PI Oversight: Trial Conduct Expectations and Ensuring Patient Safety and Rights

Andy Gordesky
Regional Director, Clinical Quality Management, North America
Merck

Linda Smith Harris
Senior Clinical Research Associate
Merck

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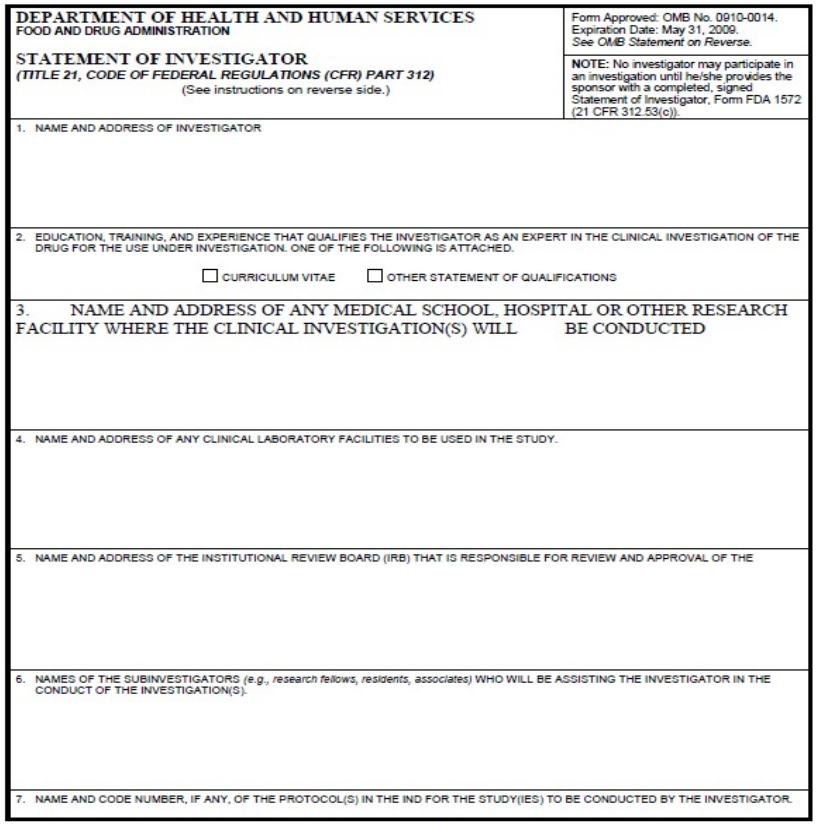
Faculty Disclosure

- In compliance with ACCME Guidelines, I hereby declare:
- I do not have financial or other relationships with the manufacturer(s) of any commercial services(s) discussed in this educational activity.
- Andy Gordesky, Regional Director, Clinical Quality Management, North America, Merck
- Linda Smith Harris, Senior Clinical Research Associate, Merck

FDA Form 1572



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

STATEMENT OF INVESTIGATOR
(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)
(See instructions on reverse side.)

Form Approved: OMB No. 0910-0014.
Expiration Date: May 31, 2009.
See OMB Statement on Reverse.

NOTE: No investigator may participate in an investigation until he/she provides the sponsor with a completed, signed Statement of Investigator, Form FDA 1572 (21 CFR 312.53(c)).

1. NAME AND ADDRESS OF INVESTIGATOR

2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFIES THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE DRUG FOR THE USE UNDER INVESTIGATION. ONE OF THE FOLLOWING IS ATTACHED.

☐ CURRICULUM VITAE ☐ OTHER STATEMENT OF QUALIFICATIONS

3. NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL OR OTHER RESEARCH FACILITY WHERE THE CLINICAL INVESTIGATION(S) WILL BE CONDUCTED

4. NAME AND ADDRESS OF ANY CLINICAL LABORATORY FACILITIES TO BE USED IN THE STUDY.

5. NAME AND ADDRESS OF THE INSTITUTIONAL REVIEW BOARD (IRB) THAT IS RESPONSIBLE FOR REVIEW AND APPROVAL OF THE

6. NAMES OF THE SUBINVESTIGATORS *(e.g., research fellows, residents, associates)* WHO WILL BE ASSISTING THE INVESTIGATOR IN THE CONDUCT OF THE INVESTIGATION(S).

7. NAME AND CODE NUMBER, IF ANY, OF THE PROTOCOL(S) IN THE IND FOR THE STUDY(IES) TO BE CONDUCTED BY THE INVESTIGATOR.

FDA Form 1572

9. COMMITMENTS:

I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

I agree to personally conduct or supervise the described investigation(s).

I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.

I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.
I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.

I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

Quick Quiz

Religious and political texts aside, what is the best-selling individual book of all time?

List of Best-Selling Individual Books

More than 100 million copies

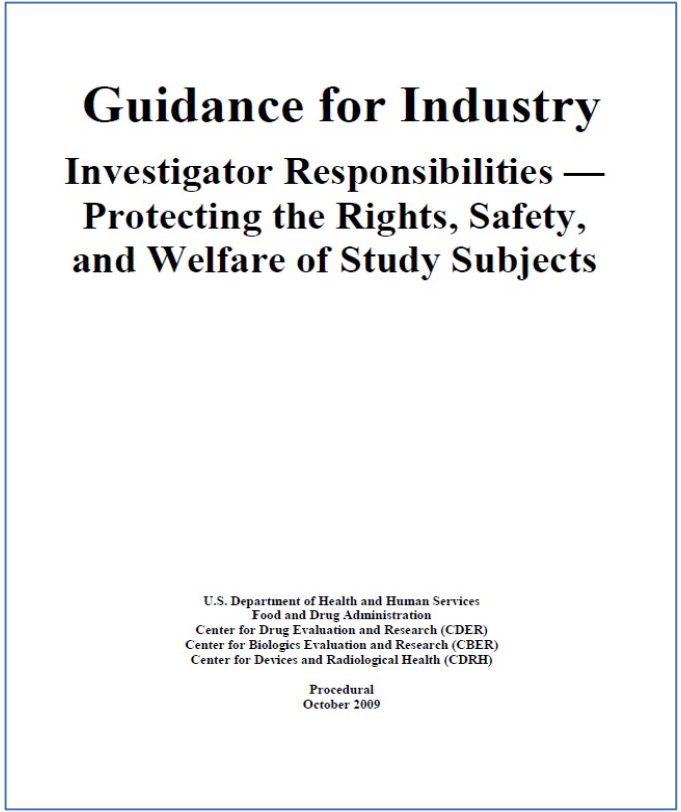
Book	Author(s)	Original language	First published	Approximate sales	Genre
The Hobbit	J. R. R. Tolkien	English	1937	140.6 million[17]	Fantasy
Harry Potter and the Philosopher's Stone	J. K. Rowling	English	1997	120 million[18][19]	Fantasy
The Little Prince	Antoine de Saint-Exupéry	French	1943	100 million[20]	Novella
Dream of the Red Chamber	Cao Xueqin	Chinese	18th century	100 million[20]	Family saga
And Then There Were None	Agatha Christie	English	1939	100 million[21]	Mystery
Guidance on Investigator Responsibilities	FDA	English	2009	100 million[22]	Guidance

FDA Guidance – Investigator Responsibilities

Investigators who conduct clinical investigations of drugs, including biological products, under 21 CFR Part 312, commit themselves to personally conduct or supervise the investigation.

When tasks are delegated by an investigator, the investigator is responsible for providing adequate supervision of those to whom tasks are delegated.

The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.



FDA Guidance – Investigator Responsibilities

In assessing the adequacy of supervision by an investigator, FDA focuses on four major areas:

(1) whether individuals who were delegated tasks were qualified to perform such tasks,

(2) whether study staff received adequate training on how to conduct the delegated tasks and were provided with an adequate understanding of the study,

(3) whether there was adequate supervision and involvement in the ongoing conduct of the study, and

(4) whether there was adequate supervision or oversight of any third parties involved in the conduct of a study to the extent such supervision or oversight was reasonably possible.

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BIMO 7348.811

Program #	Compliance Program Title	On-line Availability	
7348.003	In Vivo Bioavailability-Bioequivalence Studies - Clinical		PDF
7348.004	In Vivo Bioavailability-Bioequivalence Studies - Analytical		PDF
7348.007	Inspection of Nonclinical Laboratories Conducting Animal Rule-Specific Studies		PDF
7348.808	Good Laboratory Practice (Nonclinical Laboratories)		PDF(117 kb)
7348.808A	Good Laboratory Practice Program (Nonclinical Laboratories) EPA Data Audit Inspections	HTML	PDF(38 kb)
7348.809	Institutional Review Board		PDF(293 kb)
7348.809A	Radioactive Drug Research Committee		PDF (155 kb)
7348.810	Sponsors, Contract Research Organizations, and Monitors	HTML	PDF(80 kb)
7348.811	Clinical Investigators and Sponsor-Investigators		PDF
7353.001	Postmarketing Adverse Drug Experience (PADE) Reporting Inspections		PDF (335 kb)
7353.001C	Risk Evaluation and Mitigation Strategies (REMS) Reporting Inspections		PDF

BIMO 7348.811

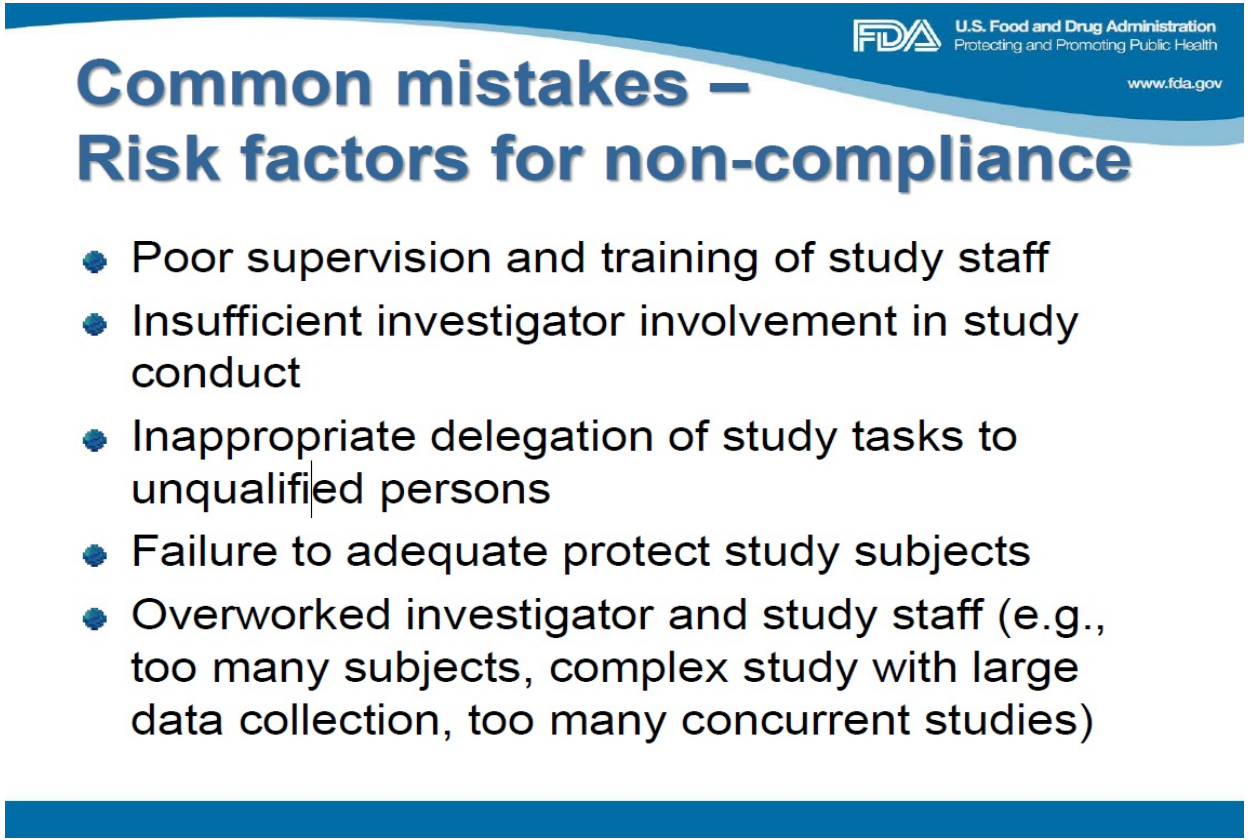
3. For each of the inspected studies, document in the EIR:

a. The names and addresses of all locations where study visits were conducted;

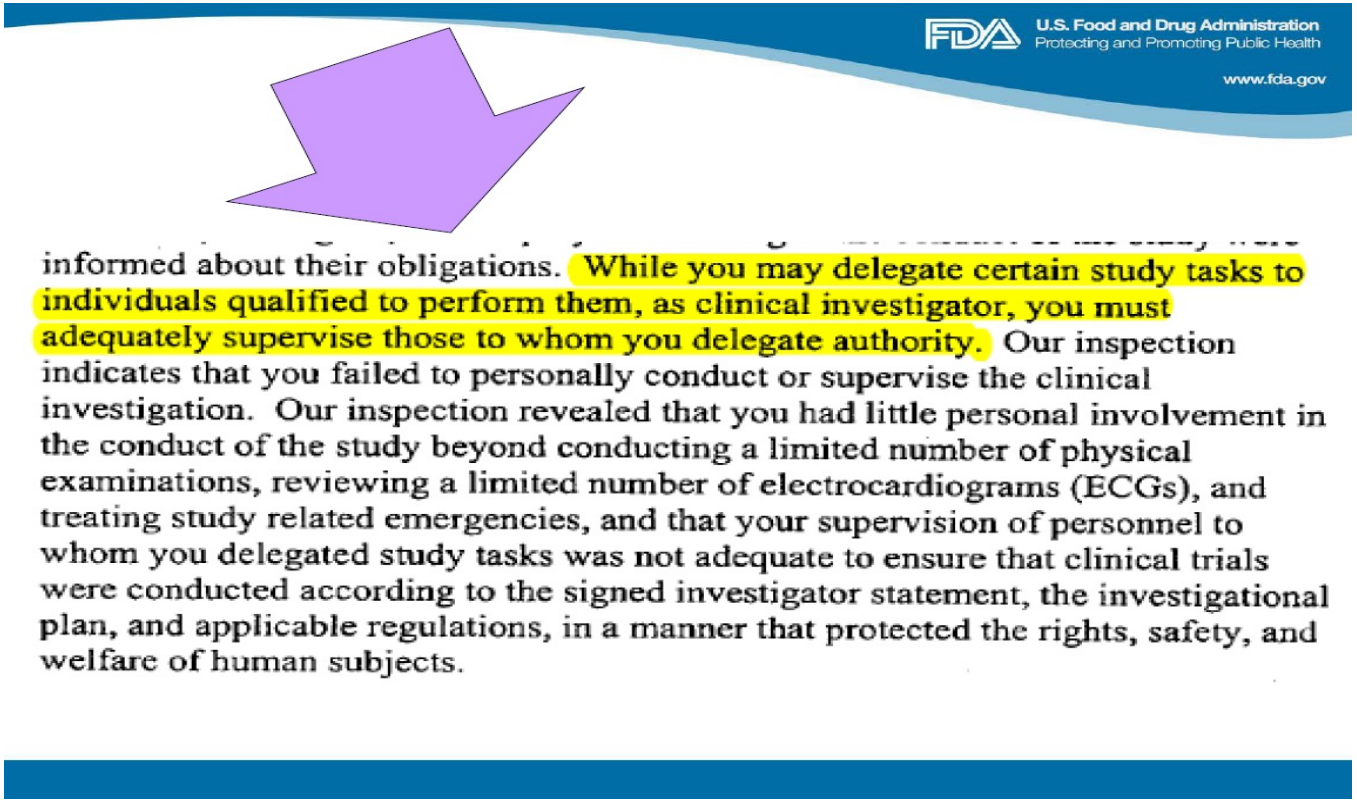
b. How the sponsor provided information and training to the clinical investigator about the investigational product, protocol, electronic systems, and the obligations of a clinical investigator (e.g., telephone, written correspondence, investigator meetings, sponsor presentations on the protocol);

c. Whether the authority for the conduct of the various aspects of the study was contracted and/or delegated properly so that the clinical investigator retained control and knowledge of the study. If there are concerns about appropriate delegation, obtain information (e.g., curriculum vitae, medical or other license, delegation of authority log) about the qualifications and training of the person performing the delegated task and the clinical investigator's oversight of the study.

FDA Investigator Training Course

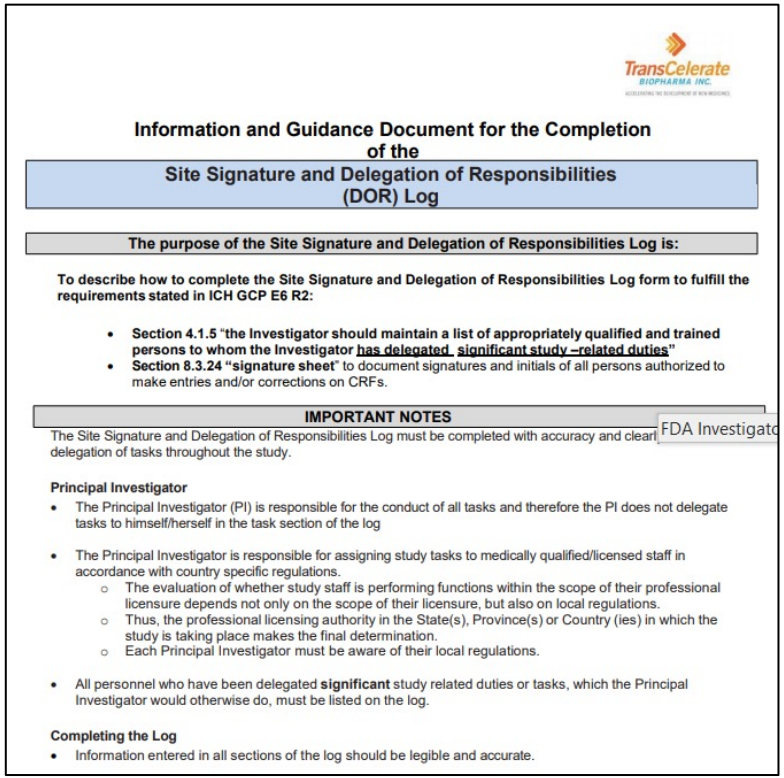


FDA Investigator Training Course



Delegation of Authority

Alignment with Transcelerate Member Companies



TransCelerate BIOPHARMA INC.

Information and Guidance Document for the Completion of the

Site Signature and Delegation of Responsibilities (DOR) Log

The purpose of the Site Signature and Delegation of Responsibilities Log is:

To describe how to complete the Site Signature and Delegation of Responsibilities Log form to fulfill the requirements stated in ICH GCP E6 R2:

- **Section 4.1.5 "the Investigator should maintain a list of appropriately qualified and trained persons to whom the Investigator has delegated significant study –related duties"**
- **Section 8.3.24 "signature sheet"** to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

IMPORTANT NOTES

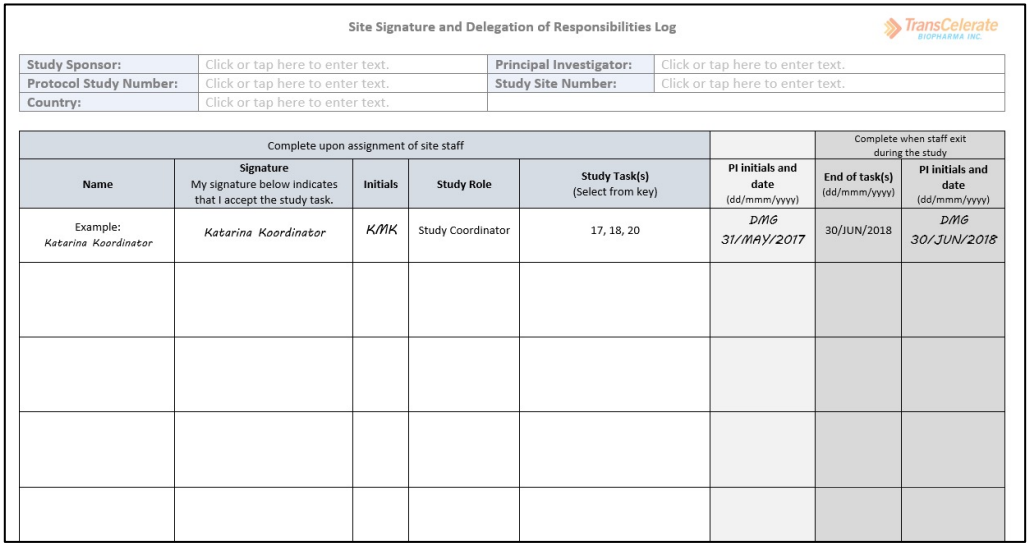
The Site Signature and Delegation of Responsibilities Log must be completed with accuracy and clear FDA Investigato delegation of tasks throughout the study.

Principal Investigator

- The Principal Investigator (PI) is responsible for the conduct of all tasks and therefore the PI does not delegate tasks to himself/herself in the task section of the log
- The Principal Investigator is responsible for assigning study tasks to medically qualified/licensed staff in accordance with country specific regulations.
  - The evaluation of whether study staff is performing functions within the scope of their professional licensure depends not only on the scope of their licensure, but also on local regulations.
  - Thus, the professional licensing authority in the State(s), Province(s) or Country (ies) in which the study is taking place makes the final determination.
  - Each Principal Investigator must be aware of their local regulations.
- All personnel who have been delegated **significant** study related duties or tasks, which the Principal Investigator would otherwise do, must be listed on the log.

Completing the Log

- Information entered in all sections of the log should be legible and accurate.



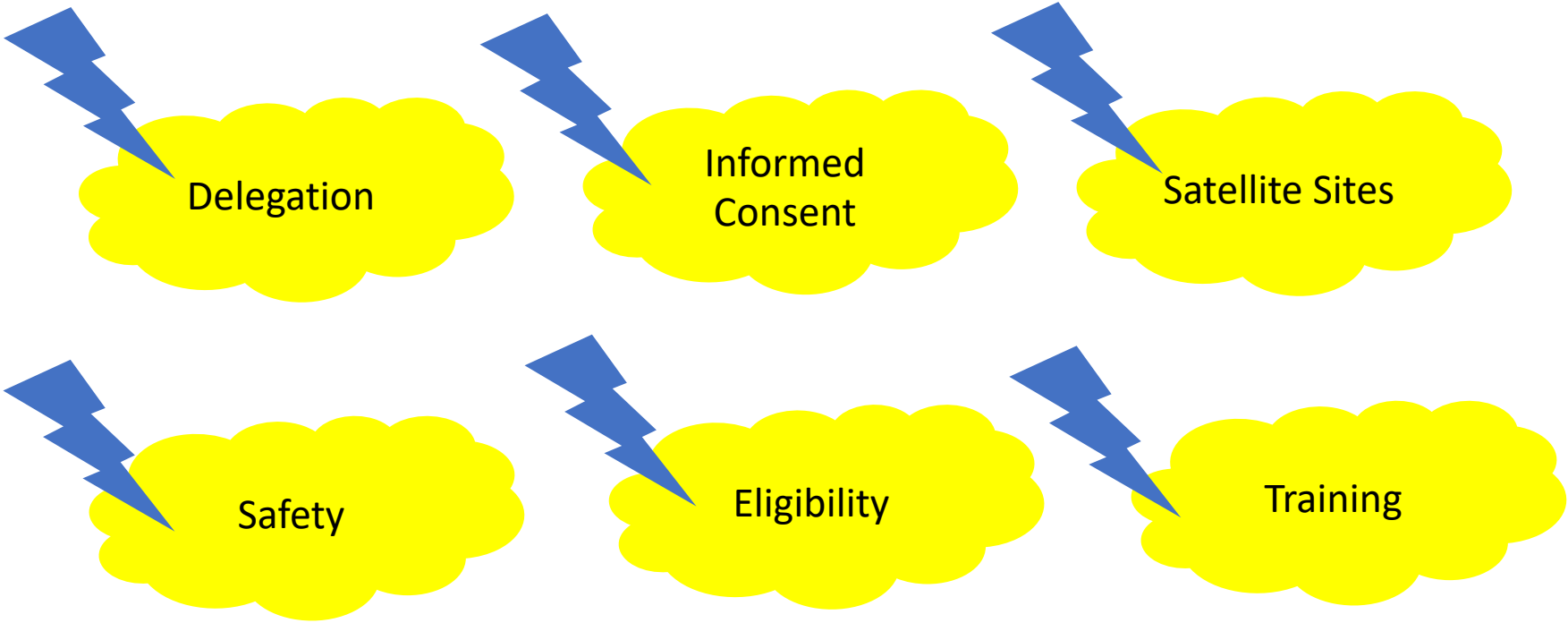
Site Signature and Delegation of Responsibilities Log

TransCelerate BIOPHARMA INC.

Study Sponsor:	Click or tap here to enter text.	**Principal Investigator:**	Click or tap here to enter text.
Protocol Study Number:	Click or tap here to enter text.	**Study Site Number:**	Click or tap here to enter text.
Country:	Click or tap here to enter text.		

Complete upon assignment of site staff						Complete when staff exit during the study	
Name	**Signature** My signature below indicates that I accept the study task.	**Initials**	**Study Role**	**Study Task(s)** (Select from key)	**PI initials and date** (dd/mmm/yyyy)	**End of task(s)** (dd/mmm/yyyy)	**PI initials and date** (dd/mmm/yyyy)
Example: *Katarina Koordinator*	*Katarina Koordinator*	*KMK*	Study Coordinator	17, 18, 20	*DMG 31/MAY/2017*	30/JUN/2018	*DMG 30/JUN/2018*

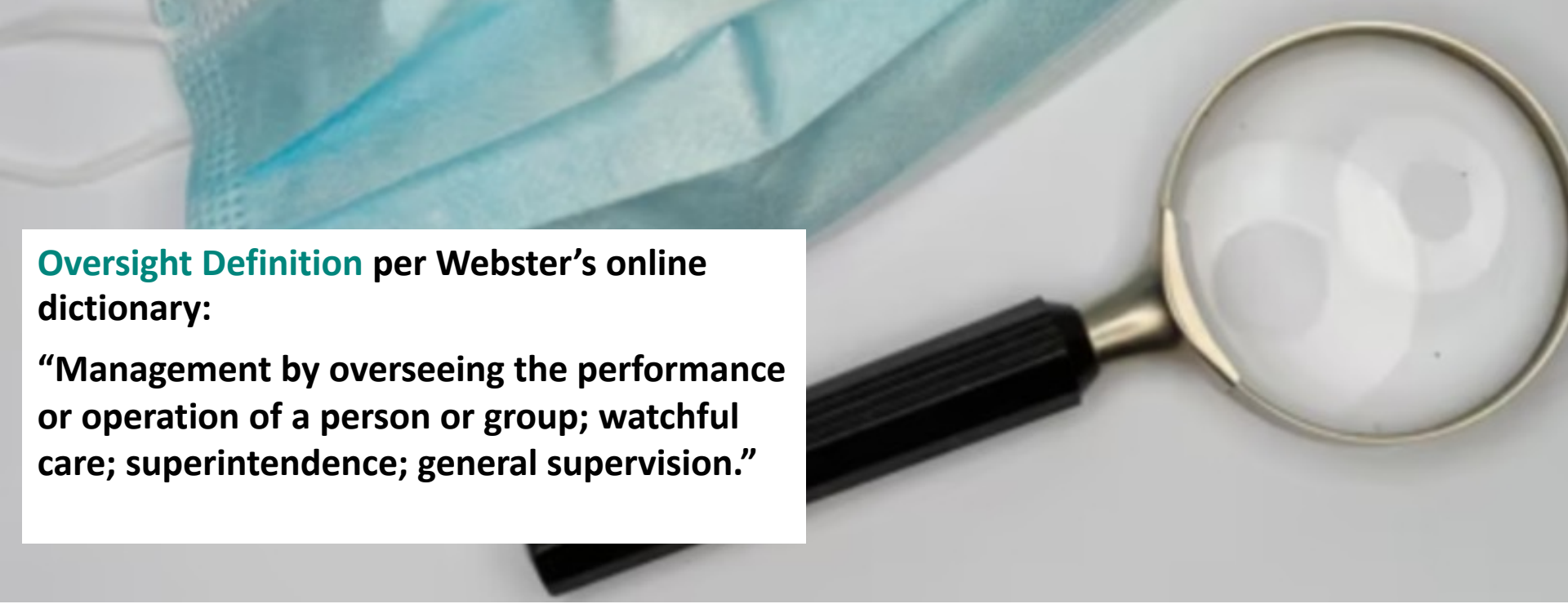
Practical Thoughts on ICH E6(R2), 4- Investigator



Who? PI
What? Overall Conduct of the Study
When? All Stages of the Trial

[1]The Clinical Investigator is responsible for overall conduct of the study at the clinical site, including directing the administration or dispensing of the investigational product to the subject and ensuring that data are collected and maintained in accordance with the protocol and applicable regulatory requirements. When the investigation is conducted by a team of individuals, the clinical investigator is the responsible leader of the team.

[1] 21 CFR 312.3; 21 CFR 511.3; 21 CFR 812.3(i)



Oversight Definition per Webster's online dictionary:

"Management by overseeing the performance or operation of a person or group; watchful care; superintendence; general supervision."

PI Oversight vs. PI Involvement

[1]PI Oversight ensures that the PI fulfills his Investigator commitments.

PI Direct Involvement in patient care contributes to the safe and ethical treatment of study patients for which the PI is responsible.

[1] WCG CENTERWATCH (2014)

Collaboration: PI ⟷ Monitor

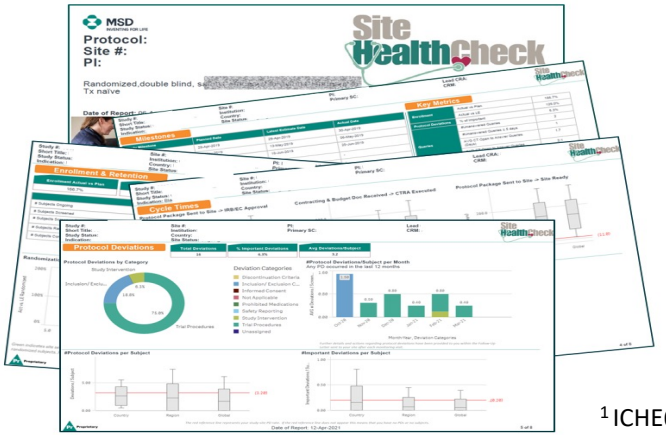
[1]The purposes of trial monitoring are to verify that:

1. The rights and well-being of human subjects are protected.

2. The reported trial data are accurate, complete, and verifiable from source documents.

3. The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).

The Site Health Check Report is a tool MERCK monitors use to share metrics with sites to support data driven discussions.



[1] ICHE6(R2), 5.18.1

PI Oversight: Validation

[1]4.2 Adequate Resources

4.2.1 The investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

4.2.2 The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.

4.2.3 The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

Screen Failure Rate	# Randomized by LPI LE
55.6%	7 by 20-Dec-2021

[1] ICHE6(R2), 4.2

PI Oversight: Initiation

[1] *4.4.1* Before initiating a trial, the investigator/institution should have written and dated approval/favorable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects.

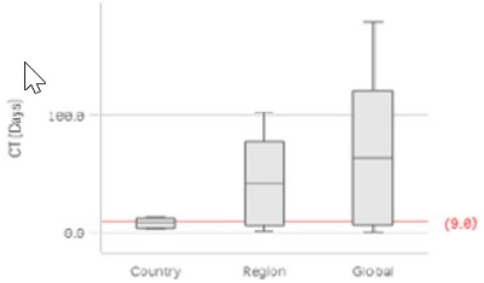
Cycle Times

Protocol Package Sent to Site -> IRB/EC Approval

Contracting & Budget Doc Received -> CTRA Executed

Protocol Package Sent to Site -> Site Ready

Site Ready → First Subject, First Visit



[1] ICHE6(R2), 3.1.2

[1] ICHE6(R2), 3.1.2

PI Oversight: Recruitment Planning for Success

Where and how does the site plan to identify patients (sources)?

Where do these interactions occur (e.g., within the institution, at another institution)?

Which I/E criteria have the biggest impact on the potential patient pool?

Which providers, staff, or other individuals could help to refer patients to the study?

When is the optimal time to approach the patient with this clinical trial opportunity?

Who will be responsible for presenting the study to the patient?

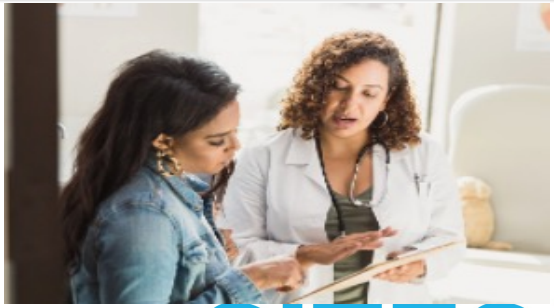
What is the pre-screening process?

What are the site's retention practices?
What is the strategy to maintain patient engagement?
How will your site build trust with patients – to maximize retention efforts.

PI Oversight: Informed Consent Process

[1] *4.8.7* Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative.

4.8.8 Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.



[1] ICHE6(R2), 4.8.7, 4.8.8

PI Oversight: Protocol Deviations

[1] *4.2.4* The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

Protocol Deviations	Total Deviations	% Important Deviations	Avg Deviations/Subject

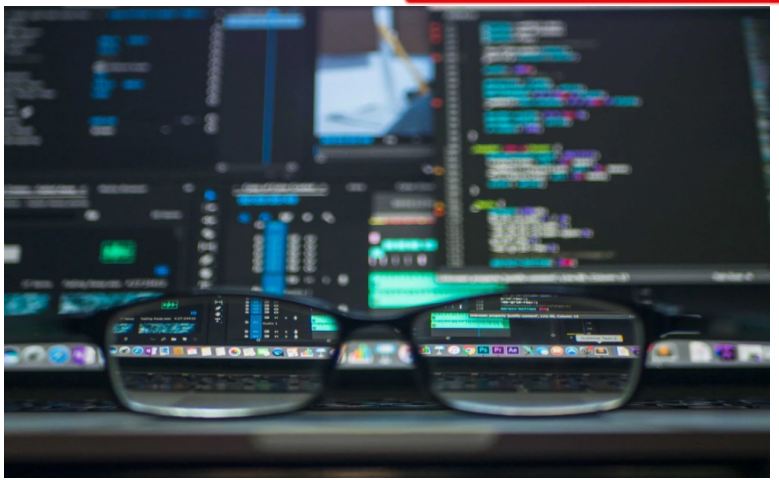
[1] ICHE6(R2), 4.2.4

PI Oversight: Data Entry and Queries

[1] *4.9.1* The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.

Data Entry

% Forms Complete ≤ 14 Days	% Forms Complete ≤ 14 Days (Current Month)	# Forms Incomplete	# Missing Visits (Open Query)
95.4%	-	0	0



Queries

Total Queries	# Open/Unanswered Queries
162	4/4

[1] ICHE6(R2), 4.9.1

PI Oversight: ALCOA-C +

One of the most common inspection findings in investigator site inspections is the lack of reliable, accurate and adequate source documentation.

Source Document is the First Recording of Result or Observation.

Source Documents must follow ALCOA-C principles:

- ✓ ATTRIBUTABLE- Who did it?
- ✓ LEGIBLE- Can you read it? Is it permanently recorded ?
- ✓ CONTEMPORANEOUS- Was it done in “real time”?
- ✓ ORIGINAL- Is it original or true copy?
- ✓ ACCURATE- Is it correct in all details- exact ?
- ✓ COMPLETE- Is it complete ? No Deletion of Documentation
  - ✓ CONSISTENT- Is it time stamped with audit trails?
  - ✓ ENDURING – Is it recorded in a manner to last a long time?
  - ✓ AVAILABLE –Is it Accessible?
  - ✓ CREDIBLE -Is it based on real and reliable facts?
  - ✓ CORROBORATED- Is the data backed up by evidence?

PI Oversight: Responsibilities

- Adequate Resources to Conduct the Study
- Ensure All Staff are Qualified and Trained
- Appropriate Delegation of Study Tasks
- Communication with IRB
- Proper Informed Consent
- Protect Subject's Rights
- Responsible for Trial Related Medical Decisions
- Investigation Product Accountability and Unblinding
- Safety Reporting
- Data Records and Reports
- Essential Documents
- Compliance with Protocol and SOPS


thank you
danke
謝謝
ngiyabonga
teşekkür ederim
gracias
merci
obrigado
dziękuję
bedankt
спасибо
Баярлалаа
рахмат
sukriya
kop khun krap
go raibh maith agat
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