Building IND Infrastructure to Ensure Compliance and Enable Growth

J. Kaitlin Morrison, PhD; Nasrin H. Babadi, PhD, RAC; Erin Crecelius, MA; Shaw Scott, JD; Robin V. Johnson, M.Med.Sc; Susan Boyle; Martha Retter; Allison Camp, PhD; Leila Kiefer, PhD; Carrie Lee, MD, MPH

Introduction

IND regulations are complex and require a high-level of subject matter expertise to ensure compliance. Historically, Lineberger Comprehensive Cancer Center (LCCC) relied on centralized University resources to submit and maintain its INDs. In 2016, LCCC identified substantial noncompliance with FDA regulations across its IND portfolio and decided to build infrastructure to move IND management in-house.

The goal of this initiative was to develop an IND management system with appropriate checks and balances to ensure LCCC's INDs followed appropriate regulations to detect early indicators of noncompliance.

Solutions/Methods

Root cause analysis identified several contributing factors to noncompliance including lack of: written procedures defining IND management, investigator involvement and awareness, and training at all levels of the organization. The methods implemented were focused on addressing these root causes and ensuring that all management steps relied on a system as opposed to a single individual to ensure compliance. Ten sets of IND-specific SOPs, work instructions and templates (**Figure 1A**) were developed covering topics ranging from IND safety reports to distribution of FDA communication. The SOPs described automated processes that heavily relied on utilization of custom reports generated from the clinical trial management system, OnCore™, to track submission deadlines, such as the IND lapse report (**Figure 1B**).

Figure 1. SOPs/Processes for IND Maintenance

A

Templates

-**Protocol** (Biospecimen, Chemotherapy, Health Services, Radiation Therapy, Cellular Therapy, Radiology, Amendment Cover Sheet)

-**Informed Consents** (CAR-T Procurement, CAR T Treatment, CAR-T Biospecimen, Phase 1- Combination, Phase 2, Phase 2- Multi-arm, Biospecimen)

-**IND Initial** (Simple, Complex, CAR-T, eCTD [purchased])

-**IND Report** (1 Study Annual Report, Multiple Studies Annual Report, 1 Study Withdraw, Multiple Studies Withdrawal)

-**IND Cover Letters** (Initial, Protocol Amendment- New Investigator, Updated Form FDA 1572, Protocol Amendment- Change in Protocol, IND Safety Report-Initial, IND Safety Report- Action Letter, IND Safety Report- Initial Aggregate Report, IND Safety Report-Follow-up, Annual Report, Updated Medical Monitor, Acceptance of Transferred IND, IND Transfer to a New Sponsor, PI Transfer, Updated Sponsor Contact Information, IND Withdrawal)

-**Action Letter**

-**IND Exemption Letter**

-**Letter of Authorization**

SOPs/Work Instructions

-Protocol Amendments
-Determining IND Status
-Administrative Letters
-Action Letters
-IND Safety Reporting (single and multicenter)
-Updates for Form FDA 1572
-CAPA Implementation and Oversight
-Drafting and Amending IBs
-Determining IDE Status
-IIT Protocol Review Meetings
-IND Annual Reports
-Distribution of FDA Communication
-Protocol Amendment- Change in Protocol Submissions
-Protocol Amendment- New Investigator Submissions
-Changes in Sponsor, Medical Monitor, and/or PI
-Changes in Multicenter PI
-PI Transfer (with and without an IND)
-IND Withdrawal
-Updating Protocol Templates
-DSMC and IND Data Report Generation
-IND Data Report Review Checklist
-IND Data Report Timelines
-IND OnCore Tracking
-Electronic Submissions through the CDER Portal
-Printing/Binding Paper FDA Submissions
-eCTD Submissions
-Checklist for IND Exemption

B

Summary | SRC/PRC | DSMC | IRB | LTFU Transfer | Other External Committee Actions

Other Committee Action History

Committee	Committee No	Submit Date	Review Date	Action	Action Date	Submission	Comment	Next Review Date
FDA				Annual Report		Serial Submission 0020: Annual Report		
FDA		11/19/2021	11/19/2021	Protocol Amendment-Change in Protocol	11/19/2021	Serial Submission 0019-Protocol Amendment #5	Amend v2.0 (v11/02/21) includes a wash out period of bridge therapy prior to lymphodepletion. Due to the aggressive nature of some patients disease as well as	05/21/2022

Custom Reports
CTRP Report
CTRP Report (no blank column color)
External Committee Action Docking Report

→ Report generated out of OnCore™ with all upcoming IND submissions:

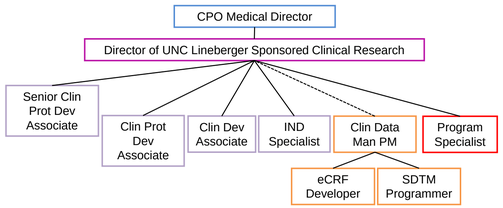
Reg Assoc	Protocol No	Management Group	Status	Committee	Committee No	Action	Next Review Date	Committee Coment	Submission
Ghidorzi, Jessica,	LCCC1632	Gastrointestinal CPO	OPEN TO ACCRUAL	FDA	null	Annual Report	null	null	Serial Submission 0002 - IND Annual Report

A. Work Instructions, Standard Operating Procedures (SOPs) and templates for IND and protocol management. B. IND submissions added into the "other external committee" screen in OnCore™ without a submission date, are pulled through custom reports indicating that they still require submission to FDA. INDs requiring annual reporting to FDA are run using a standard OnCore™ (IND lapse report).

Solutions/Methods

Subject matter experts in protocol development were hired within LCCC expanding from 1 FTE solely supporting protocols to 5 FTEs over protocol development and IND management (**Figure 2**). Their addition was justified by the need to address noncompliance, growth in portfolio and expansion in IND and protocol development services. Additional FTEs were also added in data management to develop IND reports (**Figure 2**). Electronic data reports were optimized to ease IND annual report writing and were released under a stringent quality assurance system to ensure the accuracy and completeness of the data (**Figure 3**). Additionally, a PI training lecture series was launched and covered IND-related hot topics with a focus on lessons learned (**Refer to LCCC Training Poster**). Furthermore, a series of lectures targeted to staff were developed and well received.

Figure 2. IND Infrastructure FTEs



Full-time employees (FTEs) to support IND management and protocol development. Responsibilities for these staff include: 1. Figuring out what regulations apply to the study, 2. Submitting to FDA (IND & IDEs), 3. Drafting/Submitting an IND/IDE exemption to the Protocol Review Committee (PRC), 4. Drafting Letters of Intent (LOIs) & occasionally writing clinical trial grants, 5. Drafting protocols, consent forms & patient education materials, 6. Leading protocol and correlative (lab manual) review meetings, 7. Interacting with the Institutional Conflict of Interest (COI) Board, 8. Facilitating the transition of products from the bench to the clinic, 9. Facilitating access to resources to enable clinical development, 10. Developing FDA compliant data sets and creation of eCRFs in Part 11 compliant systems, 11. Providing guidance to the PRC, Data and Safety Monitoring Committee (DSMC), Compliance Committee, and the COI Committee on FDA regulations, 12. Collaborate with patient advocates on expanding patient education, and 13. Training investigators on their responsibilities.

Figure 3. Example IND Report Data Tables

For LCCCXXXX-ATL Studies	
Total Enrollment (procurement)	15
Procured	15
Treated	13
Awaiting Treatment	
Ineligible for Treatment	
Total Enrollment (treatment)	13
On Study- First Infusion	9
On Treatment- Lymphodepletion	0
On Treatment- CAR T cell Infusion	
Completed Treatment	9
On Study- Second Infusion	
On Treatment- Lymphodepletion	0
On Treatment- CAR T cell Infusion	
Completed Treatment	9
On Follow-up	9
Off Study	3
Death	3
Completed per the Protocol	0
Withdrew	1*

Demographics Summary Table			
	Male	Female	Unknown
Total %			
Ethnicity			
Hispanic			
Non-Hispanic			
Unknown			
Age			
18-29			
30-49			
50-64			
65+			
Race			
American Indian			
Black or African American			
More than one race			
Unknown			
White			

Adverse Event Summary							
				Grade			
Toxicity Category	Toxicity	Count (%) N = 6	Treatment Type	1	2	3	4

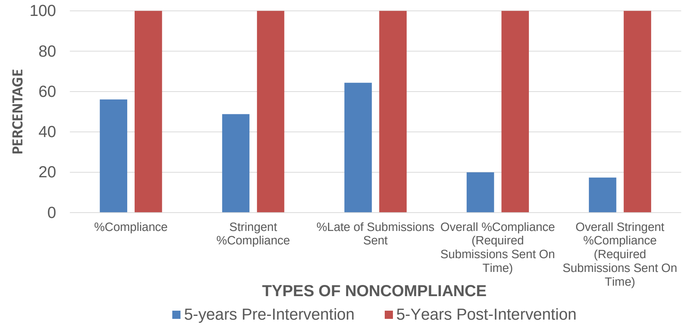
Serious Adverse Events Tabulation										
Dose	Sequence Number	Body Syst AE Term	AE Start Date	AE End Date	AE Toxicity Grade	Attribution	Attribution #2	AE Outco Race	Age/Gender	Date on study/Date off Study

Example subject status, demographic, adverse event and serious adverse event tables generated to facilitate authoring of IND annual reports.

Results

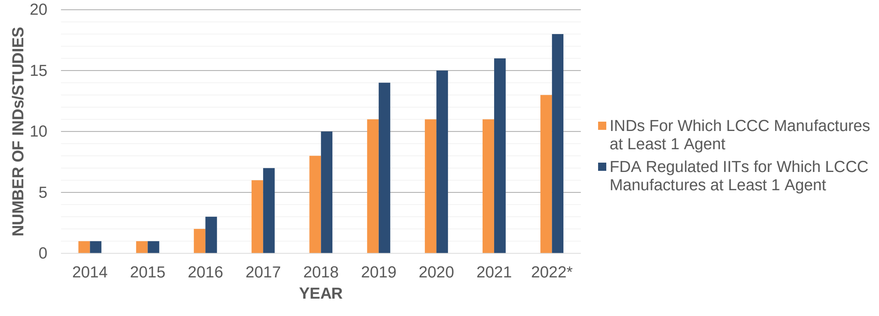
Prior to solution implementation, internal audit revealed that within the 5 years prior there was only 56% compliance with submission IND serial submissions per the regulations (**Figure 4**). Furthermore, of the serial submission that were provided to FDA, 64% of the submissions were late. This means that LCCC's IND overall compliance rating with FDA regulations was only 20%. Internal audits were completed in 2022 of the 5 years after intervention implementation and showed 100% compliance with the regulations. Importantly, the IND portfolio grew in complexity within the 5-year period post-intervention with the addition of 10 INDs for internally manufactured products covering 15 clinical protocols (**Figure 5**). Prior to transition, LCCC had only 1 IND covering 1 clinical protocol for an internally manufactured investigational product. Therefore, compliance increased significantly despite increased complexity.

Figure 4. IND Compliance



% Compliance = Submissions compliant with 21CFR312, Stringent % Compliance = Submissions compliant with 21CFR312 + Community standards (e.g., submission of all protocol amendments to FDA), % Late of Submissions Sent = Submissions sent to FDA, as required, but not submitted within the timeframes specified in 21CFR312, Overall % Compliance = Submissions compliant with 21CFR312 and submitted within the required timeframes, Overall Stringent % Compliance = Submissions compliant with 21CFR312 + Community standards (e.g., submission of all protocol amendments to FDA), and submitted within the required timeframes.

Figure 5. IND Portfolio Complexity



IND complexity increased over time as LCCC focused on development of internally manufactured investigational agents (e.g., CAR-T cells, personalized and adaptive neoantigen dose-adjusted vaccine (PANDA-VAC), C11-AMT, ^{68}Ga-PSMA-11) . Several of these INDs focused on a specific investigational agent with multiple clinical protocols managed under the product specific IND spanning multiple indications or phases of development (I, Ib/II, II). *2022 data cut-off 05/13/2022.

Conclusions

Two major lessons were learned during this process: 1. PI understanding of IND regulations at a high-level is key to ensure compliance with regulations and 2. Automated systems that are independent of a single individual are necessary to ensure long-term compliant oversight of the IND portfolio (e.g., OnCore™ and procedural processes).