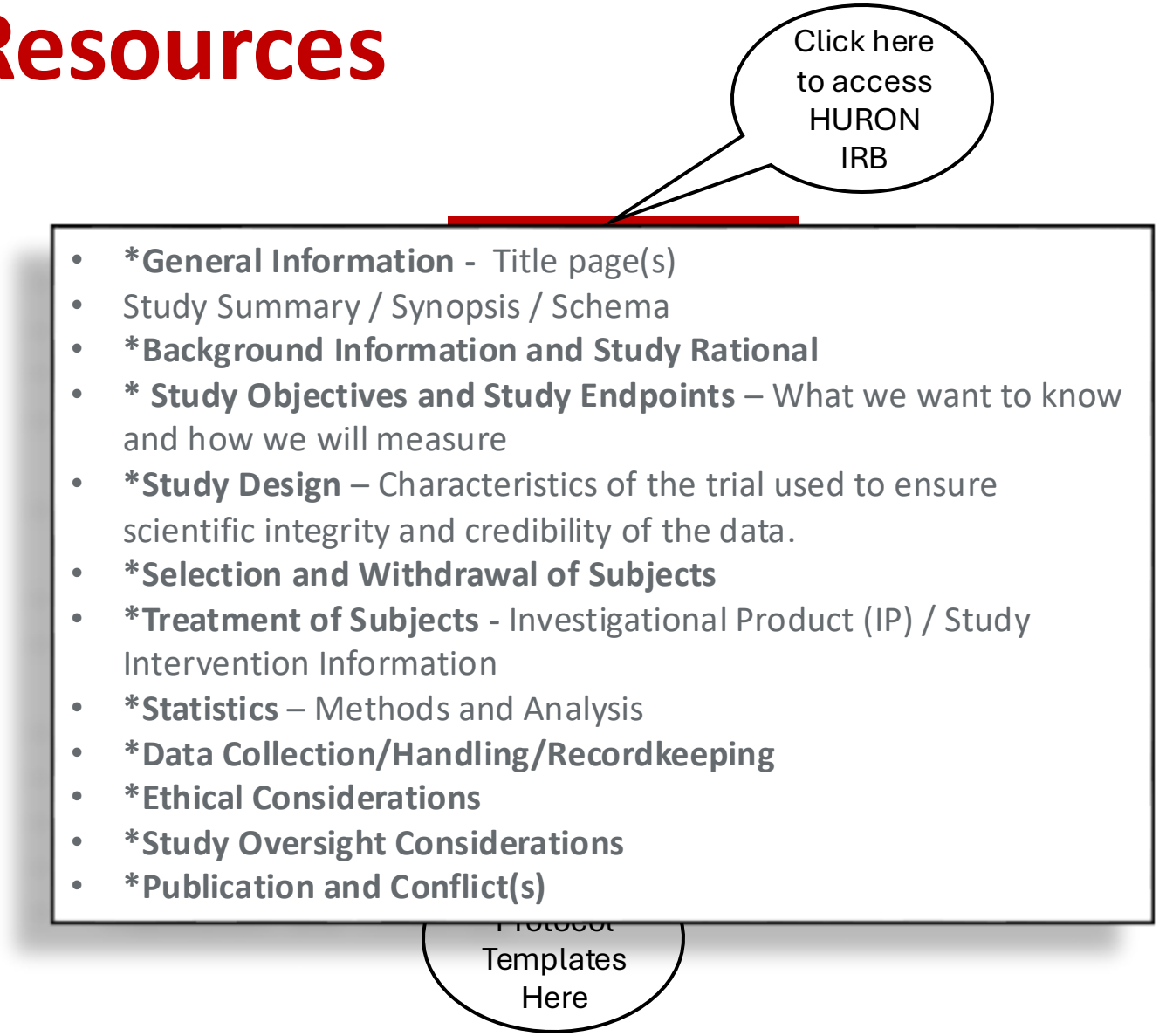
webpage: https://medicine.osu.edu/departments/biostatistics

Protocol Writing - Resources

Begin writing your protocol…

Helpful Resources:

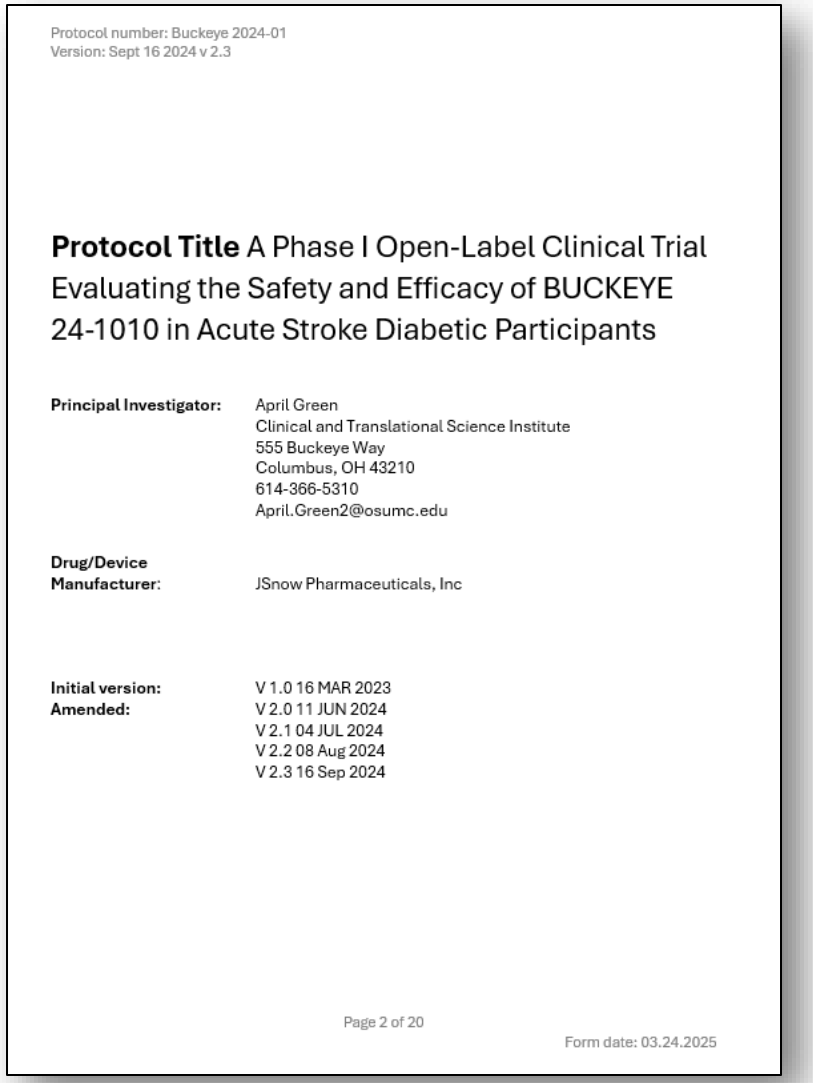
- ORRP Protocol Template – HURON – IRB
- NIH e-Protocol Writing Tool – *NIH*
- G.500 PHS Human Subjects and Clinical Trials Information – NIH Grant Application
- ICH GCP E6 – *Section 6 Clinical Trial Protocol*



Protocol Development – General Information

General Information

- Protocol Number
- Protocol Title
- Principal Investigator or Protocol Signer
- Sponsor(s)
- Other Identifiable Numbers (NCT, IRB, etc.)
- Sponsor's Medical Monitors (Experts)
- Central Laboratories
- Amendment/Version Date



Protocol number: Buckeye 2024-01
Version: Sept 16 2024 v 2.3

Protocol Title A Phase I Open-Label Clinical Trial Evaluating the Safety and Efficacy of BUCKEYE 24-1010 in Acute Stroke Diabetic Participants

Principal Investigator: April Green
Clinical and Translational Science Institute
555 Buckeye Way
Columbus, OH 43210
614-366-5310
April.Green2@osumc.edu

Drug/Device Manufacturer: JSnow Pharmaceuticals, Inc

Initial version: V 1.0 16 MAR 2023
Amended: V 2.0 11 JUN 2024
V 2.1 04 JUL 2024
V 2.2 08 Aug 2024
V 2.3 16 Sep 2024

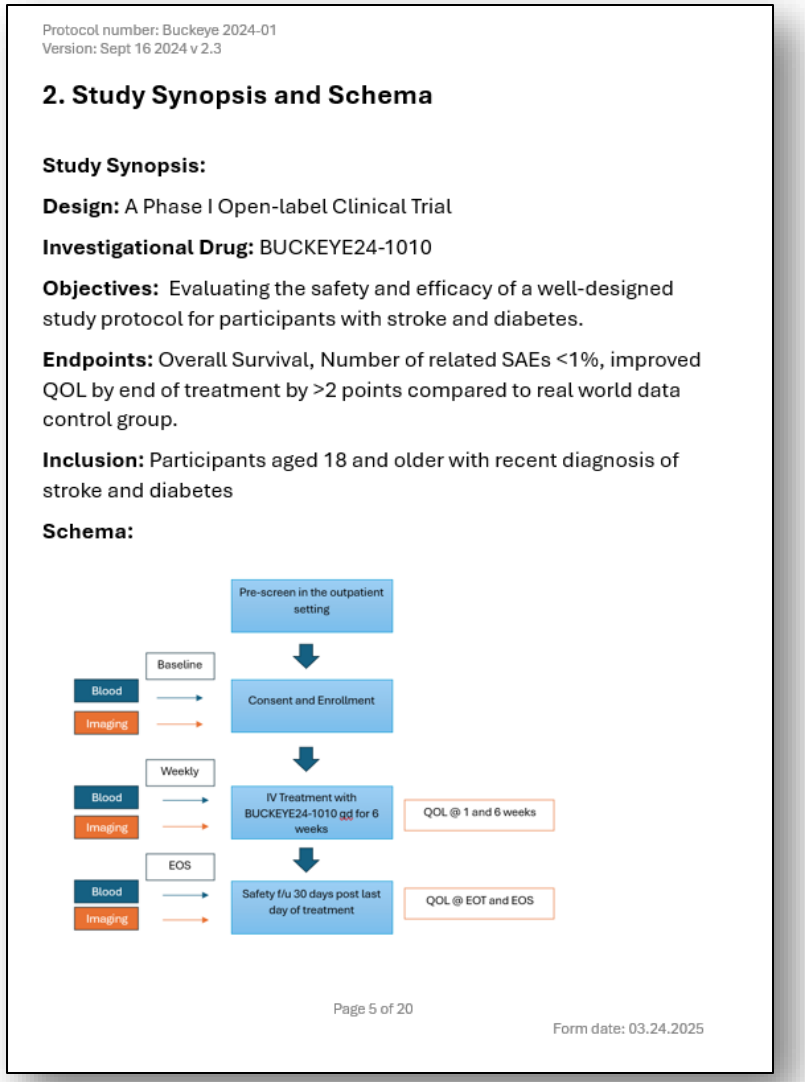
Page 2 of 20

Form date: 03.24.2025

Protocol Development – Summary/Schema

Study Summary/Synopsis/Schema

- Brief overview/outline of the study design and procedures.
- Schema Flowchart is a visual representation of the study procedures



Protocol number: Buckeye 2024-01
Version: Sept 16 2024 v 2.3

2. Study Synopsis and Schema

Study Synopsis:

Design: A Phase I Open-label Clinical Trial

Investigational Drug: BUCKEYE24-1010

Objectives: Evaluating the safety and efficacy of a well-designed study protocol for participants with stroke and diabetes.

Endpoints: Overall Survival, Number of related SAEs <1%, improved QOL by end of treatment by >2 points compared to real world data control group.

Inclusion: Participants aged 18 and older with recent diagnosis of stroke and diabetes

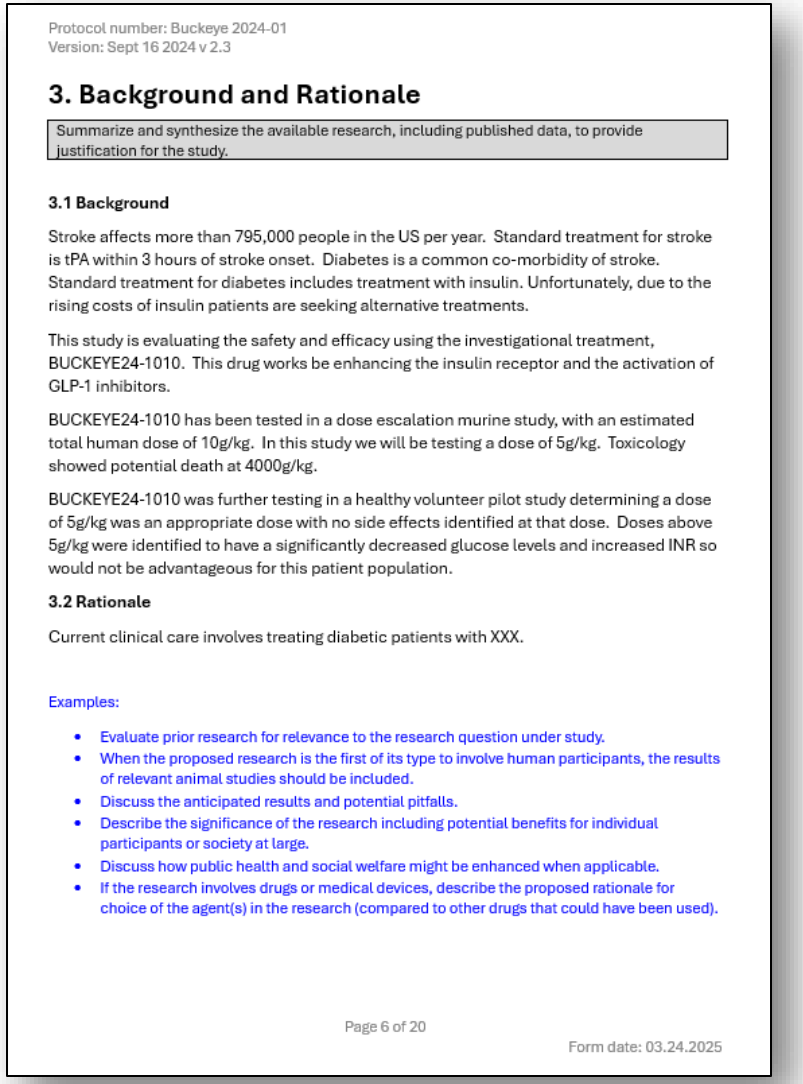
Schema:

Form date: 03.24.2025

Protocol Development – Background/Rationale

Background Information and Rationale

- Gives background of disease, interventions and a review of the relevant clinical and preclinical studies
- Rationale explains why we want to use the intervention in the intended patient population and justifies the use the intervention in the disease. Typically picks up where previous research and standard of care leaves off.



Protocol number: Buckeye 2024-01
Version: Sept 16 2024 v 2.3

3. Background and Rationale

Summarize and synthesize the available research, including published data, to provide justification for the study.

3.1 Background

Stroke affects more than 795,000 people in the US per year. Standard treatment for stroke is tPA within 3 hours of stroke onset. Diabetes is a common co-morbidity of stroke. Standard treatment for diabetes includes treatment with insulin. Unfortunately, due to the rising costs of insulin patients are seeking alternative treatments.

This study is evaluating the safety and efficacy using the investigational treatment, BUCKEYE24-1010. This drug works be enhancing the insulin receptor and the activation of GLP-1 inhibitors.

BUCKEYE24-1010 has been tested in a dose escalation murine study, with an estimated total human dose of 10g/kg. In this study we will be testing a dose of 5g/kg. Toxicology showed potential death at 4000g/kg.

BUCKEYE24-1010 was further testing in a healthy volunteer pilot study determining a dose of 5g/kg was an appropriate dose with no side effects identified at that dose. Doses above 5g/kg were identified to have a significantly decreased glucose levels and increased INR so would not be advantageous for this patient population.

3.2 Rationale

Current clinical care involves treating diabetic patients with XXX.

Examples:

- Evaluate prior research for relevance to the research question under study.
- When the proposed research is the first of its type to involve human participants, the results of relevant animal studies should be included.
- Discuss the anticipated results and potential pitfalls.
- Describe the significance of the research including potential benefits for individual participants or society at large.
- Discuss how public health and social welfare might be enhanced when applicable.
- If the research involves drugs or medical devices, describe the proposed rationale for choice of the agent(s) in the research (compared to other drugs that could have been used).

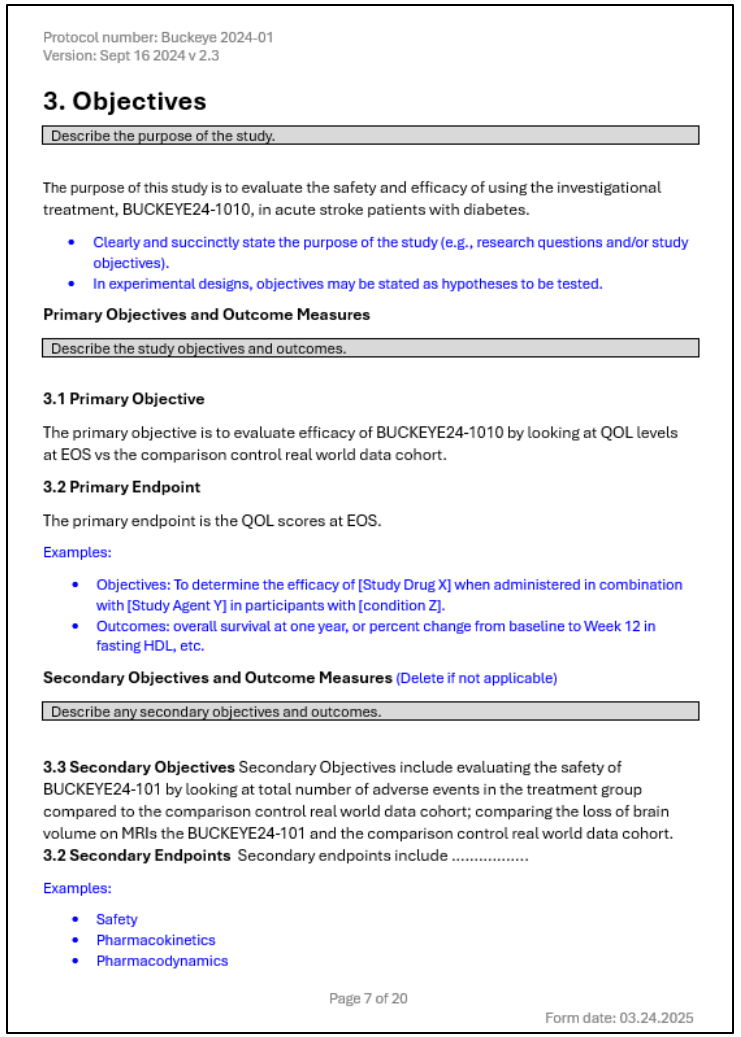
Page 6 of 20

Form date: 03.24.2025

Protocol Development – Objectives and Endpoints

Study Objectives and Endpoints

- Objectives are the specific steps taken to answer our questions and reach our aims.
  - Primary, Secondary, and potentially Exploratory
  - Follow a SMART approach – specific, measurable, achievable, realistic and time-defined.
  - Maximum Tolerable Dose, Safety, Efficacy
- Endpoints are the quantitative measurements which are used to answer the objectives.
  - Primary, Secondary and potentially Exploratory
  - Overall Survival, Patient Reported Outcomes, Time to Treatment Failure



Protocol number: Buckeye 2024-01
Version: Sept 16 2024 v 2.3

3. Objectives

Describe the purpose of the study.

The purpose of this study is to evaluate the safety and efficacy of using the investigational treatment, BUCKEYE24-1010, in acute stroke patients with diabetes.

- Clearly and succinctly state the purpose of the study (e.g., research questions and/or study objectives).
- In experimental designs, objectives may be stated as hypotheses to be tested.

Primary Objectives and Outcome Measures

Describe the study objectives and outcomes.

3.1 Primary Objective

The primary objective is to evaluate efficacy of BUCKEYE24-1010 by looking at QOL levels at EOS vs the comparison control real world data cohort.

3.2 Primary Endpoint

The primary endpoint is the QOL scores at EOS.

Examples:

- Objectives: To determine the efficacy of [Study Drug X] when administered in combination with [Study Agent Y] in participants with [condition Z].
- Outcomes: overall survival at one year, or percent change from baseline to Week 12 in fasting HDL, etc.

Secondary Objectives and Outcome Measures (Delete if not applicable)

Describe any secondary objectives and outcomes.

3.3 Secondary Objectives Secondary Objectives include evaluating the safety of BUCKEYE24-101 by looking at total number of adverse events in the treatment group compared to the comparison control real world data cohort; comparing the loss of brain volume on MRIs the BUCKEYE24-101 and the comparison control real world data cohort.
3.2 Secondary Endpoints Secondary endpoints include .....

Examples:

- Safety
- Pharmacokinetics
- Pharmacodynamics

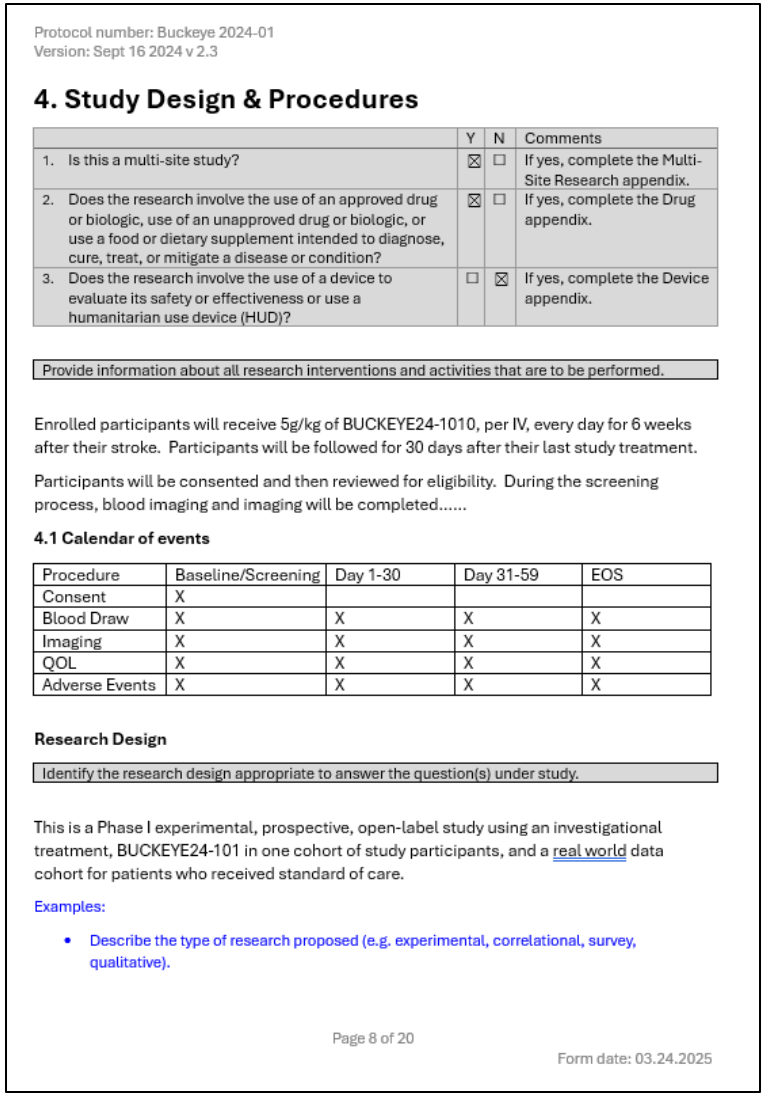
Page 7 of 20

Form date: 03.24.2025

Protocol Development – Study Design

Study Design

- Blinding
- Randomization
- Multi-Center
- Study Assessments and Procedures
  - Typically includes a calendar
  - Don’t forget time windows!
- Duration of Participation



Protocol number: Buckeye 2024-01
Version: Sept 16 2024 v 2.3

4. Study Design & Procedures

	Y	N	Comments
1. Is this a multi-site study?	☒	☐	If yes, complete the Multi-Site Research appendix.
2. Does the research involve the use of an approved drug or biologic, use of an unapproved drug or biologic, or use a food or dietary supplement intended to diagnose, cure, treat, or mitigate a disease or condition?	☒	☐	If yes, complete the Drug appendix.
3. Does the research involve the use of a device to evaluate its safety or effectiveness or use a humanitarian use device (HUD)?	☐	☒	If yes, complete the Device appendix.

Provide information about all research interventions and activities that are to be performed.

Enrolled participants will receive 5g/kg of BUCKEYE24-1010, per IV, every day for 6 weeks after their stroke. Participants will be followed for 30 days after their last study treatment.

Participants will be consented and then reviewed for eligibility. During the screening process, blood imaging and imaging will be completed.....

4.1 Calendar of events

Procedure	Baseline/Screening	Day 1-30	Day 31-59	EOS
Consent	X			
Blood Draw	X	X	X	X
Imaging	X	X	X	X
QOL	X	X	X	X
Adverse Events	X	X	X	X

Research Design

Identify the research design appropriate to answer the question(s) under study.

This is a Phase I experimental, prospective, open-label study using an investigational treatment, BUCKEYE24-101 in one cohort of study participants, and a real world data cohort for patients who received standard of care.

Examples:

- Describe the type of research proposed (e.g. experimental, correlational, survey, qualitative).

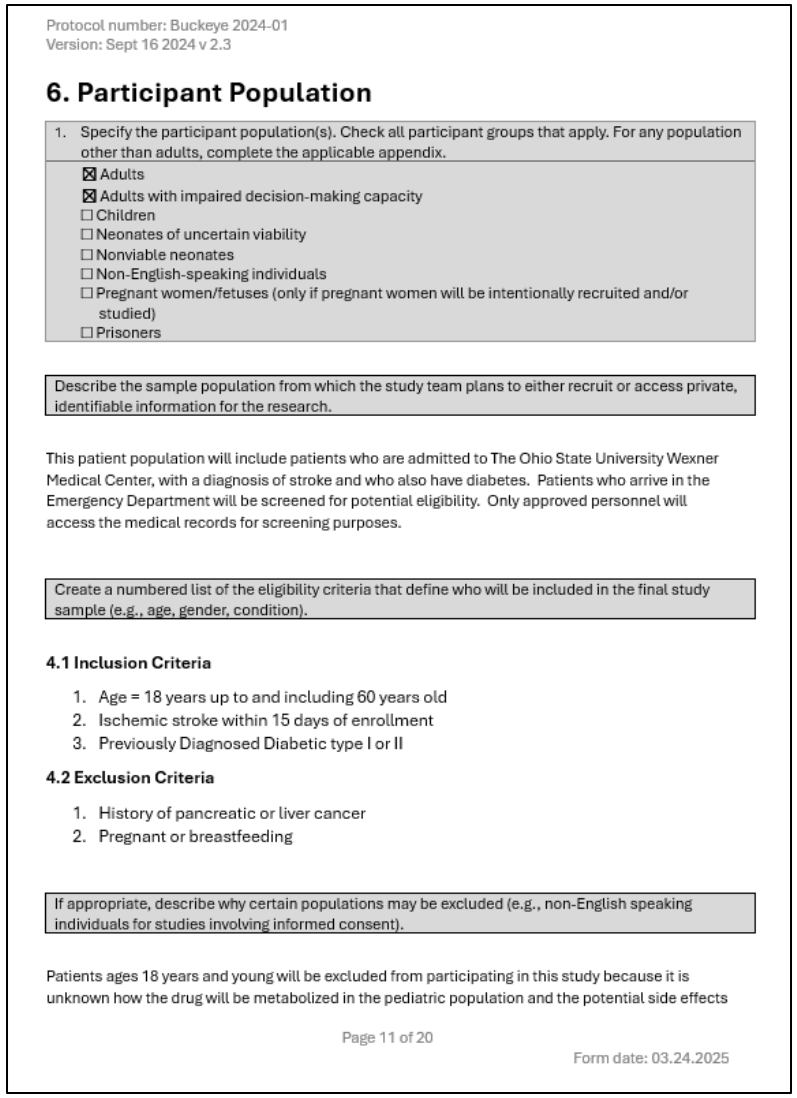
Page 8 of 20

Form date: 03.24.2025

Protocol Development – Participant Selection/Withdraw

Subject Selection/Subject Withdraws

- Inclusion/Exclusion Criteria
- Recruitment
  - CTSI Recruitment Team
    - Social Media
    - Study Search
    - Research Match
    - ClinicalTrials.gov
- Withdraw
  - If a subject withdraws and treatment stopping criteria



Protocol number: Buckeye 2024-01
Version: Sept 16 2024 v 2.3

6. Participant Population

1. Specify the participant population(s). Check all participant groups that apply. For any population other than adults, complete the applicable appendix.

☒ Adults
☒ Adults with impaired decision-making capacity
☐ Children
☐ Neonates of uncertain viability
☐ Nonviable neonates
☐ Non-English-speaking individuals
☐ Pregnant women/fetuses (only if pregnant women will be intentionally recruited and/or studied)
☐ Prisoners

Describe the sample population from which the study team plans to either recruit or access private, identifiable information for the research.

This patient population will include patients who are admitted to The Ohio State University Wexner Medical Center, with a diagnosis of stroke and who also have diabetes. Patients who arrive in the Emergency Department will be screened for potential eligibility. Only approved personnel will access the medical records for screening purposes.

Create a numbered list of the eligibility criteria that define who will be included in the final study sample (e.g., age, gender, condition).

4.1 Inclusion Criteria

1. Age = 18 years up to and including 60 years old
2. Ischemic stroke within 15 days of enrollment
3. Previously Diagnosed Diabetic type I or II

4.2 Exclusion Criteria

1. History of pancreatic or liver cancer
2. Pregnant or breastfeeding

If appropriate, describe why certain populations may be excluded (e.g., non-English speaking individuals for studies involving informed consent).

Patients ages 18 years and young will be excluded from participating in this study because it is unknown how the drug will be metabolized in the pediatric population and the potential side effects

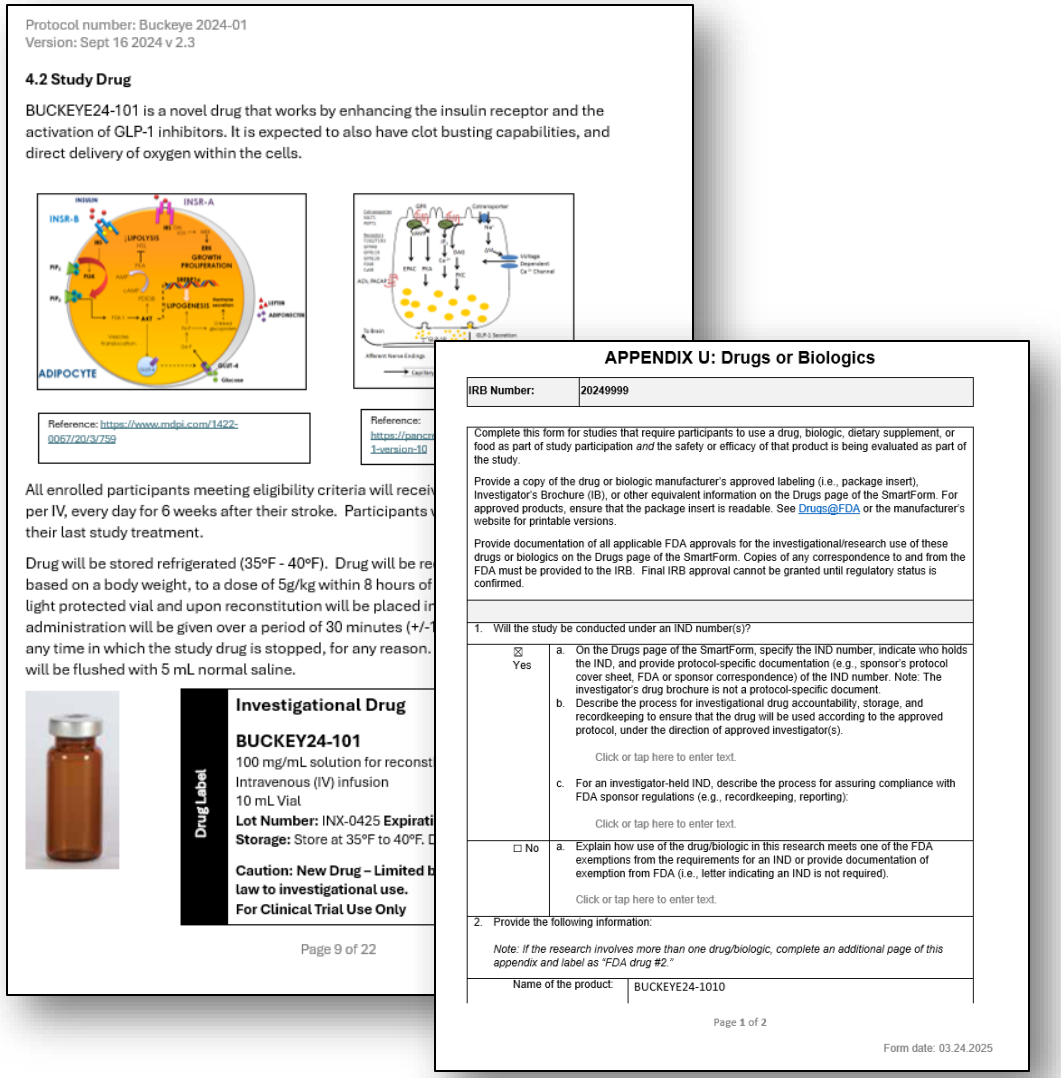
Page 11 of 20

Form date: 03.24.2025

Protocol Development – Interventions

Subject Interventions

- Includes a description of the Investigational Product/Intervention (usually pulled from Investigator Brochure, Package Insert, labelling materials and/or material safety data sheets)
- Dosing and administration
- Preparation/Handling/Storage/ Accountability
- Subject Safety – Adverse Events (AEs), Serious Adverse Events (SAEs), Dose Limiting Toxicities, Dose Delays and Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs), Protocol Deviations.
- Treatment/Study Stopping Criteria



Protocol number: Buckeye 2024-01
Version: Sept 16 2024 v 2.3

4.2 Study Drug

BUCKEYE24-101 is a novel drug that works by enhancing the insulin receptor and the activation of GLP-1 inhibitors. It is expected to also have clot busting capabilities, and direct delivery of oxygen within the cells.

Reference: https://www.mdpi.com/1422-0067/20/3/759

All enrolled participants meeting eligibility criteria will receiv
per IV, every day for 6 weeks after their stroke. Participants v
their last study treatment.

Drug will be stored refrigerated (35°F - 40°F). Drug will be re
based on a body weight, to a dose of 5g/kg within 8 hours of
light protected vial and upon reconstitution will be placed in
administration will be given over a period of 30 minutes (+/-
any time in which the study drug is stopped, for any reason.
will be flushed with 5 mL normal saline.

Drug Label
Investigational Drug
BUCKEY24-101
100 mg/mL solution for reconst
Intravenous (IV) infusion
10 mL Vial
Lot Number: INX-0425 **Expirati**
Storage: Store at 35°F to 40°F. D
Caution: New Drug – Limited b
law to investigational use.
For Clinical Trial Use Only

Page 9 of 22

APPENDIX U: Drugs or Biologics

IRB Number:	20249999

Complete this form for studies that require participants to use a drug, biologic, dietary supplement, or food as part of study participation *and* the safety or efficacy of that product is being evaluated as part of the study.

Provide a copy of the drug or biologic manufacturer's approved labeling (i.e., package insert), Investigator's Brochure (IB), or other equivalent information on the Drugs page of the SmartForm. For approved products, ensure that the package insert is readable. See Drugs@FDA or the manufacturer's website for printable versions.

Provide documentation of all applicable FDA approvals for the investigational/research use of these drugs or biologics on the Drugs page of the SmartForm. Copies of any correspondence to and from the FDA must be provided to the IRB. Final IRB approval cannot be granted until regulatory status is confirmed.

1. Will the study be conducted under an IND number(s)?

☒ Yes	a. On the Drugs page of the SmartForm, specify the IND number, indicate who holds the IND, and provide protocol-specific documentation (e.g., sponsor's protocol cover sheet, FDA or sponsor correspondence) of the IND number. Note: The investigator's drug brochure is not a protocol-specific document. b. Describe the process for investigational drug accountability, storage, and recordkeeping to ensure that the drug will be used according to the approved protocol, under the direction of approved investigator(s). Click or tap here to enter text. c. For an investigator-held IND, describe the process for assuring compliance with FDA sponsor regulations (e.g., recordkeeping, reporting): Click or tap here to enter text.
☐ No	a. Explain how use of the drug/biologic in this research meets one of the FDA exemptions from the requirements for an IND or provide documentation of exemption from FDA (i.e., letter indicating an IND is not required). Click or tap here to enter text.

2. Provide the following information:

Note: If the research involves more than one drug/biologic, complete an additional page of this appendix and label as "FDA drug #2."

Name of the product:	BUCKEYE24-1010

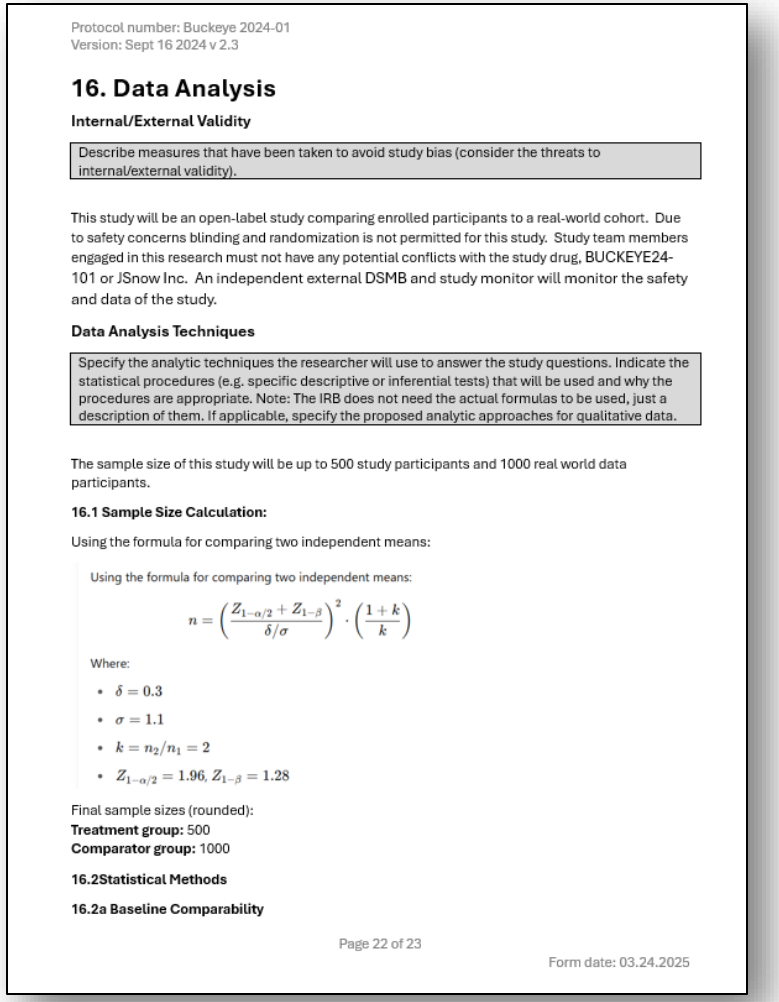
Page 1 of 2

Form date: 03.24.2025

Protocol Development – Statistical Plan

Statistical Plan

- Research needs to answer important clinical questions.
- Goal is to have clear and interpretable results that support your objectives.
- Negative Results are still a success because the data will help to shape future studies.
- Work with your Biostatistician



Protocol number: Buckeye 2024-01
Version: Sept 16 2024 v 2.3

16. Data Analysis

Internal/External Validity

Describe measures that have been taken to avoid study bias (consider the threats to internal/external validity).

This study will be an open-label study comparing enrolled participants to a real-world cohort. Due to safety concerns blinding and randomization is not permitted for this study. Study team members engaged in this research must not have any potential conflicts with the study drug, BUCKEYE24-101 or JSnow Inc. An independent external DSMB and study monitor will monitor the safety and data of the study.

Data Analysis Techniques

Specify the analytic techniques the researcher will use to answer the study questions. Indicate the statistical procedures (e.g. specific descriptive or inferential tests) that will be used and why the procedures are appropriate. Note: The IRB does not need the actual formulas to be used, just a description of them. If applicable, specify the proposed analytic approaches for qualitative data.

The sample size of this study will be up to 500 study participants and 1000 real world data participants.

16.1 Sample Size Calculation:

Using the formula for comparing two independent means:

Using the formula for comparing two independent means:

$$n = \left(\frac{Z_{1-\alpha/2} + Z_{1-\beta}}{\delta/\sigma}\right)^2 \cdot \left(\frac{1+k}{k}\right)$$

Where:

- $\delta = 0.3$
- $\sigma = 1.1$
- $k = n_2/n_1 = 2$
- $Z_{1-\alpha/2} = 1.96, Z_{1-\beta} = 1.28$

Final sample sizes (rounded):
Treatment group: 500
Comparator group: 1000

16.2Statistical Methods

16.2a Baseline Comparability

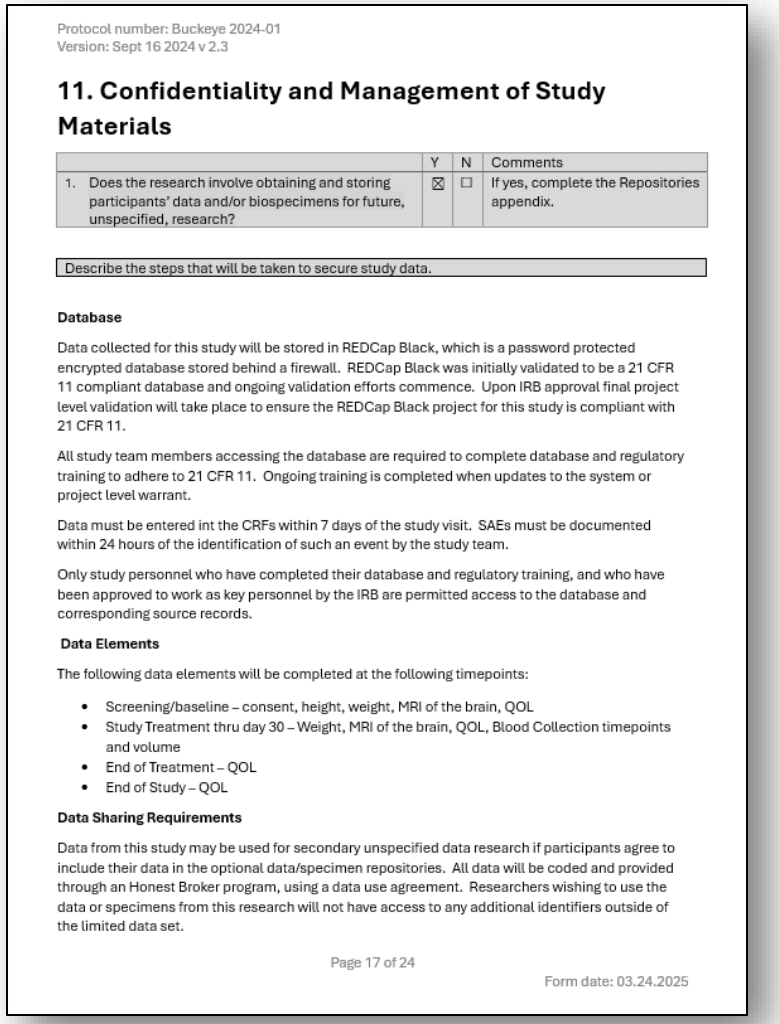
Page 22 of 23

Form date: 03.24.2025

Protocol Development – Data Management

Data Management (Collection and Handling)

- Databases used
- Data elements to be collected at each timepoint
- Submission and reporting requirements
- Data Sharing Requirements
- Secondary Data Use



Protocol number: Buckeye 2024-01
Version: Sept 16 2024 v 2.3

11. Confidentiality and Management of Study Materials

	Y	N	Comments
1. Does the research involve obtaining and storing participants' data and/or biospecimens for future, unspecified, research?	☒	☐	If yes, complete the Repositories appendix.

Describe the steps that will be taken to secure study data.

Database

Data collected for this study will be stored in REDCap Black, which is a password protected encrypted database stored behind a firewall. REDCap Black was initially validated to be a 21 CFR 11 compliant database and ongoing validation efforts commence. Upon IRB approval final project level validation will take place to ensure the REDCap Black project for this study is compliant with 21 CFR 11.

All study team members accessing the database are required to complete database and regulatory training to adhere to 21 CFR 11. Ongoing training is completed when updates to the system or project level warrant.

Data must be entered int the CRFs within 7 days of the study visit. SAEs must be documented within 24 hours of the identification of such an event by the study team.

Only study personnel who have completed their database and regulatory training, and who have been approved to work as key personnel by the IRB are permitted access to the database and corresponding source records.

Data Elements

The following data elements will be completed at the following timepoints:

- Screening/baseline – consent, height, weight, MRI of the brain, QOL
- Study Treatment thru day 30 – Weight, MRI of the brain, QOL, Blood Collection timepoints and volume
- End of Treatment – QOL
- End of Study – QOL

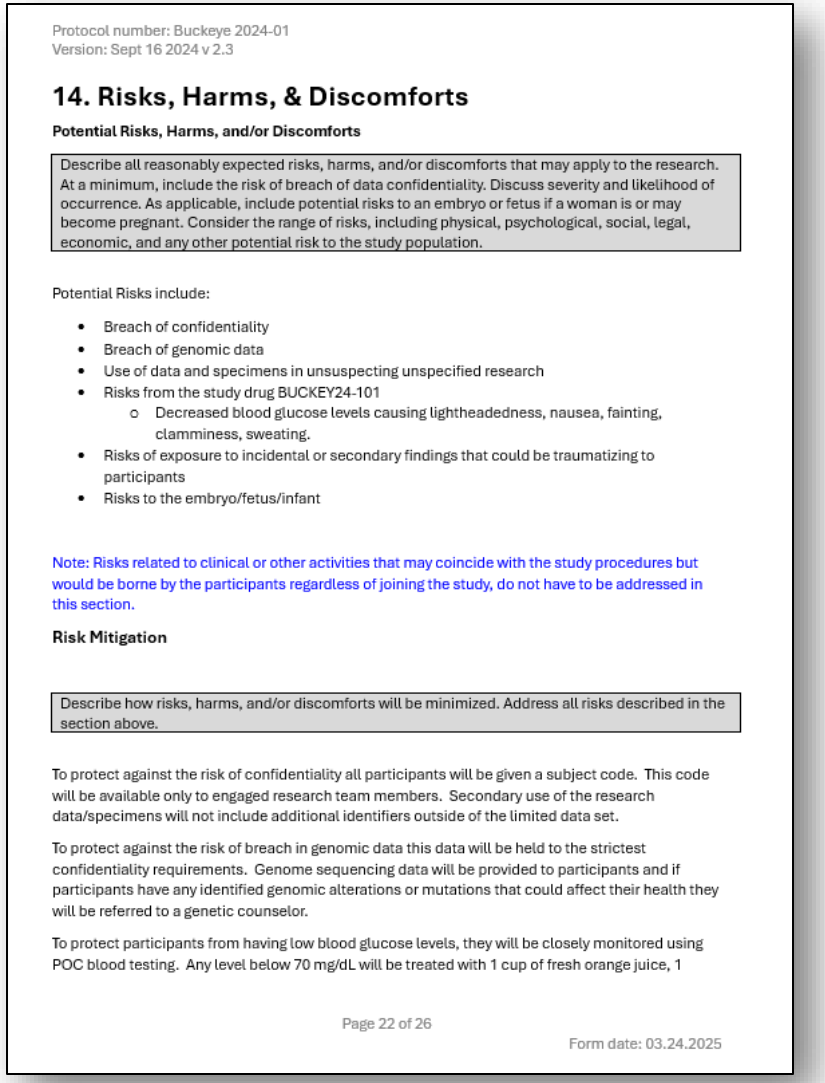
Data Sharing Requirements

Data from this study may be used for secondary unspecified data research if participants agree to include their data in the optional data/specimen repositories. All data will be coded and provided through an Honest Broker program, using a data use agreement. Researchers wishing to use the data or specimens from this research will not have access to any additional identifiers outside of the limited data set.

Protocol Development – Ethical Considerations

Ethical Considerations

- Subject confidentiality
- Genomic Data
- Future use of specimens and data
- Benefits and Risks
- Incidental/Secondary Findings
- Inclusion of women, minorities and children



Protocol number: Buckeye 2024-01
Version: Sept 16 2024 v 2.3

14. Risks, Harms, & Discomforts

Potential Risks, Harms, and/or Discomforts

Describe all reasonably expected risks, harms, and/or discomforts that may apply to the research. At a minimum, include the risk of breach of data confidentiality. Discuss severity and likelihood of occurrence. As applicable, include potential risks to an embryo or fetus if a woman is or may become pregnant. Consider the range of risks, including physical, psychological, social, legal, economic, and any other potential risk to the study population.

Potential Risks include:

- Breach of confidentiality
- Breach of genomic data
- Use of data and specimens in unsuspecting unspecified research
- Risks from the study drug BUCKEY24-101
  - Decreased blood glucose levels causing lightheadedness, nausea, fainting, clamminess, sweating.
- Risks of exposure to incidental or secondary findings that could be traumatizing to participants
- Risks to the embryo/fetus/infant

Note: Risks related to clinical or other activities that may coincide with the study procedures but would be borne by the participants regardless of joining the study, do not have to be addressed in this section.

Risk Mitigation

Describe how risks, harms, and/or discomforts will be minimized. Address all risks described in the section above.

To protect against the risk of confidentiality all participants will be given a subject code. This code will be available only to engaged research team members. Secondary use of the research data/specimens will not include additional identifiers outside of the limited data set.

To protect against the risk of breach in genomic data this data will be held to the strictest confidentiality requirements. Genome sequencing data will be provided to participants and if participants have any identified genomic alterations or mutations that could affect their health they will be referred to a genetic counselor.

To protect participants from having low blood glucose levels, they will be closely monitored using POC blood testing. Any level below 70 mg/dL will be treated with 1 cup of fresh orange juice, 1

Page 22 of 26

Form date: 03.24.2025

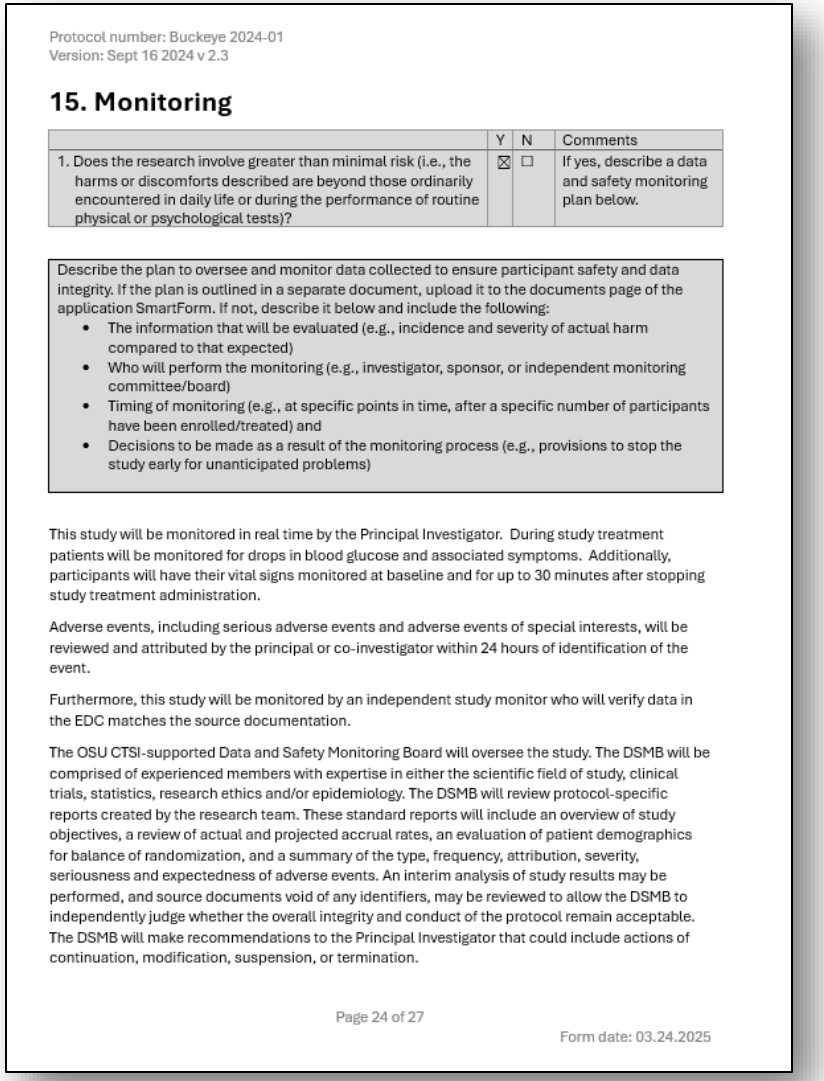
Protocol Development – Study Oversight

Study Oversight

- Ensures
  - Rights and well-being of subjects are protected
  - Data is accurate, complete, and verifiable
  - Trial is conducted in compliance with the approved protocol, ICH GCP and applicable regulatory requirements

- Internal or External Oversight
  - Internal – Quality Checks, Audits, assessing AEs and Deviations
  - External - Sponsor Monitoring, Sponsor Audits, FDA if FDA Regulated, IRB, DSMB or Safety Monitor

CTSI Study Oversight Services (DSMB, Safety Monitor, Study Monitor, Quality Checks/Audits)



Protocol number: Buckeye 2024-01
Version: Sept 16 2024 v 2.3

15. Monitoring

	Y	N	Comments
1. Does the research involve greater than minimal risk (i.e., the harms or discomforts described are beyond those ordinarily encountered in daily life or during the performance of routine physical or psychological tests)?	☒	☐	If yes, describe a data and safety monitoring plan below.

Describe the plan to oversee and monitor data collected to ensure participant safety and data integrity. If the plan is outlined in a separate document, upload it to the documents page of the application SmartForm. If not, describe it below and include the following:

- The information that will be evaluated (e.g., incidence and severity of actual harm compared to that expected)
- Who will perform the monitoring (e.g., investigator, sponsor, or independent monitoring committee/board)
- Timing of monitoring (e.g., at specific points in time, after a specific number of participants have been enrolled/treated) and
- Decisions to be made as a result of the monitoring process (e.g., provisions to stop the study early for unanticipated problems)

This study will be monitored in real time by the Principal Investigator. During study treatment patients will be monitored for drops in blood glucose and associated symptoms. Additionally, participants will have their vital signs monitored at baseline and for up to 30 minutes after stopping study treatment administration.

Adverse events, including serious adverse events and adverse events of special interests, will be reviewed and attributed by the principal or co-investigator within 24 hours of identification of the event.

Furthermore, this study will be monitored by an independent study monitor who will verify data in the EDC matches the source documentation.

The OSU CTSI-supported Data and Safety Monitoring Board will oversee the study. The DSMB will be comprised of experienced members with expertise in either the scientific field of study, clinical trials, statistics, research ethics and/or epidemiology. The DSMB will review protocol-specific reports created by the research team. These standard reports will include an overview of study objectives, a review of actual and projected accrual rates, an evaluation of patient demographics for balance of randomization, and a summary of the type, frequency, attribution, severity, seriousness and expectedness of adverse events. An interim analysis of study results may be performed, and source documents void of any identifiers, may be reviewed to allow the DSMB to independently judge whether the overall integrity and conduct of the protocol remain acceptable. The DSMB will make recommendations to the Principal Investigator that could include actions of continuation, modification, suspension, or termination.

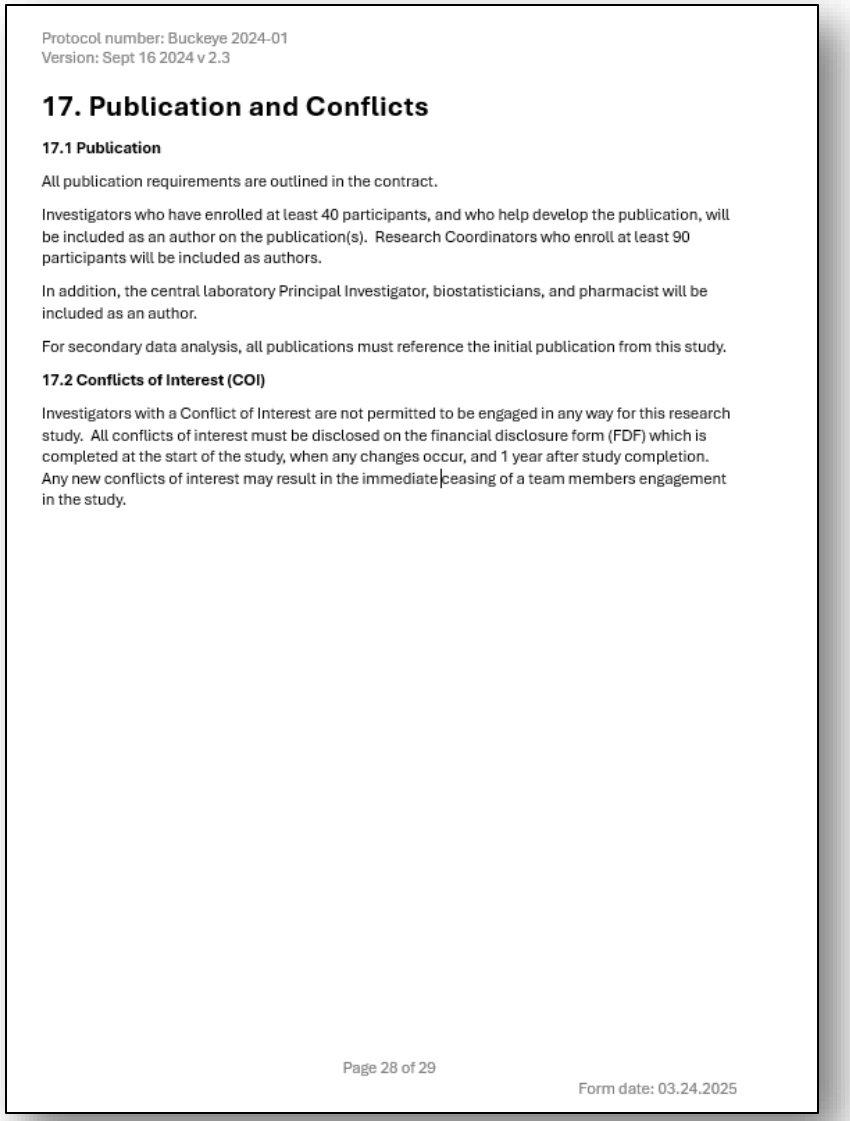
Page 24 of 27

Form date: 03.24.2025

Protocol Development – Publication and Conflicts

Publication and Conflicts

- Often in a contract, but for IITs, ensure everyone is clear on publication and authorship information
- Conflicts of Interest (COIs) – must be disclosed



Protocol number: Buckeye 2024-01
Version: Sept 16 2024 v 2.3

17. Publication and Conflicts

17.1 Publication

All publication requirements are outlined in the contract.

Investigators who have enrolled at least 40 participants, and who help develop the publication, will be included as an author on the publication(s). Research Coordinators who enroll at least 90 participants will be included as authors.

In addition, the central laboratory Principal Investigator, biostatisticians, and pharmacist will be included as an author.

For secondary data analysis, all publications must reference the initial publication from this study.

17.2 Conflicts of Interest (COI)

Investigators with a Conflict of Interest are not permitted to be engaged in any way for this research study. All conflicts of interest must be disclosed on the financial disclosure form (FDF) which is completed at the start of the study, when any changes occur, and 1 year after study completion. Any new conflicts of interest may result in the immediate ceasing of a team members engagement in the study.

Page 28 of 29

Form date: 03.24.2025

Protocol Development - Finalization

After writing your protocol….

Have your collaborative and research teams review the protocol for additional feedback.

- Research Coordinator/Regulatory Officer/Research Manager
- Statisticians
- Pharmacists
- Laboratory Techs
- Sub-sites
- DSMB/Medical Monitor/Study Monitor

And Finalize:

- *Quality Management Plan*
- *Data Management Plan*
- *Recruitment and Retention Plan*
- *Clinical Monitoring Plan*
- *Communication Plan*
- *Manual of Procedures*
- *Medical Monitor Policy and Procedures*
- *Lab Manual*

Submit to the appropriate agencies (as applicable):

- Food and Drug Administration
- Scientific Review Committee
- Institutional Review Board
  - Privacy Board
  - Radiation Committee
  - Maternal-Fetal Welfare Committee
- Institutional Biosafety Committee
- Research Stakeholders/IT Risk Assessment
- Conflict Approval Committee

Register (if applicable):

- ClinicalTrials.gov

After approvals can begin your research – Note: protocol amendments may be required.

CTSI Regulatory Knowledge and Support (RKS) Services

Services

- Data Safety Monitoring Board
- Independent Safety Monitor/Officer
- Study Monitoring
- Quality Checks/Audits
- Education and Training Regulatory Principles/Best Practices

Consultations/Guidance

- Data Safety Monitoring Plans
- IND/IDE Support
- Essential Documents
- NIH Requirements
- IRB Submissions
- Protocol and Consent Form Development
- ClincialTrials.gov

Michael Para, MD
RKS Program Director

April Green, MACPR, CCRC
RKS Program Manager

Sarah Stenger, MA
RKS Research Compliance Analyst

Contact:
CTSI-Regulatory@osumc.edu

Request for Services:
https://myccts.osu.edu/

Questions

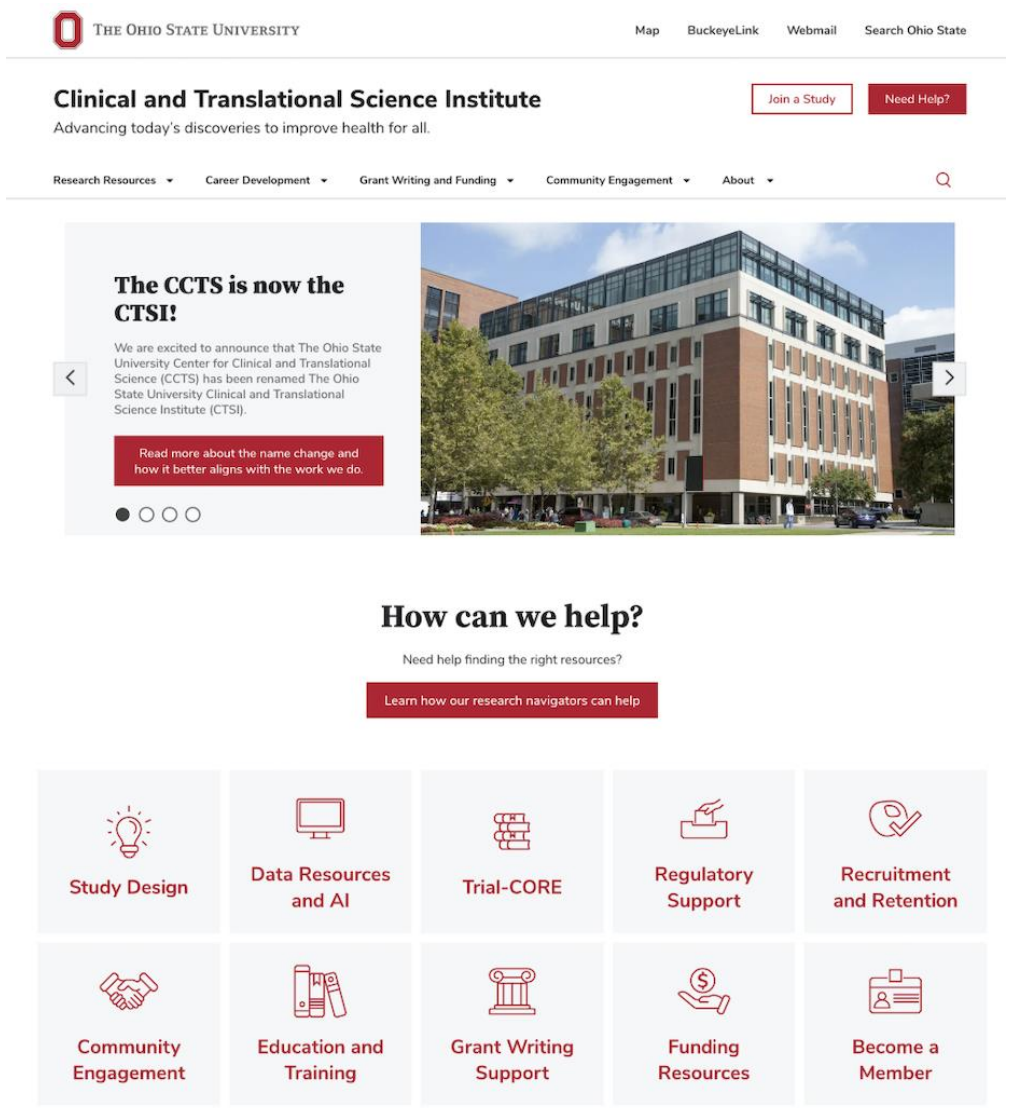
Contact:

April.Green2@osumc.edu

CTSI-Regulatory@osumc.edu

Resources:

ctsi.osu.edu

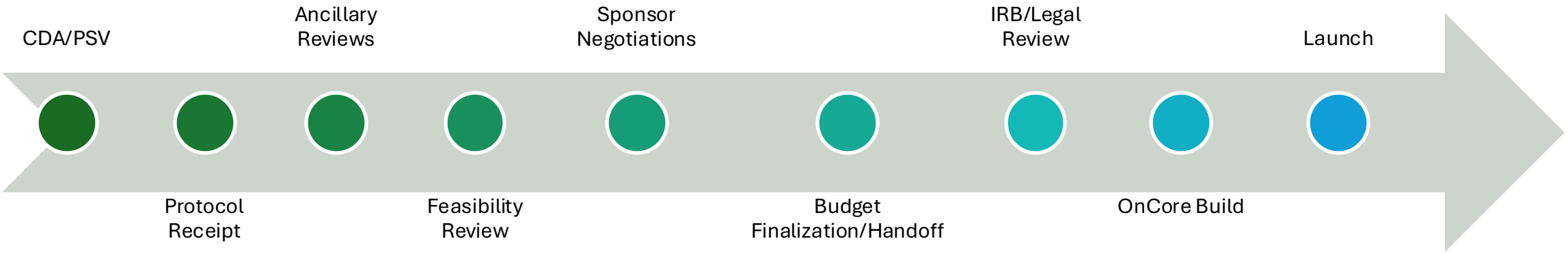


Protocol Implementation

Kristy Ott, CCRP

Nationwide Children's Hospital

High Level Workflow



NATIONWIDE CHILDREN'S
When your child needs a hospital, everything matters.

Timeline guess?

- 1- 3 months
- 4- 6 months
- 7- 9 months
- Year
- Longer?

Most often, it takes a year from start to finish.

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CDA/PSV

- Confidential Disclosure Agreement -also known as a **Non-Disclosure Agreement (NDA)**, is a legal agreement that outlines the terms under which parties will exchange information for a specified purpose
  - Executed by Legal/Office of Tech Commercialization between the two entities for protocol release
- Pre-Site Visit – sponsor conducts a visit either onsite or remotely to ensure institution's adequacy

Upfront Ancillary Reviews

- Disease Teams
- Journal Club
- Clinical Scientific Review Committee (CSRC)
  - At OSU, Oncology focused?
- Tumor Board
- Other examples?

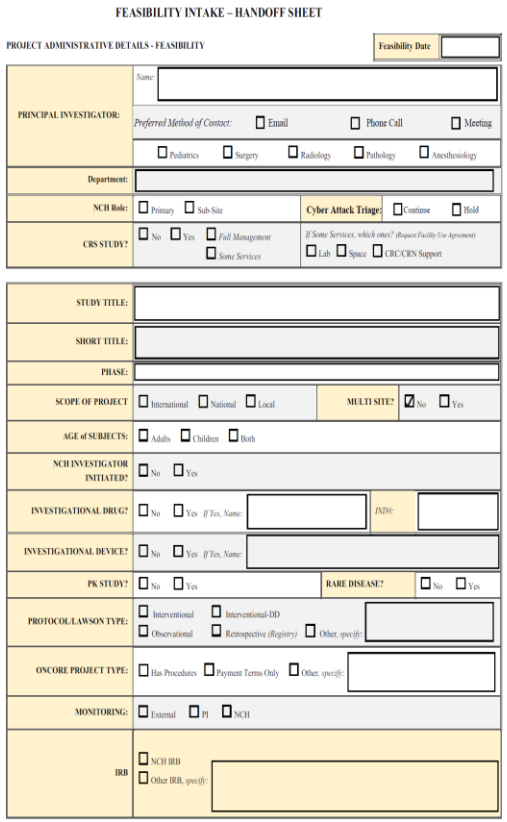
Institutional Ancillary Reviews

- Data Trust and Value Committee
  - Studies that involve data exchange with outside institutions
  - Studies that utilize DUA (data use agreements)
  - Committee meets monthly

Feasibility Analysis

- Study population
- Staff availability
- Space
- Competing studies
- Sponsor/CRO/PI experience
- Budget Adequacy
- Time
- Current study load

Intake Form



FEASIBILITY INTAKE – HANDOFF SHEET

PROJECT ADMINISTRATIVE DETAILS - FEASIBILITY

Feasibility Date

PRINCIPAL INVESTIGATOR: Name:

Preferred Method of Contact: ☐ Email ☐ Phone Call ☐ Meeting

☐ Pediatrics ☐ Surgery ☐ Radiology ☐ Pathology ☐ Anesthesiology

Department:

NCH Role: ☐ Primary ☐ Sub-Site | Cyber Attack Triage: ☐ Continue ☐ Hold

CRS STUDY? ☐ No ☐ Yes ☐ Full Management ☐ Some Services | If Some Services, which ones? (Request Facility Use Agreement) ☐ Lab ☐ Space ☐ CRC/CRN Support

STUDY TITLE:

SHORT TITLE:

PHASE:

SCOPE OF PROJECT: ☐ International ☐ National ☐ Local | MULTI SITE? ☑ No ☐ Yes

AGE of SUBJECTS: ☐ Adults ☐ Children ☐ Both

NCH INVESTIGATOR INITIATED? ☐ No ☐ Yes

INVESTIGATIONAL DRUG? ☐ No ☐ Yes If Yes, Name: | IND#:

INVESTIGATIONAL DEVICE? ☐ No ☐ Yes If Yes, Name:

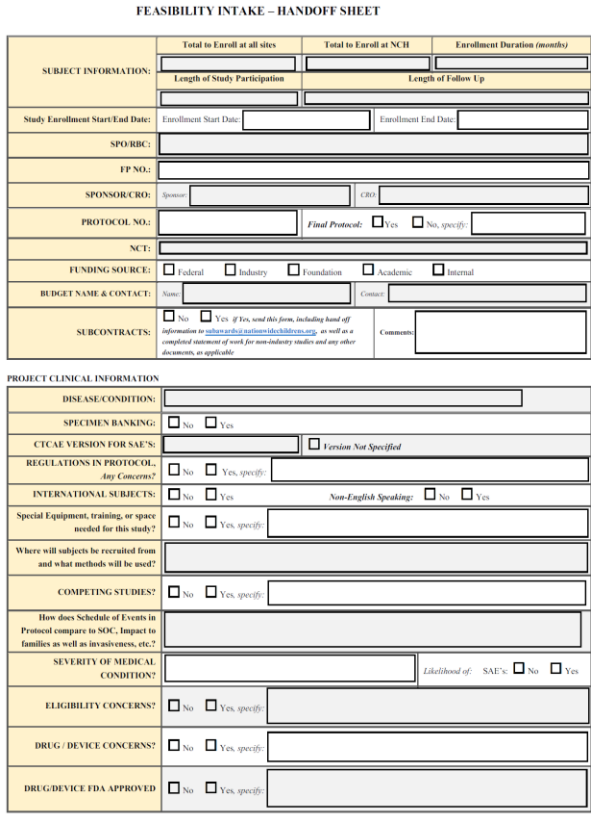
PK STUDY? ☐ No ☐ Yes | RARE DISEASE? ☐ No ☐ Yes

PROTOCOL/LAWSON TYPE: ☐ Interventional ☐ Interventional-DD ☐ Observational ☐ Retrospective (Registry) ☐ Other, specify:

ONCORE PROJECT TYPE: ☐ Has Procedures ☐ Payment Terms Only ☐ Other, specify:

MONITORING: ☐ External ☐ PI ☐ NCH

IRB: ☐ NCH IRB ☐ Other IRB, specify:



FEASIBILITY INTAKE – HANDOFF SHEET

SUBJECT INFORMATION:	Total to Enroll at all sites	Total to Enroll at NCH	Enrollment Duration (months)
	Length of Study Participation	Length of Follow Up	

Study Enrollment Start/End Date: Enrollment Start Date: | Enrollment End Date:

SPO/RBC:

FP NO.:

SPONSOR/CRO: Sponsor: | CRO:

PROTOCOL NO.: | Final Protocol: ☐ Yes ☐ No, specify:

NCT:

FUNDING SOURCE: ☐ Federal ☐ Industry ☐ Foundation ☐ Academic ☐ Internal

BUDGET NAME & CONTACT: Name: | Contact:

SUBCONTRACTS: ☐ No ☐ Yes If Yes, send this form, including hand off information to subawards@nationwidechildrens.org, as well as a completed statement of work for non-industry studies and any other documents, as applicable | Comments:

PROJECT CLINICAL INFORMATION

DISEASE/CONDITION:

SPECIMEN BANKING: ☐ No ☐ Yes

CTCAE VERSION FOR SAE'S: ☐ Version Not Specified

REGULATIONS IN PROTOCOL, Any Concerns? ☐ No ☐ Yes, specify:

INTERNATIONAL SUBJECTS: ☐ No ☐ Yes | Non-English Speaking: ☐ No ☐ Yes

Special Equipment, training, or space needed for this study? ☐ No ☐ Yes, specify:

Where will subjects be recruited from and what methods will be used?

COMPETING STUDIES? ☐ No ☐ Yes, specify:

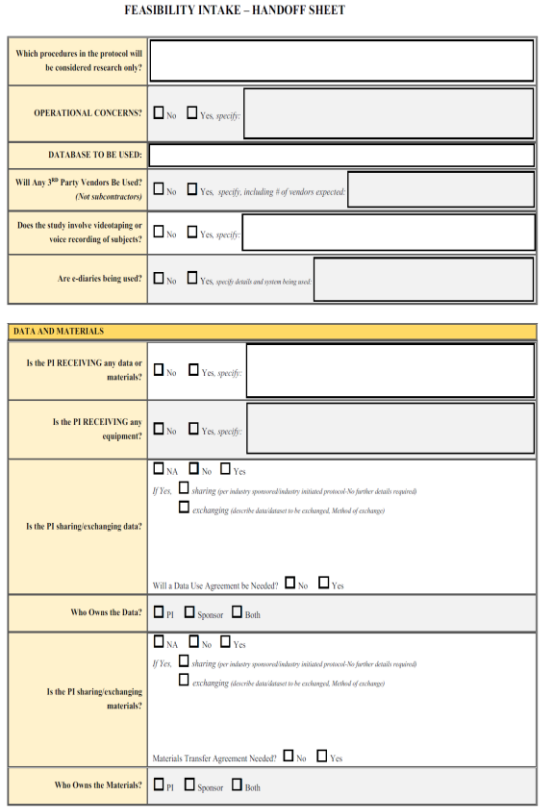
How does Schedule of Events in Protocol compare to SOC, Impact to families as well as invasiveness, etc.?

SEVERITY OF MEDICAL CONDITION? | Likelihood of: SAE's: ☐ No ☐ Yes

ELIGIBILITY CONCERNS? ☐ No ☐ Yes, specify:

DRUG / DEVICE CONCERNS? ☐ No ☐ Yes, specify:

DRUG/DEVICE FDA APPROVED ☐ No ☐ Yes, specify:



FEASIBILITY INTAKE – HANDOFF SHEET

Which procedures in the protocol will be considered research only?

OPERATIONAL CONCERNS? ☐ No ☐ Yes, specify:

DATABASE TO BE USED:

Will Any 3RD Party Vendors Be Used? (Not subcontractors) ☐ No ☐ Yes, specify, including # of vendors expected:

Does the study involve videotaping or voice recording of subjects? ☐ No ☐ Yes, specify:

Are e-diaries being used? ☐ No ☐ Yes, specify details and system being used:

DATA AND MATERIALS

Is the PI RECEIVING any data or materials? ☐ No ☐ Yes, specify:

Is the PI RECEIVING any equipment? ☐ No ☐ Yes, specify:

Is the PI sharing/exchanging data? ☐ NA ☐ No ☐ Yes

If Yes, ☐ sharing (per industry sponsored/industry initiated protocol-No further details required) ☐ exchanging (describe data/dataset to be exchanged, Method of exchange)

Will a Data Use Agreement be Needed? ☐ No ☐ Yes

Who Owns the Data? ☐ PI ☐ Sponsor ☐ Both

Is the PI sharing/exchanging materials? ☐ NA ☐ No ☐ Yes

If Yes, ☐ sharing (per industry sponsored/industry initiated protocol-No further details required) ☐ exchanging (describe data/dataset to be exchanged, Method of exchange)

Materials Transfer Agreement Needed? ☐ No ☐ Yes

Who Owns the Materials? ☐ PI ☐ Sponsor ☐ Both

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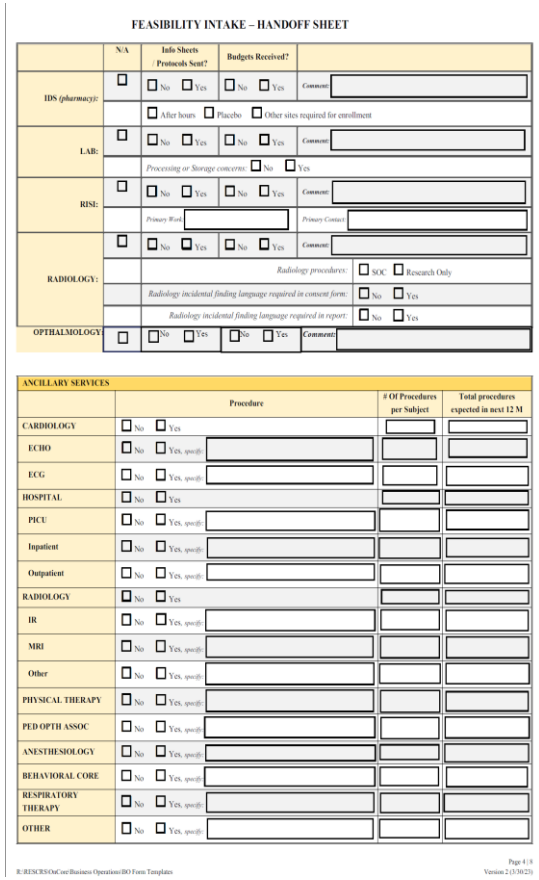
Intake Form Cont.

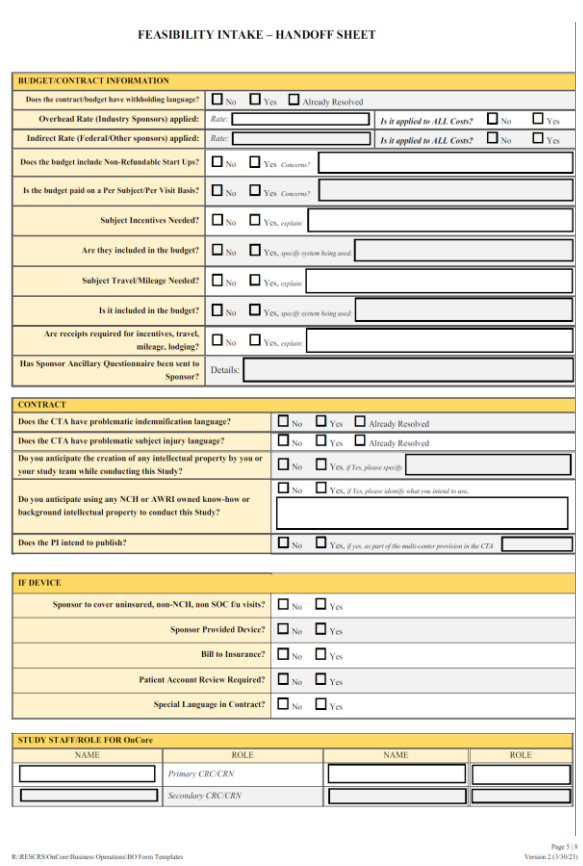


FEASIBILITY INTAKE – HANDOFF SHEET

	N/A	Info Sheets / Protocols Sent?	Budgets Received?	
IDS (*pharmacy*):	☐	☐ No ☐ Yes	☐ No ☐ Yes	*Comment:*
		☐ After hours ☐ Placebo ☐ Other sites required for enrollment		
LAB:	☐	☐ No ☐ Yes	☐ No ☐ Yes	*Comment:*
		Processing or Storage concerns: ☐ No ☐ Yes		
RISI:	☐	☐ No ☐ Yes	☐ No ☐ Yes	*Comment:*
		Primary Work:		*Primary Contact:*
RADIOLOGY:	☐	☐ No ☐ Yes	☐ No ☐ Yes	*Comment:*
		Radiology procedures: ☐ SOC ☐ Research Only		
		Radiology incidental finding language required in consent form: ☐ No ☐ Yes		
		Radiology incidental finding language required in report: ☐ No ☐ Yes		
OPTHALMOLOGY:	☐	☐ No ☐ Yes	☐ No ☐ Yes	*Comment:*

ANCILLARY SERVICES

	Procedure	# Of Procedures per Subject	Total procedures expected in next 12 M
CARDIOLOGY	☐ No ☐ Yes		
ECHO	☐ No ☐ Yes, specify:		
ECG	☐ No ☐ Yes, specify:		
HOSPITAL	☐ No ☐ Yes		
PICU	☐ No ☐ Yes, specify:		
Inpatient	☐ No ☐ Yes, specify:		
Outpatient	☐ No ☐ Yes, specify:		
RADIOLOGY	☐ No ☐ Yes		
IR	☐ No ☐ Yes, specify:		
MRI	☐ No ☐ Yes, specify:		
Other	☐ No ☐ Yes, specify:		
PHYSICAL THERAPY	☐ No ☐ Yes, specify:		
PED OPTH ASSOC	☐ No ☐ Yes, specify:		
ANESTHESIOLOGY	☐ No ☐ Yes, specify:		
BEHAVIORAL CORE	☐ No ☐ Yes, specify:		
RESPIRATORY THERAPY	☐ No ☐ Yes, specify:		
OTHER	☐ No ☐ Yes, specify:		



FEASIBILITY INTAKE – HANDOFF SHEET

BUDGET/CONTRACT INFORMATION

Does the contract/budget have withholding language?	☐ No ☐ Yes ☐ Already Resolved
Overhead Rate (Industry Sponsors) applied:	*Rate:* *Is it applied to ALL Costs?* ☐ No ☐ Yes
Indirect Rate (Federal/Other sponsors) applied:	*Rate:* *Is it applied to ALL Costs?* ☐ No ☐ Yes
Does the budget include Non-Refundable Start Ups?	☐ No ☐ Yes *Concerns?*
Is the budget paid on a Per Subject/Per Visit Basis?	☐ No ☐ Yes *Concerns?*
Subject Incentives Needed?	☐ No ☐ Yes, *explain:*
Are they included in the budget?	☐ No ☐ Yes, *specify system being used:*
Subject Travel/Mileage Needed?	☐ No ☐ Yes, *explain:*
Is it included in the budget?	☐ No ☐ Yes, *specify system being used:*
Are receipts required for incentives, travel, mileage, lodging?	☐ No ☐ Yes, *explain:*
Has Sponsor Ancillary Questionnaire been sent to Sponsor?	Details:

CONTRACT

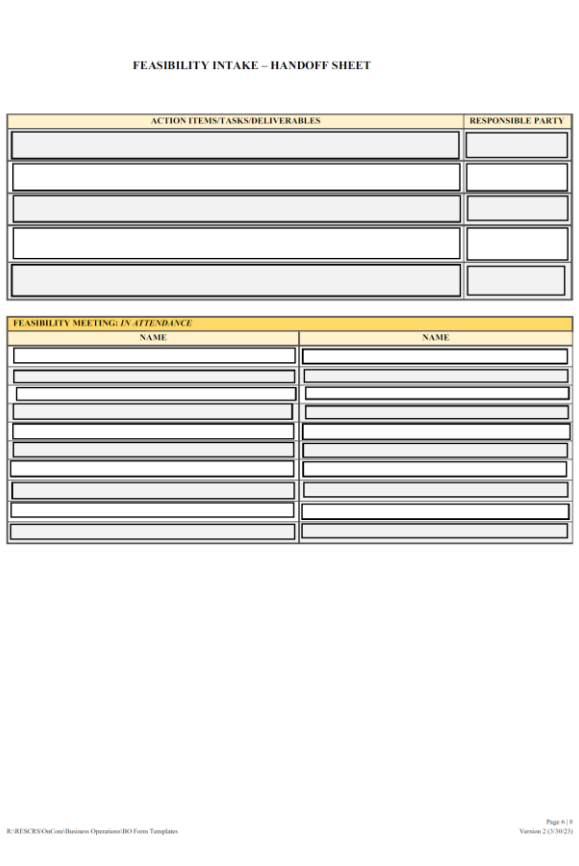
Does the CTA have problematic indemnification language?	☐ No ☐ Yes ☐ Already Resolved
Does the CTA have problematic subject injury language?	☐ No ☐ Yes ☐ Already Resolved
Do you anticipate the creation of any intellectual property by you or your study team while conducting this Study?	☐ No ☐ Yes, *if Yes, please specify:*
Do you anticipate using any NCH or AWRI owned know-how or background intellectual property to conduct this Study?	☐ No ☐ Yes, *if Yes, please identify what you intend to use.*
Does the PI intend to publish?	☐ No ☐ Yes, *if yes, as part of the multi-center provision in the CTA*

IF DEVICE

Sponsor to cover uninsured, non-NCH, non SOC f/u visits?	☐ No ☐ Yes
Sponsor Provided Device?	☐ No ☐ Yes
Bill to Insurance?	☐ No ☐ Yes
Patient Account Review Required?	☐ No ☐ Yes
Special Language in Contract?	☐ No ☐ Yes

STUDY STAFF/ROLE FOR OnCore

NAME	ROLE	NAME	ROLE
	Primary CRC/CRN		
	Secondary CRC/CRN		



FEASIBILITY INTAKE – HANDOFF SHEET

ACTION ITEMS/TASKS/DELIVERABLES	RESPONSIBLE PARTY

FEASIBILITY MEETING: *IN ATTENDANCE*

NAME	NAME

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Feasibility Meeting

- Documents reqd: Protocol, CTA and Budget
- Attendees: PI, study staff, feasibility, RBC, SPO
- Meet and review protocol, CTA, budget and intake form

Budget Review

- Upon meeting completion, ancillary service quotes are obtained and added
  - Ex: Investigational radiology, IDS pharmacy, Local lab, Cardiology, etc.
- Budget is reviewed for adequacy. Items to think about:
  - Inflation
  - Staff time (this is a big one)
  - All procedures accounted for? Screen fails/ratio?
  - Invoiceables (travel, incentives, etc.)
- Local administrative costs (start ups, maintenance, close out, etc.) are added
- Budget returned to sponsor for approval

Negotiation

- This is an art and can be an arduous process
- You try to budget to break even and have to know when the worst case scenario has occurred and to walk away
- It's best to keep your PI in the loop

Budget Finalization

Study handoff can occur at this point

IRB/CTA review

- IRB and CTA review occur in tandem at NCH
  - Same at OSU?
- OnCore calendar build can begin
- For IITs, start registration in Clinicaltrials.gov

IRB Submission

- Local vs Reliance
- ICF (Informed Consent) integrated into local template
- IRB application completed
- COI (Conflict of Interest) need completed
- Trainings need completed (CITI, etc.)

CTA Review

- Study contract reviewed by legal counsel
  - Withholding
  - Indemnification
  - Subject Injury
  - eCRF timetable
  - Screen failure language
  - Invoicing frequency
  - Equipment provided
  - Travel/Incentive stipends

OnCore

- OnCore builds are completed for tracking of research subjects
- At NCH, OnCore and EPIC interface for billing reconciliation
  - Bill to study vs. Bill to insurance
- At NCH, Financials console is utilized for sponsor invoicing

Launch Meeting

- CTA is fully executed
- IRB approved
- OnCore calendar finalized
- SIV completion
- Meeting held with staff to review and study is opened to accrual

You made it!

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When your child needs a hospital, everything matters.

Thank you to everyone who make this happen!

Principal Investigators	Co-Investigators	Review Committee Members
Feasibility Coordinators	Research Nurses	Clinical Research Coordinators
Compliance Staff	Regulatory Staff	IT Support
IRB staff	Nurse Practitioners	DSMB Members
EPIC Staff	OnCore Staff	OTC Office
Legal Counsel	Ancillary Services	BPC
Research Accounting	SPO/RBC Staff	Divisional Staff

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When your child needs a hospital, everything matters.

Developing a Recruitment Plan

Lindsay Hanes, BS, CRCC

The Ohio State University

Developing Your Clinical Trial Recruitment Plan

It’s not just inclusion and exclusion criteria

THE OHIO STATE UNIVERSITY
COLLEGE OF MEDICINE

Lindsay Hanes, B.S., CCRC
Clinical Research Manager
Department of Anesthesiology
Spine Research Institute
Lindsay.hanes@osumc.edu

Why Recruitment Planning Matters

- **Recruitment delays affect up to 90% of clinical trials and are a leading cause of trial failure.**
  - Fogel DB. Contemp Clin Trials Commun. 2018;11:156–164. PMID: 29780874
- Poor recruitment reduces statistical power, compromises data quality, and can delay or prevent regulatory approval.
- Strategic recruitment planning helps ensure:
  - Ethical conduct (equitable access to research participation)
  - Generalizability of results
  - Representative participant populations

The Foundation: Inclusion & Exclusion Criteria

- These criteria define who can and cannot participate, ensuring safety and internal validity.
- However, overly restrictive criteria may:
  - Limit feasibility
  - Decrease external validity
  - Exclude underrepresented or real-world populations
- Strive for balance between scientific rigor and real-world relevance.

Understanding Your Target Population

- Recruitment success hinges on knowing who you're trying to reach and how best to reach them.
- Factors to consider:
  - Demographics (age, race/ethnicity, SES)
  - Comorbidities and healthcare utilization
  - Trust in research and historical medical mistrust
  - Social determinants of health: transportation, childcare, income, technology access
  - Health literacy and language proficiency

- Many groups remain underrepresented due to systemic and cultural barriers.
  -  George S, Duran N, Norris K. Am J Public Health. 2014;104(2):e16-31. PMID: 24328648

Site & Setting Realities

- Recruitment feasibility is shaped by where and how a trial is conducted:
- Academic medical centers may have more infrastructure (e.g., CRCs, EHR access) but may face slower startup timelines.
- Community sites may better reflect diverse, real-world populations but often lack dedicated research support.
- Multi-site trials require standardized protocols and training but offer broader reach.
- Consider:
  - Staff recruitment experience and bandwidth
  - EHR capabilities for patient identification
  - Relationships with referring clinicians
  - Patient flow and clinic volume
- Tailor recruitment strategies to the strengths and limitations of each site.

Engaging Stakeholders

- Stakeholder involvement improves trust, cultural alignment, and effectiveness of recruitment.
- Collaborate with:
  - Patient advocates to ensure relevance and respectful communication
  - Community leaders to build trust and access underrepresented groups
  - Clinicians for referrals and integrating recruitment into clinical flow
  - Research coordinators to streamline logistics and communication
- Stakeholders can:
  - Co-develop recruitment materials
  - Identify cultural or logistical barriers
  - Promote study opportunities within their networks
- Engagement should be early, ongoing, and bidirectional.
  - Duchenne Muscular Dystrophy Patient Advocates helped bring eteplirsen to market, the first FDA-approved treatment for DMD
    -  Peay HL, Biesecker BB. The involvement of patient advocacy groups in research. Orphanet J Rare Dis. 2014;9:107. PMID: 25022236

Strategic Outreach: Channels & Tools

- Use a multi-pronged approach to cast a wide but targeted net:
  - Provider referrals remain one of the most effective strategies—trusted messengers drive action.
  - Social media and digital ads are efficient for reaching younger or tech-savvy populations.
  - Clinic-based recruitment (posters, brochures, point-of-care discussion) supports patients already in care.
  - EHR-based outreach enables precision targeting of eligible participants.
  - Community-based recruitment builds trust in historically excluded populations.

Crafting Clear, Culturally Sensitive Messaging

- Messaging should be tailored to the literacy, language, and cultural norms of your target population.
- Use:
  - Plain language (avoid jargon and complex consent forms)
  - Translations by culturally competent professionals
  - Inclusive imagery reflecting your audience
- A/B testing can refine headlines, calls to action, and imagery based on response rates.
- Culturally sensitive messaging improves trust, engagement, and consent rates.
  - George S, Duran N, Norris K. Am J Public Health. 2014;104(2):e16-31. PMID: 24328648
- A breast cancer screening trial for Latina women used culturally resonant messaging and bilingual community health workers. Enrollment rates were more than double those of the control group that received standard materials.
  - Fernandez ME, et al. Am J Public Health. 2009;99(5):936–43. PMID: 19299679

Streamlining Screening & Enrollment

- Efficient processes reduce participant drop-off and increase enrollment speed.
- Tools and strategies:
  - Online pre-screening forms (e.g., REDCap surveys, EHR-integrated tools)
  - Phone screening scripts to ensure consistent, compliant, and friendly communication
  - Clear recruitment packets: FAQs, visit schedules, visual flowcharts
  - EHR-supported lists or manual queries to identify potentially eligible patients (e.g., via inclusion/exclusion filters in EPIC Reporting Workbench)
- Staff training ensures:
  - Consistent screening procedures
  - Comfort addressing common concerns (e.g., safety, time commitment)
  - Professional and respectful communication
- Standardized phone scripts and structured communication tools reduce variability and improve participant understanding during recruitment.
  -  Treweek S, et al. Cochrane Database Syst Rev. 2018;2:MR000013. PMID: 29468637

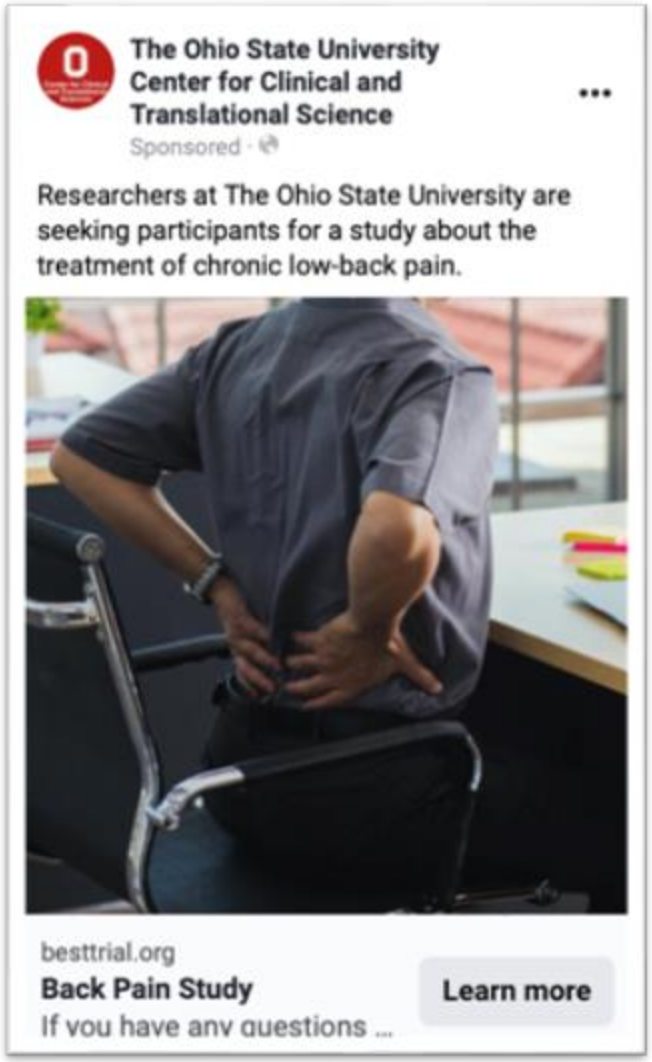
Budgeting & Timelines

- Effective recruitment requires dedicated funding and planning from the start.
- Key cost areas to account for:
  - Marketing & outreach (ads, flyers, digital campaigns)
  - Staff time for pre-screening, consent, follow-up
  - Participant stipends (e.g., travel, meals, lost wages)
  - Translation and interpretation services
  - Technology tools (REDCap forms, texting platforms, social media ad management)
- Build in realistic timelines that:
  - Include pre-launch outreach and IRB approvals
  - Allow for early slowdowns and mid-course adjustments
  - Reflect site startup variability and holidays
- Overestimate costs and time rather than under-plan—delays are costly as insufficient recruitment budgeting is a major reason why trials fail to meet enrollment goals.
  -  Fogel DB. Contemp Clin Trials Commun. 2018;11:156–164. PMID: 29780874

Monitoring & Adapting Your Recruitment Plan

- Continuous monitoring helps you identify bottlenecks and make timely course corrections.
- Key metrics to track:
  - Total contacts, pre-screens, and enrollments
  - Screen failure reasons (e.g., ineligibility, declined participation)
  - Demographic breakdowns (to monitor equity and diversity)
  - Time to enrollment from first contact
- Trial success depends not just on recruitment planning, but on real-time strategy adjustment based on ongoing data.
  -  Treweek S, et al. Cochrane Database Syst Rev. 2018;2:MR000013. PMID: 29468637
- Use tools like:
  - Recruitment dashboards
  - Weekly or monthly review meetings
  - Feedback from recruiters and participants
  - Make data-driven adjustments, such as:
    - Revising ads or outreach messages
    - Reallocating staff or budget
    - Engaging new recruitment partners

Real World Examples of Recruitment



Non-Facebook Recruitment	# of People	
Total Screened Potentially Eligible	242	7.44% of Screened scheduled enrollment visit
Total People who Answered	167	10.78% of Answered scheduled enrollment visit
Not interested	117	70.06% of Answered were not interested
PRE Done	41	
Not Eligible after Call	21	51.21% not eligible after PRE
Eligible After Call	20	90.00% of Eligible scheduled Enrollment visit
Scheduled Enrollment Visit	18	

Facebook Recruitment	# of People	
Total Screened Potentially Eligible	51	23.53% of Screened scheduled enrollment visit
Total People who Answered	34	35.29% of Answered scheduled enrollment visit
Not interested/ No pre	8	23.53% of Answered were not interested
PRE Done	26	
Not Eligible after Call	13	50.00% not eligible after PRE
Eligible After Call	13	92.31% of Eligible scheduled Enrollment visit
Scheduled Enrollment Visit	12	

Ethics, Equity & IRB Considerations

- All recruitment activities must be:
  - IRB-approved, including scripts, flyers, outreach platforms
  - Aligned with ethical principles of respect, beneficence, and justice
- Recruitment begins the ethical relationship — be transparent, respectful, and non-coercive.
- Ensure:
  - Use of non-technical, honest language
  - No overpromising benefits or minimizing risks
  - That participants feel free to say no without pressure
- Equity considerations:
  - Avoid recruitment practices that systematically exclude certain groups
  - Ensure access for non-English speakers and individuals with disabilities

Innovative Approaches to Recruitment

- Technology and digital tools are reshaping recruitment by increasing reach and efficiency:
  - AI-driven pre-screening: Extracts eligibility data from EHRs and flags candidates (e.g., Deep 6 AI, IBM Watson)
  - Text message reminders: Boost engagement, reduce no-shows, and nudge hesitant participants
  - Decentralized trials: Home visits, remote consent, and telehealth increase convenience and access
  - Patient portal messaging: Secure outreach through tools like MyChart directly connects with patients
- At Mayo Clinic, integrating IBM Watson with the EHR allowed real-time AI-driven trial matching for cancer patients. This reduced screening time and increased trial enrollment.
  -  Ferrucci D, et al. Artificial Intelligence for Clinical Trial Matching at Mayo Clinic. 2017.

Key Take Aways

- Inclusion and exclusion criteria are foundational, but recruitment success depends on much more.
- Recruitment must be:
  - Strategically planned
  - Culturally tailored
  - Continuously monitored and adapted
- Engage:
  - Stakeholders early to co-design and refine outreach
  - Multiple channels — digital, community-based, and provider-driven
- Invest in:
  - Strong recruitment materials (scripts, visuals, FAQs)
  - Training and time for recruitment staff
  - Technology tools (EHR reports, AI screening, telehealth)
- Start early. Stay flexible. Stay ethical.

Break

2:45 – 3 p.m.

Preparing for an FDA Inspection

Michelle Bright, MA, CCRP

The Ohio State University

Michelle Bright, MA, CCRP

Director of Operations, *Protocol Implementation and Personnel Management*

Center for Clinical Research Management (CCRM)

College of Medicine (COM)

Objectives:

1. Understand the Importance of FDA Inspection Preparedness
2. Identify Tools and Resources for Inspection Preparation
3. Embrace Change in FDA Regulations and Practices
4. Promote a Proactive Approach to Inspection Preparedness

"By failing to prepare, you're preparing to fail."

Benjamin Franklin

"Hope for the best, prepare for the worst."

Chris Bradford

Navigating FDA Inspections

Navigating FDA Inspections

"An ounce of **prevention** is worth a pound of cure."

Benjamin Franklin

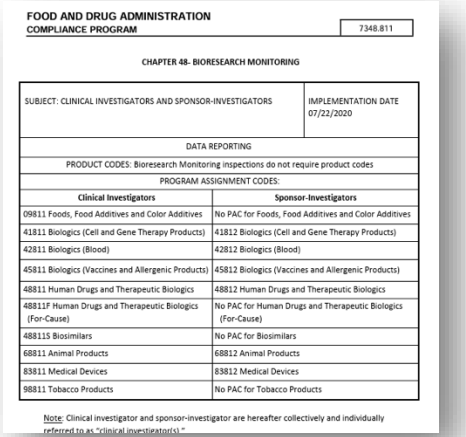
FDA Inspections: A Survival Guide (2018)

- Types of FDA Inspections
- Pre, during and post audit best practices

FDA Inspections: The Good, the Bad, & the Ugly (2019)

- The Good
  - Plenty of information and resources
  - Plenty of time
- The Bad
  - FDA Form 483
- The Ugly
  - Warning letters
  - NIDPOE

Tools to prepare for FDA Inspection

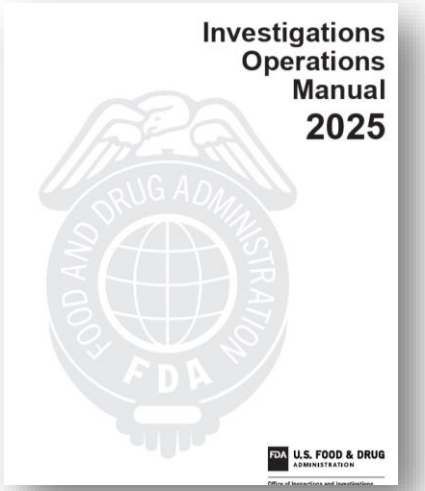

FOOD AND DRUG ADMINISTRATION
COMPLIANCE PROGRAM 7348.811

CHAPTER 48- BIORESEARCH MONITORING

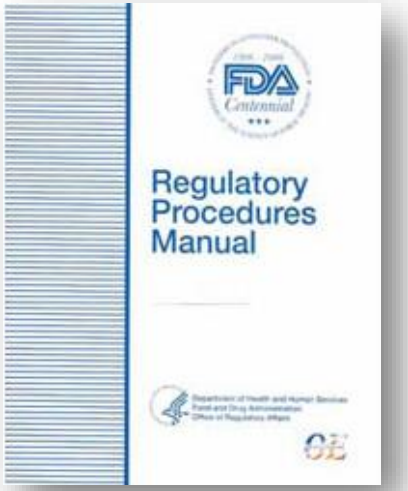
SUBJECT: CLINICAL INVESTIGATORS AND SPONSOR-INVESTIGATORS	IMPLEMENTATION DATE 07/22/2020
DATA REPORTING	
PRODUCT CODES: Bioresearch Monitoring inspections do not require product codes	
PROGRAM ASSIGNMENT CODES:	
Clinical Investigators	**Sponsor-Investigators**
09811 Foods, Food Additives and Color Additives	No PAC for Foods, Food Additives and Color Additives
41811 Biologics (Cell and Gene Therapy Products)	41812 Biologics (Cell and Gene Therapy Products)
42811 Biologics (Blood)	42812 Biologics (Blood)
45811 Biologics (Vaccines and Allergenic Products)	45812 Biologics (Vaccines and Allergenic Products)
48811 Human Drugs and Therapeutic Biologics	48812 Human Drugs and Therapeutic Biologics
48811F Human Drugs and Therapeutic Biologics (For-Cause)	No PAC for Human Drugs and Therapeutic Biologics (For-Cause)
488115 Biosimilars	No PAC for Biosimilars
68811 Animal Products	68812 Animal Products
83811 Medical Devices	83812 Medical Devices
98811 Tobacco Products	No PAC for Tobacco Products

Note: Clinical investigator and sponsor-investigator are hereafter collectively and individually referred to as "clinical investigator(s)."

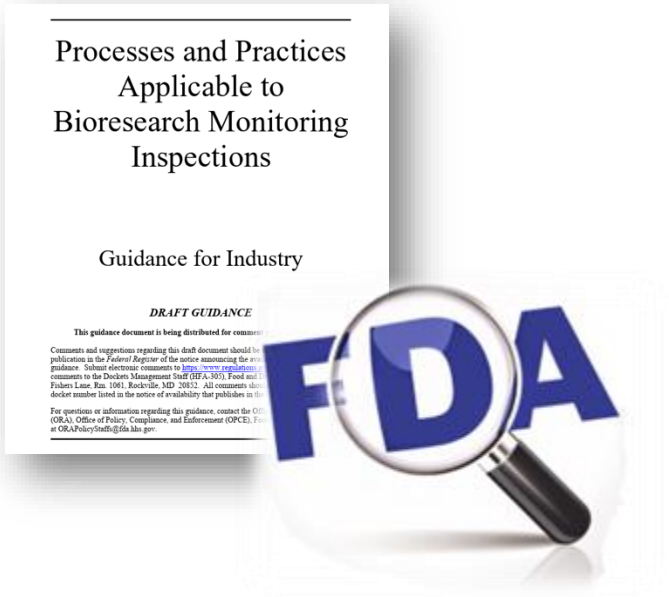
BIMO Program



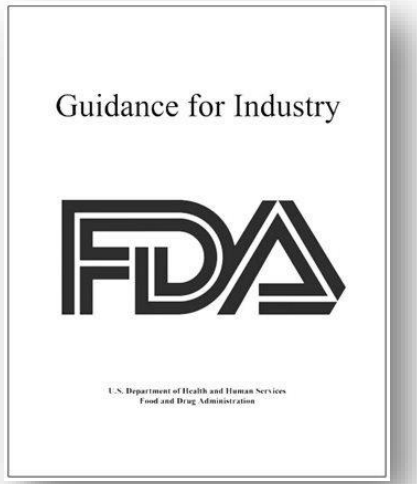
Investigations Operations Manual



Regulatory Procedures Manual

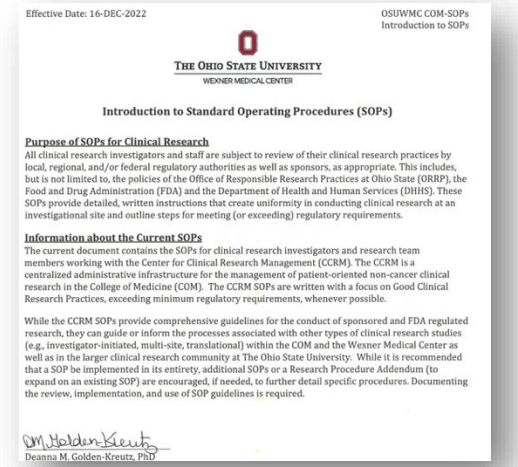


CFRs



Guidances

Tools to prepare for FDA Inspection



Effective Date: 16-DEC-2022

OSUWMC COM-SOPs
Introduction to SOPs

THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER

Introduction to Standard Operating Procedures (SOPs)

Purpose of SOPs for Clinical Research

All clinical research investigators and staff are subject to review of their clinical research practices by local, regional, and/or federal regulatory authorities as well as sponsors, as appropriate. This includes, but is not limited to, the policies of the Office of Responsible Research Practices at Ohio State (ORRP), the Food and Drug Administration (FDA) and the Department of Health and Human Services (DHHS). These SOPs provide detailed, written instructions that create uniformity in conducting clinical research at an investigational site and outline steps for meeting (or exceeding) regulatory requirements.

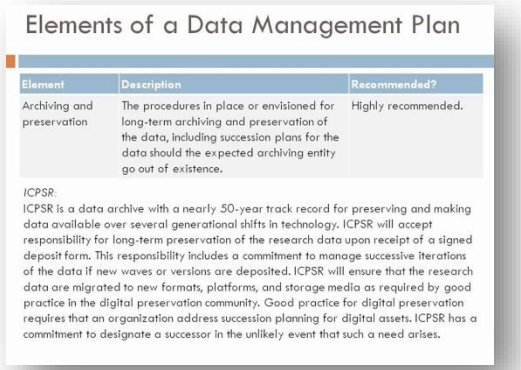
Information about the Current SOPs

The current document contains the SOPs for clinical research investigators and research team members working with the Center for Clinical Research Management (CCRM). The CCRM is a centralized administrative infrastructure for the management of patient-oriented non-cancer clinical research in the College of Medicine (COM). The CCRM SOPs are written with a focus on Good Clinical Research Practices, exceeding minimum regulatory requirements, whenever possible.

While the CCRM SOPs provide comprehensive guidelines for the conduct of sponsored and FDA regulated research, they can guide or inform the processes associated with other types of clinical research studies (e.g., investigator-initiated, multi-site, translational) within the COM and the Wexner Medical Center as well as in the larger clinical research community at The Ohio State University. While it is recommended that a SOP be implemented in its entirety, additional SOPs or a Research Procedure Addendum (to expand on an existing SOP) are encouraged, if needed, to further detail specific procedures. Documenting the review, implementation, and use of SOP guidelines is required.

Deanna M. Golden-Kreutz, PhD

Standard Operating Procedures



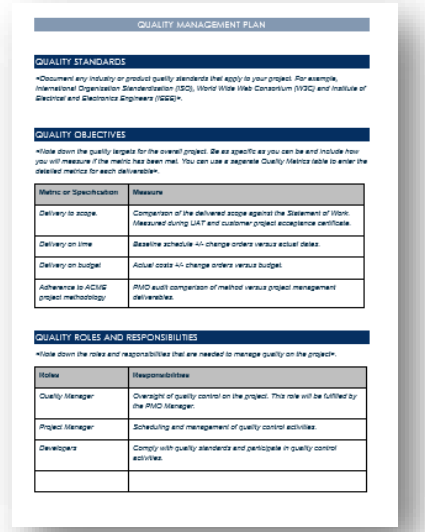
Elements of a Data Management Plan

Element	Description	Recommended?
Archiving and preservation	The procedures in place or envisioned for long-term archiving and preservation of the data, including succession plans for the data should the expected archiving entity go out of existence.	Highly recommended.

ICPSR:

ICPSR is a data archive with a nearly 50-year track record for preserving and making data available over several generational shifts in technology. ICPSR will accept responsibility for long-term preservation of the research data upon receipt of a signed deposit form. This responsibility includes a commitment to manage successive iterations of the data if new waves or versions are deposited. ICPSR will ensure that the research data are migrated to new formats, platforms, and storage media as required by good practice in the digital preservation community. Good practice for digital preservation requires that an organization address succession planning for digital assets. ICPSR has a commitment to designate a successor in the unlikely event that such a need arises.

Data Management Plan



QUALITY MANAGEMENT PLAN

QUALITY STANDARDS

•Document any industry or product quality standards that apply to your project. For example, International Organization Standardization (ISO), World Wide Web Consortium (W3C) and Institute of Electrical and Electronics Engineers (IEEE).•

QUALITY OBJECTIVES

•Note down the quality targets for the overall project. Be as specific as you can be and include how you will measure if the metric has been met. You can use a separate Quality Metrics table to enter the detailed metrics for each deliverable•.

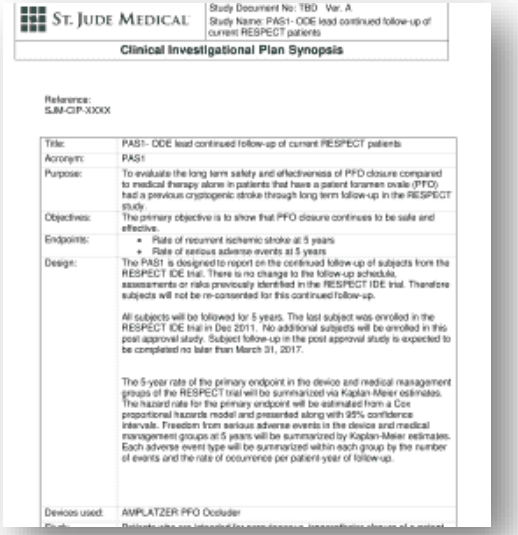
Metric or Specification	Measure
Delivery to scope.	*Comparison of the delivered scope against the Statement of Work. Measured during UAT and customer project acceptance certificate.*
Delivery on time	*Baseline schedule +/- change orders versus actual dates.*
Delivery on budget	*Actual costs +/- change orders versus budget.*
Adherence to ACME project methodology	*PMO audit comparison of method versus project management deliverables.*

QUALITY ROLES AND RESPONSIBILITIES

•Note down the roles and responsibilities that are needed to manage quality on the project•.

Roles	Responsibilities
Quality Manager	*Oversight of quality control on the project. This role will be fulfilled by the PMO Manager.*
Project Manager	*Scheduling and management of quality control activities.*
Developers	*Comply with quality standards and participate in quality control activities.*

Quality Management Plan



ST. JUDE MEDICAL

Study Document No: TBD Ver. A
Study Name: PAS1- ODE lead continued follow-up of current RESPECT patients

Clinical Investigational Plan Synopsis

Reference:
SJM-CIP-XXXX

Title:	PAS1- ODE lead continued follow-up of current RESPECT patients
Acronym:	PAS1
Purpose:	To evaluate the long term safety and effectiveness of PFO closure compared to medical therapy alone in patients that have a patent foramen ovale (PFO) had a previous cryptogenic stroke through long term follow-up in the RESPECT study.
Objectives:	The primary objective is to show that PFO closure continues to be safe and effective.
Endpoints:	• Rate of recurrent ischemic stroke at 5 years • Rate of serious adverse events at 5 years
Design:	The PAS1 is designed to report on the continued follow-up of subjects from the RESPECT IDE trial. There is no change to the follow-up schedule, assessments or risks previously identified in the RESPECT IDE trial. Therefore subjects will not be re-consented for this continued follow-up. All subjects will be followed for 5 years. The last subject was enrolled in the RESPECT IDE trial in Dec 2011. No additional subjects will be enrolled in this post approval study. Subject follow-up in the post approval study is expected to be completed no later than March 31, 2017. The 5-year rate of the primary endpoint in the device and medical management groups of the RESPECT trial will be summarized via Kaplan-Meier estimates. The hazard rate for the primary endpoint will be estimated from a Cox proportional hazards model and presented along with 95% confidence intervals. Freedom from serious adverse events in the device and medical management groups at 5 years will be summarized by Kaplan-Meier estimates. Each adverse event type will be summarized within each group by the number of events and the rate of occurrence per patient-year of follow-up.
Devices used:	AMPLATZER PFO Occluder

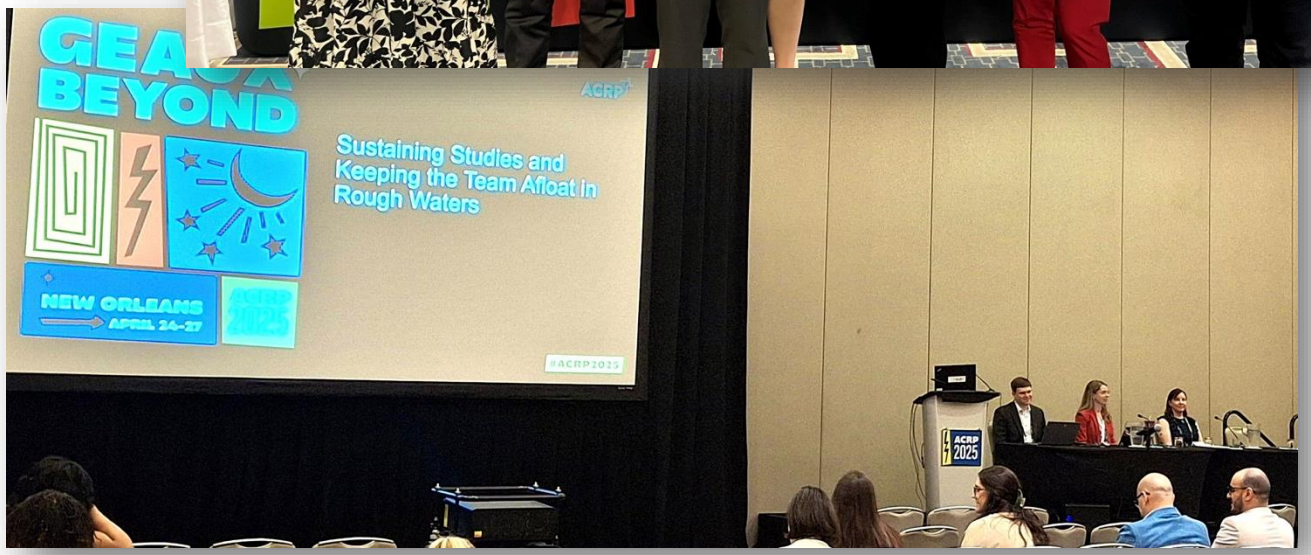
Investigational Plan

Embracing Change

ACRP 2025

Key takeaways related to FDA inspections:

- “Change is constant”
- “Fit-for-purpose”
- “It depends”



“Change is constant”

Everything is in a state of flux.

FDA Guidances

FDA record of 50 guidances dropped in 2024!

Electronic Systems, Electronic Records, and Electronic Signatures in Clinical Investigations: Questions and Answers

Conducting Clinical Trials With Decentralized Elements

Integrating Randomized Controlled Trials for Drug and Biological Products Into Routine Clinical Practice

Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products

Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies


Electronic Systems, Electronic Records, and Electronic Signatures in Clinical Investigations
Questions and Answers
Guidance for Industry
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Center for Food Safety and Applied Nutrition (CFSAN)
Center for Tobacco Products (CTP)
Center for Veterinary Medicine (CVM)
Office of Regulatory Affairs (ORA)
Office of Clinical Policy (OCLiP)
Oncology Center of Excellence (OCE)
October 2024
Procedural
Revision 1
Conducting Clinical Trials With Decentralized Elements
Guidance for Industry, Investigators, and Other Interested Parties
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Oncology Center of Excellence (OCE)
September 2024
Clinical/Medical
Integrating Randomized Controlled Trials for Drug and Biological Products Into Routine Clinical Practice
Guidance for Industry
DRAFT GUIDANCE
Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products
Guidance for Industry
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)
July 2024
Real-World Data/Real-World Evidence (RWD/RWE)
Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies
Guidance for Industry
DRAFT GUIDANCE
This guidance document is being distributed for comment purposes only.
U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Office of Minority Health and Health Equity (OMHHE)
Office of Women's Health (OWH)
June 2024
Clinical/Medical

FDA Reorganization

Largest reorg in FDA history!

Workforce Reductions

- Reduction in force (RIF) of about 3,500 employees
- Primarily affected administrative functions, but also impacted policy, communications, and management staff

Reorganizing and Streamlining

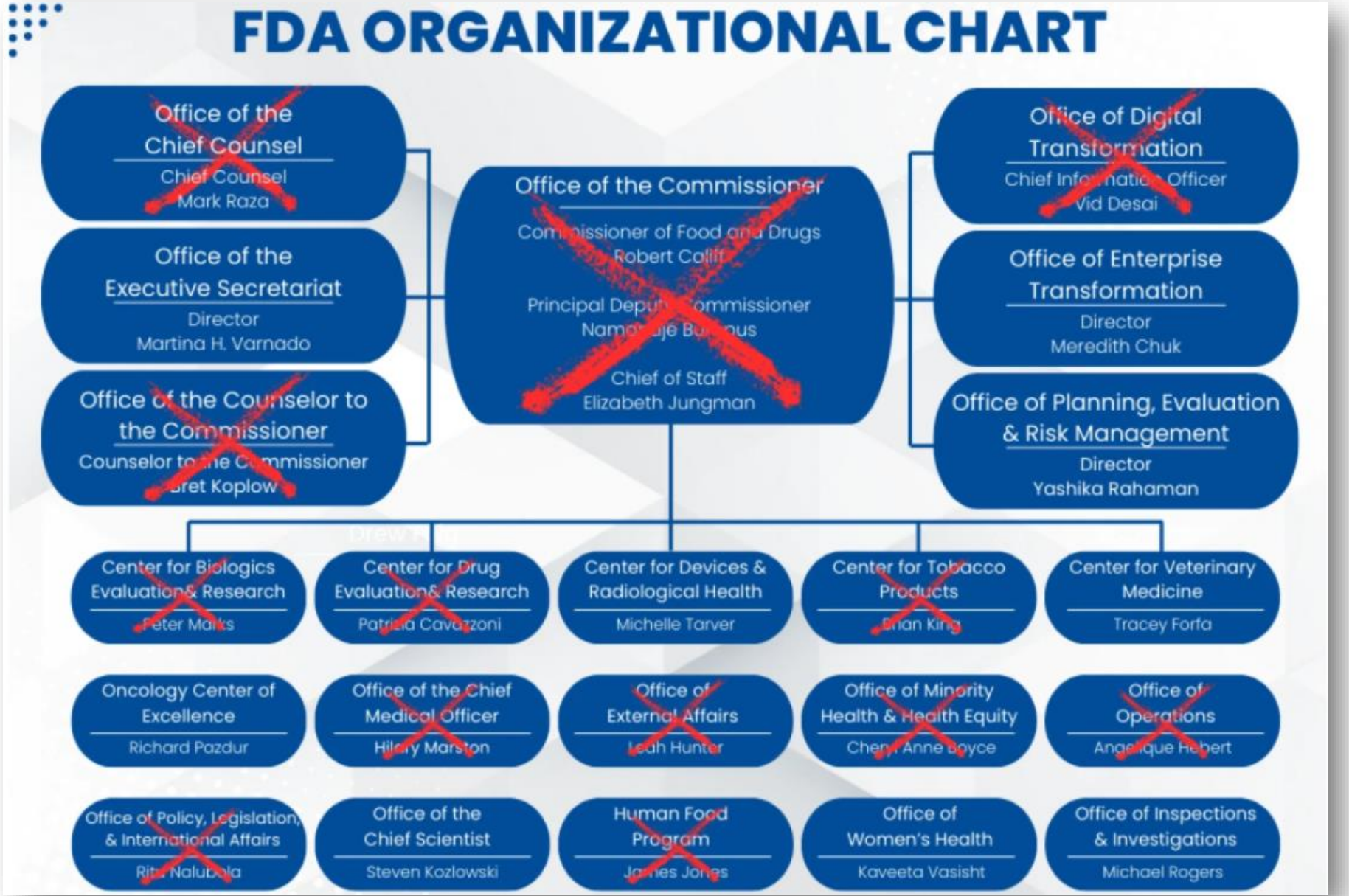
- Reorg involved consolidating 28 divisions into 15
- Regional offices were reduced from 10 to 5
- Structure was also reshaped, with some key functions, like compliance and laboratory safety, being realigned to different parts of the agency
- New Office of Inspections, Compliance, and Enforcement was created, and an Office of Scientific and Regulatory Policy was also formed

Potential Impacts

- Slower application reviews, missed deadlines, and potentially less engagement with sponsors during the development process
- Concerns about the potential to weaken the agency's expertise and effectiveness

Ongoing Efforts

- Actively working to ensure the continuity of its critical programs and inspections during the reorganization period


FDA ORGANIZATIONAL CHART
Office of the Chief Counsel
Chief Counsel
Mark Raza
Office of the Executive Secretariat
Director
Martina H. Varnado
Office of the Counselor to the Commissioner
Counselor to the Commissioner
Bret Koplow
Office of the Commissioner
Commissioner of Food and Drugs
Robert Califf
Principal Deputy Commissioner
Namandjé Bumpus
Chief of Staff
Elizabeth Jungman
Office of Digital Transformation
Chief Information Officer
Vid Desai
Office of Enterprise Transformation
Director
Meredith Chuk
Office of Planning, Evaluation & Risk Management
Director
Yashika Rahaman
Center for Biologics Evaluation & Research
Peter Marks
Center for Drug Evaluation & Research
Patrizia Cavazzoni
Center for Devices & Radiological Health
Michelle Tarver
Center for Tobacco Products
Brian King
Center for Veterinary Medicine
Tracey Forfa
Oncology Center of Excellence
Richard Pazdur
Office of the Chief Medical Officer
Hilary Marston
Office of External Affairs
Leah Hunter
Office of Minority Health & Health Equity
Cheryl Anne Boyce
Office of Operations
Angelique Hebert
Office of Policy, Legislation, & International Affairs
Rita Nalubola
Office of the Chief Scientist
Steven Kozlowski
Human Food Program
James Jones
Office of Women's Health
Kaveeta Vasisht
Office of Inspections & Investigations
Michael Rogers

“Fit-for-purpose”

Something is appropriate, suitable, and up to the necessary standard for it’s intended use.

FDA's Fit-for-Purpose (FFP) Initiative

- Provides a pathway for regulatory acceptance of dynamic tools for use in drug development programs
- Establishes a designation of FFP due to the evolving nature of technology and the inability to provide formal qualification
- Allows the use of tools and methods that are *adequately* validated and *appropriate* for the specific purpose of the trial, rather than requiring full, formal validation

21 CFR Part 11's validation requirements are a key aspect of demonstrating that a system is "fit for purpose.“ – FDA website

21 CFR Part 11

Key Requirements:

- **Validation:** Systems must be validated to demonstrate they are fit for their intended use.
- **Audit Trails:** Systems must maintain audit trails to track changes, including who made them and when.
- **Security Controls:** Access to electronic records must be controlled, and appropriate security measures must be in place.
- **Electronic Signatures:** Digital signatures must meet specific requirements to be considered equivalent to wet signatures.
- **Record Retention:** Electronic records must be stored securely and for the appropriate retention period.

"The new guideline introduces a more flexible and adaptive approach to GCP, aiming to be as future-proof as possible." - CITI website

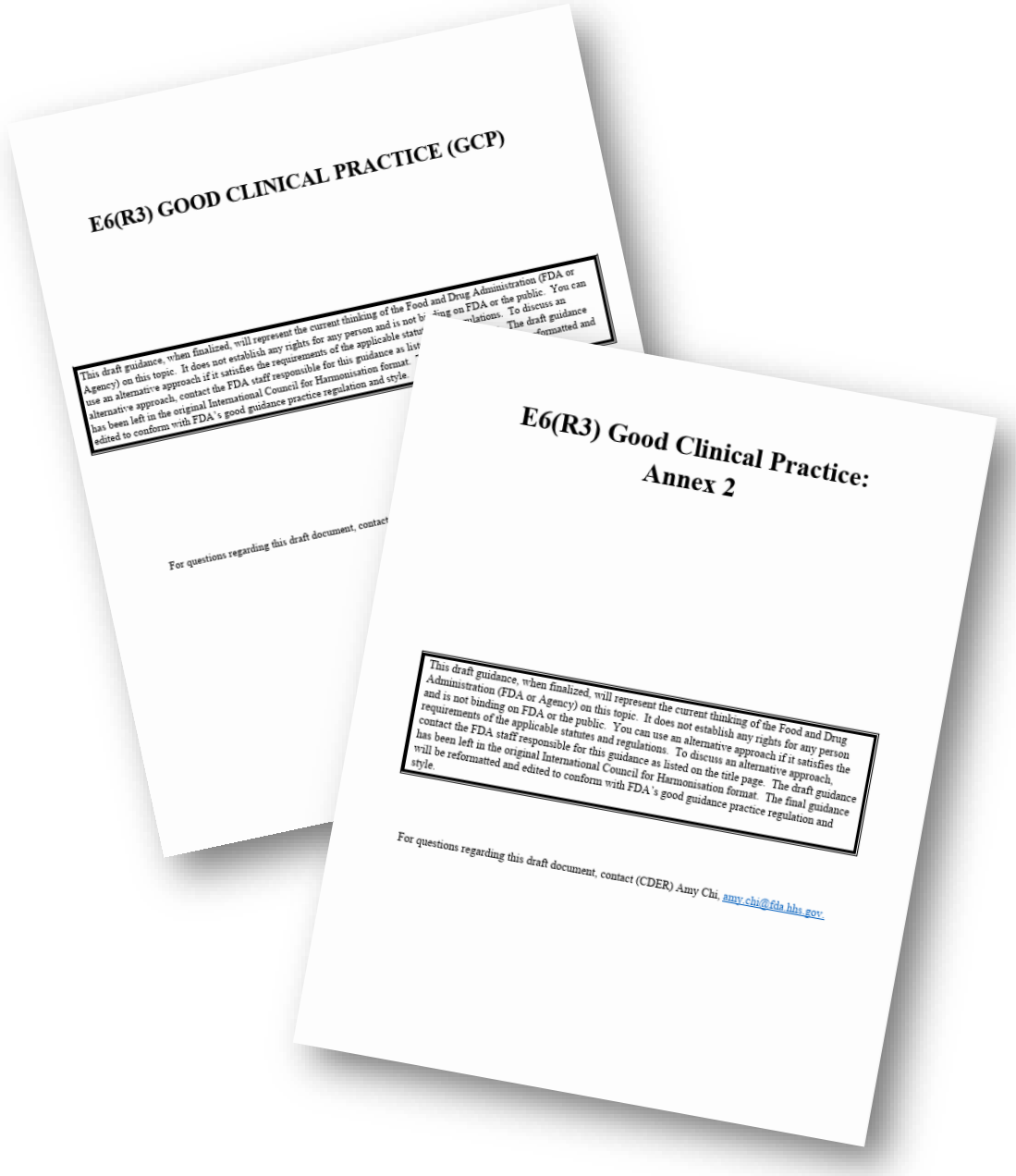
GCP E6(R3)

Key Changes:

- Recognition of the increasing use of decentralized clinical trial designs
- Greater emphasis on Quality Management Systems (QMSs) to ensure trial quality
- Introduction of a "fit for purpose" approach to quality-by-design
- Increased focus on study participants, considering their perspective in trial design and conduct
- More detailed guidance on obtaining informed consent, including the use of technologies to inform participants and obtain consent
- Expanded guidance on the use of electronic systems, including digital health technologies (DHTs) and electronic sources (eSources)
- Recognition of the varied roles of contract research organizations
- Adoption of a "media neutral" approach to applying GCP principles

FDA's Response to E6(R3)

- Following the release of the E6(R3) draft in May 2023, the FDA issued its guidance document to accompany the guideline.
- The draft guidance aligns with the FDA's steps to modernize clinical trials.
- However, similar to E6(R2), the guidance includes a disclaimer stating that ICH E6(R3) will only "represent the current thinking" of the FDA and will not be "binding on the FDA or the public."
- Currently, the final version of E6(R3) is pending adoption by the FDA.



“It depends”

Different in different situations.

It depends ≠ Unclear/Uncertain

- Circumstances Matter
- Nuanced Response
- Ambiguity

David Burrow, PharmD, JD

Director, Office of Scientific Investigations FDA

FDA remains committed to protecting the public health and safety as well as supportive of clinical trials initiatives.

Barbara Wright, JD

Sr Advisor, Office of Bioresearch Monitoring Inspectorate, FDA

The agency considers electronic records and electronic signatures to be trustworthy, reliable, and generally equivalent to paper records and handwritten signatures executed on paper.

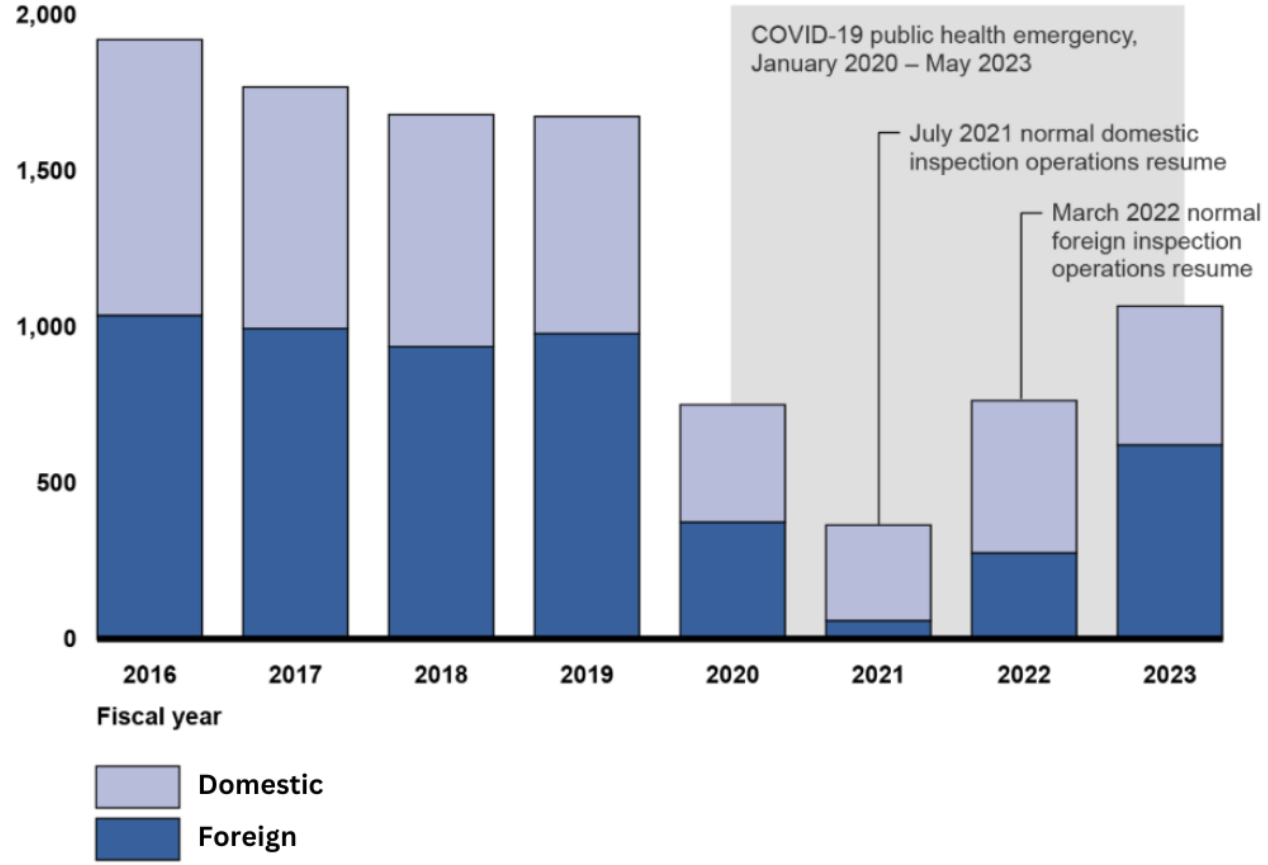
Leslie Sam, BA, CSSBB, CQIA

President, Leslie Sam and Associates, LLC

"Effective oversight requires critical thinking, as the most suitable approach will vary depending on the specific situation. There is no universal, 'one-size-fits-all' solution."

So…what's this all mean for FDA inspections?

FDA Inspections Trends



Source: GAO analysis of Food and Drug Administration (FDA) inspection data. | GAO-25-106775

FDA Inspections FY 2023

October 1, 2022-September 30, 2023

693

BIOMO Inspections

Clinical Investigator

Inspections

142

483s issued

483s/Warning Letters

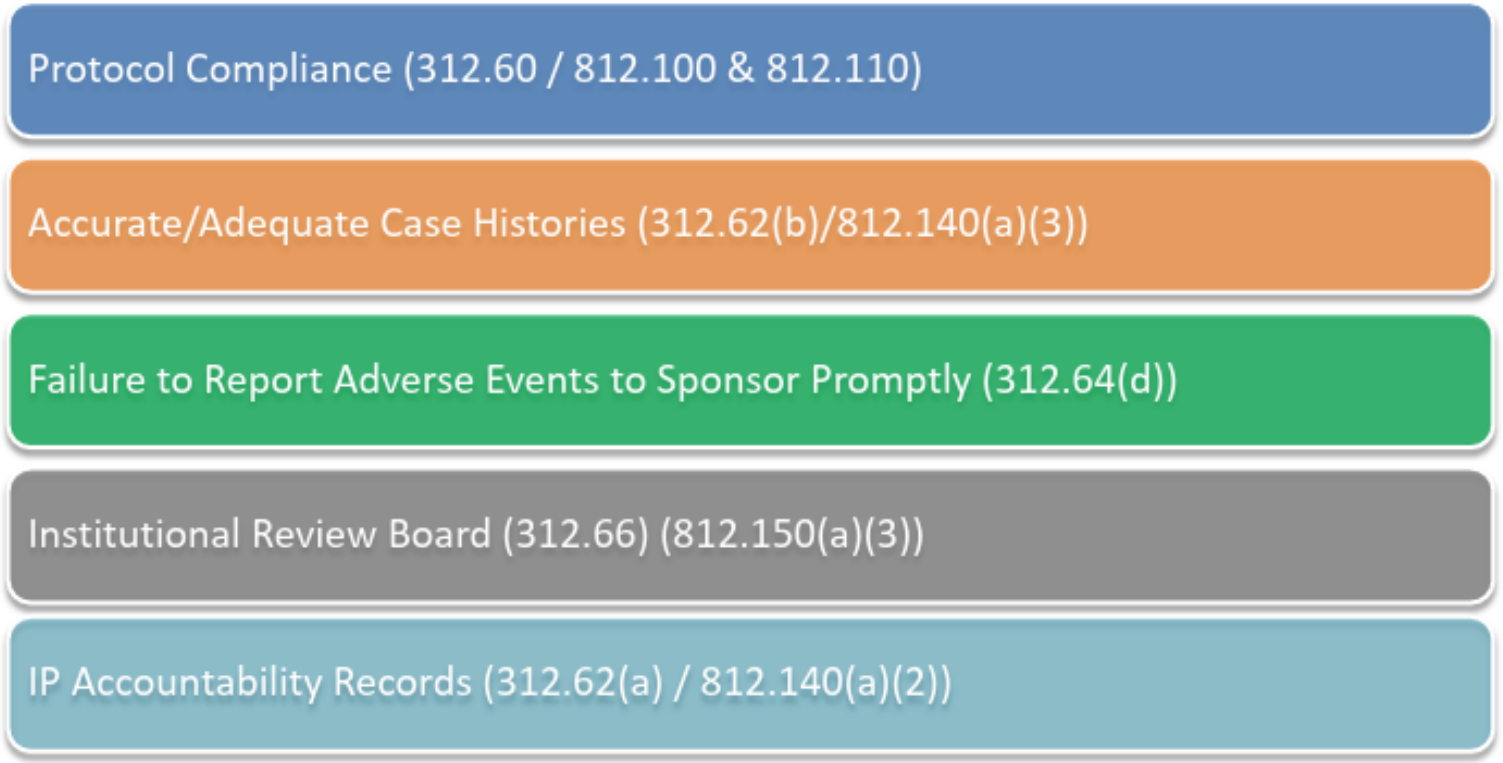
9

Warning Letters

OAIs

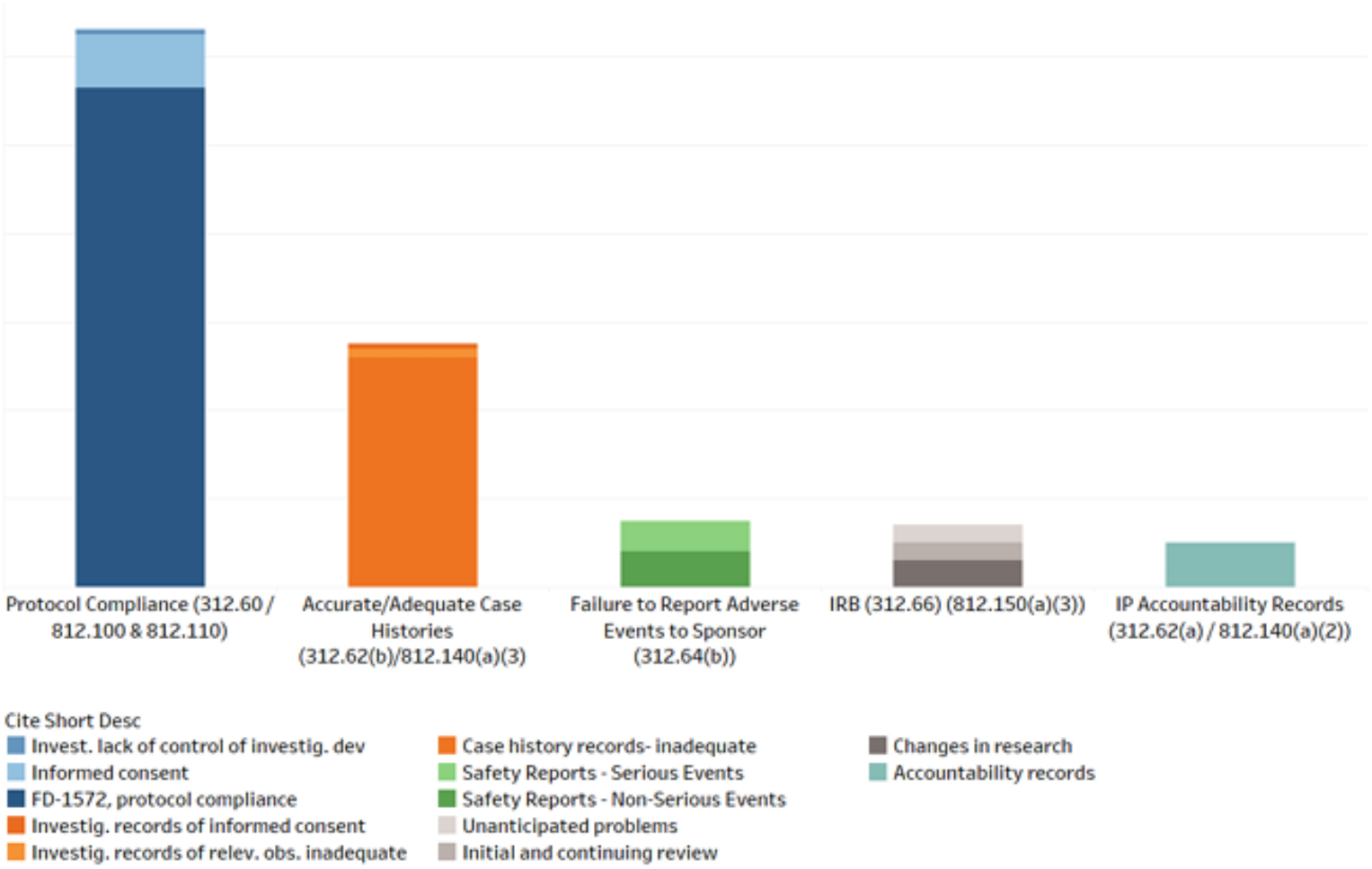
Compliance Actions

FDA 483 Observation Trends FY 2023



FDA FY 2023 Data

FDA 483 Observation Trends FY 2023



So…what's this all mean for FDA inspection *preparedness*?

Navigate Inspections

- Be proactive
- Use your resources
- Lean on:
  - Administration
  - Institution IT
  - Sponsor
  - 3rd party vendor

Embrace Change

- Stay current and in-the-know
- Keep open communication
- Remember…Patient safety and Data integrity

Be mindful

- Conduct mock inspections
- Practice empathy
- Take a deep breath!

"The best preparation for tomorrow is doing your best today."

H. Jackson Brown Jr.

Post Inspection/CAPAs

Jen Zvosec, MCR, CCRP

The Ohio State University

Closing Meeting

- The inspector will discuss any observations, findings and concerns
- The inspector may issue an FDA Form 483
  - Written report of any conditions or practices, which, in the inspector's judgment, indicate objectionable conditions or practices
- You may provide a verbal response to the FDA-483 during the discussion with the inspector

FDA Form 483

- Notifies the investigator of objectionable conditions
- Issued when an inspector has observed conditions that constitute violations of the Food Drug and Cosmetic (FD&C) Act and related Acts
- Does not include observations of questionable or unknown significance at the time of the inspection
- Each observation is read and discussed so there is a full understanding of what the observations are and what they mean
- Not a final determination of whether any condition is in violation of the FD&C Act or any of its relevant regulations

Common 483 Observations

Citation Program Area	Cite ID	Reference Number	Short Description	Long Description
Bioresearch Monitoring	7560	21 CFR 312.60	FD-1572, protocol compliance	An investigation was not conducted in accordance with the [signed statement of investigator] [investigational plan]. Specifically, ***
Bioresearch Monitoring	7530	21 CFR 312.62(b)	Case history records- inadequate or inadequate	Failure to prepare or maintain [adequate] [accurate] case histories with respect to [observations and data pertinent to the investigation] [informed consent]. Specifically, ***
Bioresearch Monitoring	7482	21 CFR 312.50	General responsibilities of sponsors	Failure to [select qualified investigators] [provide investigators with the information needed to conduct the study properly] [ensure proper monitoring of the study] [ensure the study is conducted in accordance with the protocol and/or investigational plan] [ensure that FDA and all investigators are promptly informed of significant new adverse effects or risks]. Specifically, ***
Biologics	76	21 CFR 606.100(b)	Establish, maintain and follow manufacturing SOPs	Written standard operating procedures including all steps to be followed in the [collection] [processing] [compatibility testing] [storage] [distribution] of blood and blood components for [allogeneic transfusion] [autologous transfusion] [further manufacturing purposes] were not always [established] [maintained] [followed] [available to personnel in the areas where procedures were performed]. Specifically, ***
Biologics	154	21 CFR 606.160(a)(1)	Concurrent documentation	Records are not concurrently maintained with the performance of each significant step in the [collection] [processing] [compatibility testing] [storage] [distribution] of each unit of blood and blood components so that all steps can be clearly traced. Specifically, ***
Biologics	155	21 CFR 606.160(b)	Required records	Failure to maintain [donor] [processing] [storage and distribution] [compatibility testing] [quality control] [general] records. Specifically, ***

Common 483 Observations

Citation Program Area	Cite ID	Reference Number	Short Description	Long Description
Devices	3130	21 CFR 820.100(a)	Lack of or inadequate procedures	Procedures for corrective and preventive action have not been [adequately] established. Specifically, ***
Devices	14713	21 CFR 820.198(a)	Lack of or inadequate complaint procedures	Procedures for receiving, reviewing, and evaluating complaints by a formally designated unit have not been [adequately] established. Specifically,***
Devices	3282	21 CFR 820.90(a)	Nonconforming product, Lack of or inadequate procedures	Procedures have not been [adequately] established to control product that does not conform to specified requirements. Specifically, ***
Drugs	1105	21 CFR 211.22(d)	Procedures not in writing, fully followed	The responsibilities and procedures applicable to the quality control unit are not [in writing] [fully followed]. Specifically, ***
Drugs	2027	21 CFR 211.192	Investigations of discrepancies, failures	There is a failure to thoroughly review [any unexplained discrepancy] [the failure of a batch or any of its components to meet any of its specifications] whether or not the batch has been already distributed. Specifically, ***
Drugs	1361	21 CFR 211.100(a)	Absence of Written Procedures	Your firm failed to establish [adequate] written procedures for production and process controls designed to assure that the drug products have the identity, strength, purity, and quality that they are purported or represented to possess. Specifically, ***

FDA Form 483 Response

- Respond in writing, within 15 working days from the issuance of the FDA 483
- Cover letter
  - Thank the FDA inspector for their time and identify opportunities for improvement
  - State your commitment to compliance and commitment to continuous improvement

FDA Form 483 Response

- Body
  - Restate each Form 483 observation
  - Relevant background information for each observation
  - Assessment of the root cause of the problem
  - Corrective actions
  - Preventative actions
- Attachments
  - Include and reference attachments as needed
  - Organized and easy for the FDA to find and reference

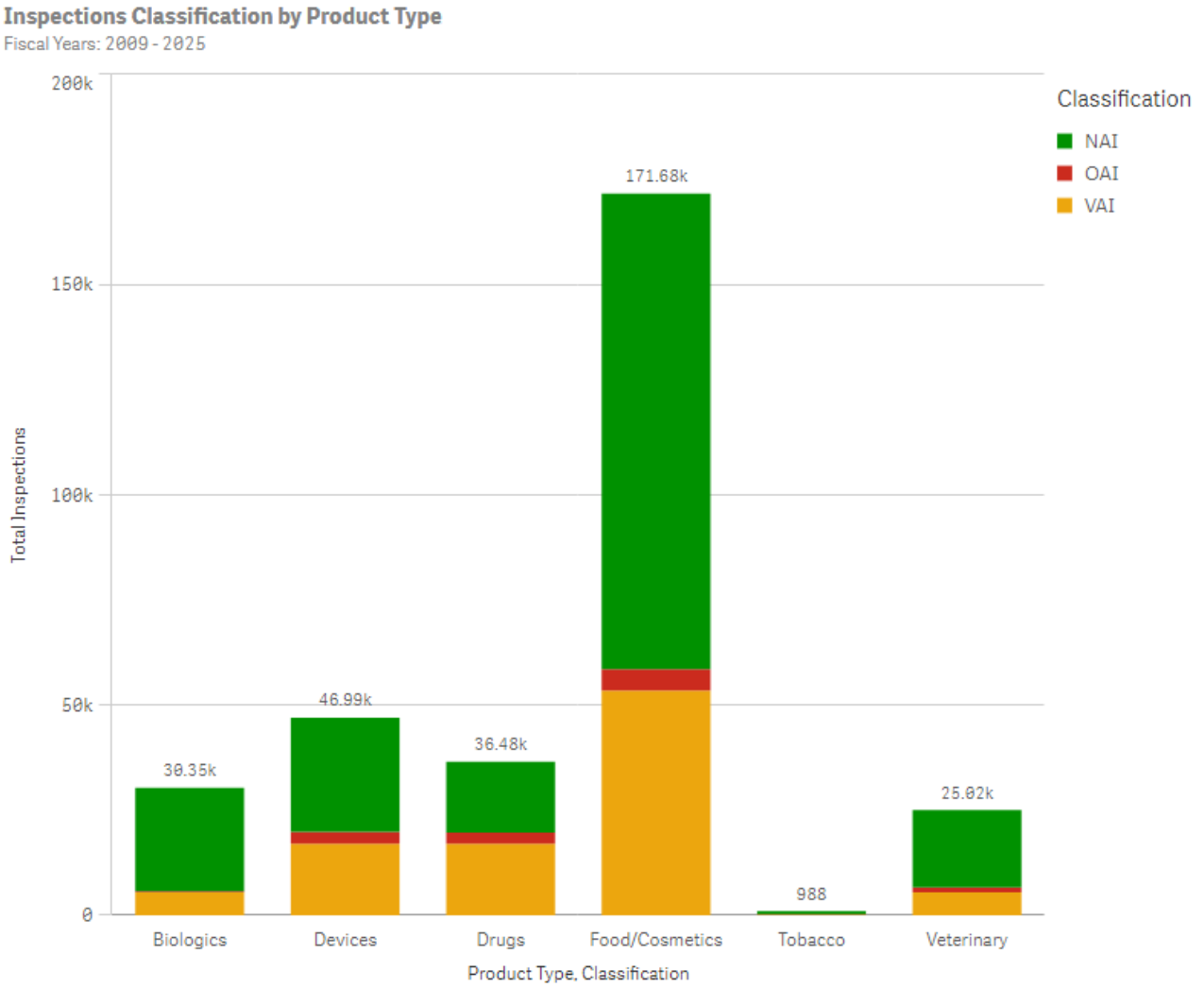
Establishment Inspection Report (EIR)

- The FDA Form 483 is not a final Agency determination
- Usually sent in a letter within 45 - 90 days from the close of an inspection
- The FDA Form 483 is considered, along with an Establishment Inspection Report (EIR), all evidence or documentation collected on-site, and any responses made by the company

Inspection Classifications

- No action indicated (NAI)
  - No objectionable conditions or practices were found during the inspection
- Voluntary action indicated (VAI)
  - Objectionable conditions or practices were found, but the agency is not prepared to take or recommend any administrative or regulatory action
- Official action indicated (OAI)
  - Regulatory and/or administrative actions are recommended

Inspection Classifications



The James

The Ohio State University
Comprehensive Cancer Center

Regulatory Impact

- Warning Letters
- Import Alerts
- Consent Decrees
- Product Approvals or Delays

Summary

- At the conclusion of the inspection, the inspector will discuss any significant findings and concerns
- An FDA Form 483 is issued at the conclusion of an inspection when an inspector has observed any conditions that in their judgment may constitute violations of the FD&C Act and related Acts
- Respond to the FDA Form 483 in writing within 15 working days
- Develop feasible solutions that can be implemented within a reasonable timeframe and address the correction of both specific and systemic issues
- The FDA is looking for understanding of the problem and identification/implementation of a solution

Thank You

The James

The Ohio State University
COMPREHENSIVE CANCER CENTER

FDA Inspections
Moderated Q&A

Closing Comments

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