Part 1 - Audit Trail Case Study

Introduction

You are a recently hired medical officer in the Office of New Drugs (OND) at FDA. Your first assignment involves a New Drug Application (NDA) for creseltamivir, a new antiviral for the treatment of H2N5 virus. The FDA granted breakthrough therapy review status because creseltamivir shows substantial clinical improvement over existing therapies. The review clock is furiously ticking away, and you eagerly begin reviewing the report for study ABCD2015.

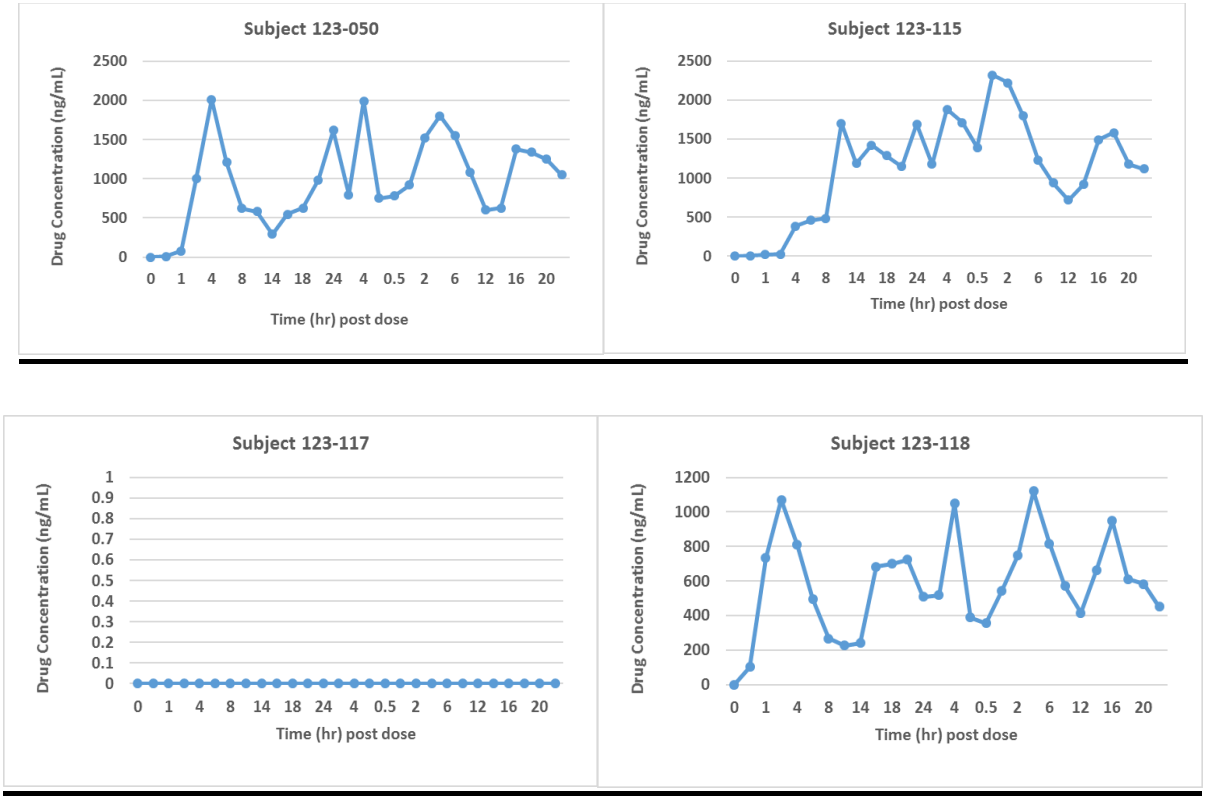
Section 1 - Study report submitted to FDA

Study number:	ABCD2015
Study title:	An expanded double-blind, randomized, placebo-controlled study to assess the safety, tolerability, and pharmacokinetics of creseltamivir when administered as oral dose QD for 14 days
Subjects enrolled:	422
Clinical sites:	50
Study design:	Lead-in Cohort: 40 subjects will be randomized at a 4:1 creseltamivir:placebo ratio (creseltamivir, n = 32; Placebo, n = 8). Expanded cohort: 382 additional subjects will be randomized at a 4:1 ratio (creseltamivir, n = 306; Placebo n = 76)
Drug product:	Creseltamivir
Indication:	Treatment of H2N5 virus
Study phase:	Phase 3
Study dates:	July 1, 2015 to October 30, 2016
Dosing information:	In each cohort, subjects received two bottles of creseltamivir or placebo. Each bottle had a 7-day drug supply.
Other information:	Collected PK blood samples on days 1 and 14 on both cohorts. All sites collected PK. An Interactive Web Response System (IWRS) monitored all clinical sites.
Sponsor:	PK Enterprises, LLC.
IWRS provider:	Clinical Research Solutions, Inc.

Table 1 Excerpt from randomization schedule in the study report submitted to FDA.

Subject ID	Cohort	Dietary condition	Bottles dispensed	Treatment description
123-050	Lead in	Fed	11236/12345	Placebo/Placebo
123-115	Lead in	Fasted	11334/14233	Creseltamivir/Placebo
123-117	Lead in	Fed	13134/14524	Creseltamivir/Creseltamivir
123-118	Lead in	Fed	11876/11880	Creseltamivir/Creseltamivir
124-119	Lead in	Fed	93455/92222	Creseltamivir/Creseltamivir
124-120	Lead in	Fasted	94567/96543	Placebo/Placebo
124-121	Lead in	Fasted	91345/91346	Placebo/Placebo
124-122	Lead in	Fasted	91347/91349	Creseltamivir/Creseltamivir
124-101	Lead in	Fed	91356/91398	Creseltamivir/Creseltamivir
124-102	Lead in	Fed	92345/92346	Creseltamivir/Creseltamivir
124-103	Lead in	Fasted	92456/92457	Creseltamivir/Creseltamivir
124-104	Lead in	Fed	92567/92678	Placebo/Placebo
124-105	Lead in	Fasted	92889/92998	Creseltamivir/Creseltamivir
124-106	Lead in	Fasted	94245/94256	Creseltamivir/Creseltamivir
124-107	Lead in	Fed	94267/94678	Creseltamivir/Creseltamivir
124-108	Lead in	Fed	95256/25267	Creseltamivir/Creseltamivir
124-109	Lead in	Fed	96268/96269	Placebo/Placebo
124-110	Lead in	Fasted	97289/97278	Creseltamivir/Creseltamivir
124-111	Lead in	Fasted	98134/98145	Placebo/Placebo
124-112	Lead in	Fed	91345/91467	Placebo/Placebo
124-113	Lead in	Fasted	92345/92789	Creseltamivir/Creseltamivir
201-101	Expanded	Fed	94356/94357	Placebo/Placebo
201-102	Expanded	Fed	94456/94567	Placebo/Placebo
201-103	Expanded	Fasted	94678/94789	Creseltamivir/Creseltamivir
201-104	Expanded	Fed	94987/94765	Placebo/Placebo
201-105	Expanded	Fasted	94123/94234	Placebo/Placebo
201-106	Expanded	Fasted	95123/95345	Creseltamivir/Creseltamivir
201-107	Expanded	Fed	95567/95789	Creseltamivir/Creseltamivir
201-108	Expanded	Fed	96123/96789	Creseltamivir/Creseltamivir
201-109	Expanded	Fed	97374/97902	Creseltamivir/Creseltamivir

Figure 1. Cumulative (days 1 and 14) concentration data from four subjects in the lead-in cohort. Data submitted to FDA.



Section 1 Questions

1. **What discrepancies do you notice?**

Section 2 - Inspection consult

Seventy-five percent (75%) of study data has discrepancies. Your management recommends issuing an inspection request to the Office of Study Integrity and Surveillance (OSIS), the office which deals with inspection of clinical and analytical portions of bioavailability and bioequivalence studies.

Section 2 Questions

1. **How do you select sites to inspect?**
2. **What inspection instructions do you convey to OSIS?**

Section 3 - Inspection findings

OSIS receives your inspection request and issues an inspection memo to ORA. Three weeks later, ORA investigators conduct the inspections. The ORA investigators collected a copy of drug accountability log from site 123. They confirmed dispensed bottle numbers; however, they could not confirm the data discrepancies. You volunteer to review some of the inspectional findings shown below.

Table 2 Partial drug accountability log found at site 123.

Subject ID	Cohort	Dietary condition	Bottles dispensed
123-050	Lead in	Fed	11236/12345
123-115	Lead in	Fasted	11334/14233
123-117	Lead in	Fed	13134/14524
123-118	Lead in	Fed	11876/11880

Table 3. Inspection exhibit – eCRF collected by ORA investigators at site 123

Protocol ABCD2015 – Serious Medicine, LLC; Dr. Wayne Jones, MD: Site 123
Folder: Day 1; Form: Randomization and vital signs; Generated on: July 1, 2015, 08:05:45; Data signed: (WJones), 1 JUL 2015, 13:10:36

Cohort	Lead-in
Randomization date	1JUL2015
Subject number	123-050
Visit date	1JUL2015
Pulse rate (beats/min)	54
Systolic blood pressure (mmHg)	121
Diastolic blood pressure (mmHg)	77
Respiratory rate (breaths/min)	16
Dietary condition	Fed
Time of meal	12:00:10
Bottle number	11236 and 12345
Time of first dose	12:30:00

Section 3 Questions

1. **What are possible explanations that the ORA investigator's findings don't support your initial concerns?**

Medicines & Healthcare products Regulatory Agency

U.S. FOOD & DRUG ADMINISTRATION

Case Study on Audit Trails

Ruben Ayala, FDA/CDER/OTS/OSIS
Arindam Dasgupta, FDA/CDER/OTS/OSIS
Phillip Kronstein, FDA/CDER/OC/OSI

Agenda

- 5 min Intro/background (11:40-11:45 AM)
- 35 min Group Discussion (11:45 to 12:20 PM)
- 10 min Case Wrap-up (12:20 to 12:30 PM)

Medicines & Healthcare products Regulatory Agency

Introduction

FDA

- You are a recently hired medical officer in FDA/OND
- Your first assignment involves a New Drug Application (NDA) for creseltamivir, a new antiviral for the treatment of H2N5 virus
- The FDA granted breakthrough therapy review status because creseltamivir shows substantial clinical improvement over existing therapies
- The review clock is furiously ticking away, and you eagerly begin reviewing the application starting with study ABCD2015

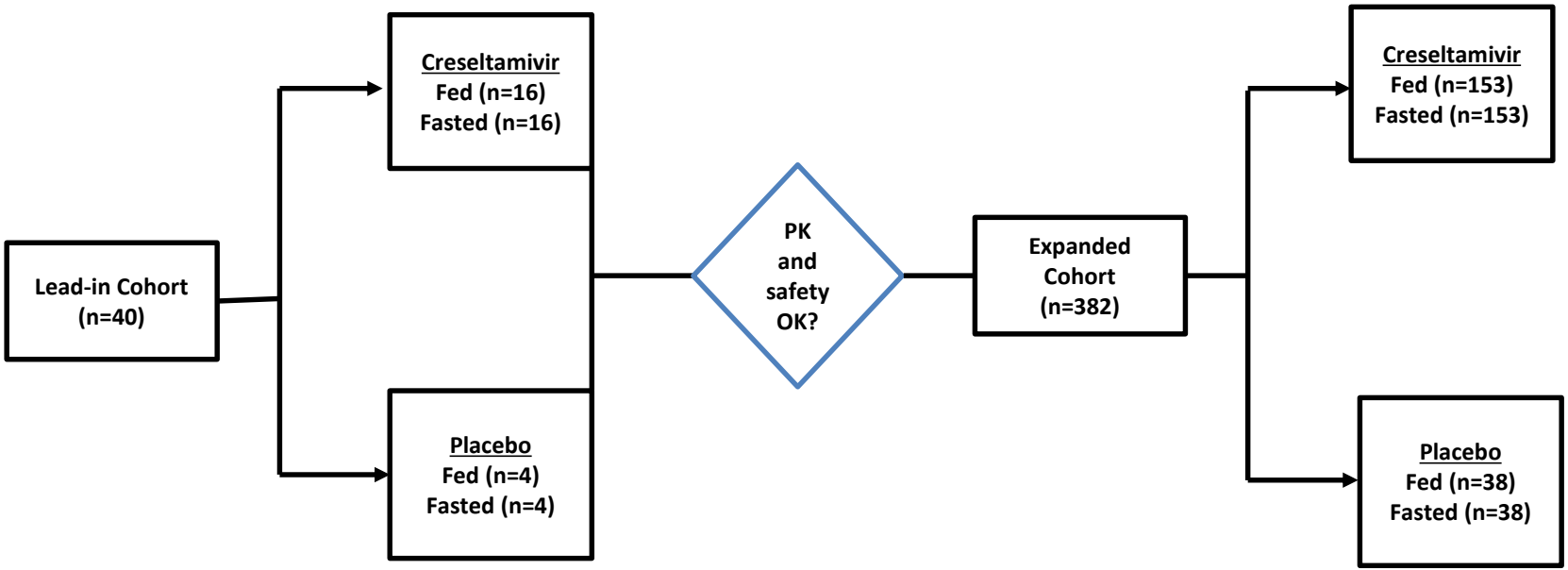
Background - Study ABCD2015

- An expanded double-blind, randomized, placebo-controlled study to assess the safety, tolerability, and pharmacokinetics of creseltamivir when administered orally with or without food once daily for 14 days
  - 50 clinical sites
  - 442 subjects enrolled
  - An interactive web response system (IWRS) managed all clinical sites

Medicines & Healthcare products Regulatory Agency

Study Design

FDA



Medicines & Healthcare products Regulatory Agency

Dosing and PK Information

FDA

- Subjects were randomized to receive one treatment in the study
- Subjects were dispensed two bottles of creseltamivir or placebo
- Each bottle had a 7-day drug supply
- Blood samples for PK were collected on days 1 and 14. All sites collected PK

Medicines & Healthcare products Regulatory Agency

Material Provided

FDA

Sponsor Submitted to FDA	• Study report • Randomization schedule • Concentration data
ORA inspection exhibits	• Partial drug accountability log • eCRF
Sponsor correspondence post inspection	• CRO + IWRS vendor contract • IWRS audit trail • Second randomization schedule

Medicines & Healthcare products Regulatory Agency

Your Assignment

FDA

- Identify data discrepancies
- Initiate an OSIS inspection consult, including site selection
- Assess inspectional findings
- Evaluate post-inspectional correspondence from the sponsor
- Determine the possible root cause of data discrepancies
- Comment on study data reliability and acceptability

Begin Group Discussion

- A facilitator is available to answer questions
- Reconvene at 12:20 PM for case wrap up

- **Case Wrap Up**

Section 1 - Study report submitted to FDA

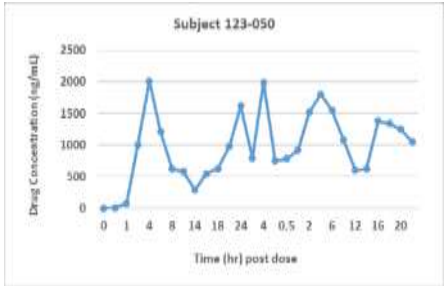
- **What discrepancies do you notice?**
  - Treatment does not correlate with concentration data
    - Subjects randomized to placebo had measurable creseltamivir concentrations
    - Subjects randomized to creseltamivir had no measurable concentrations
  - Subjects received mixed treatments

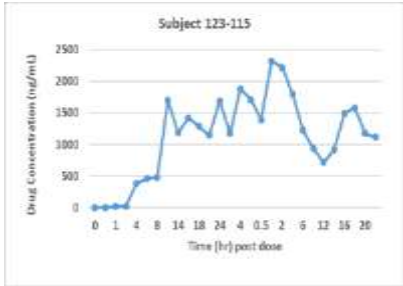
Medicines & Healthcare products Regulatory Agency

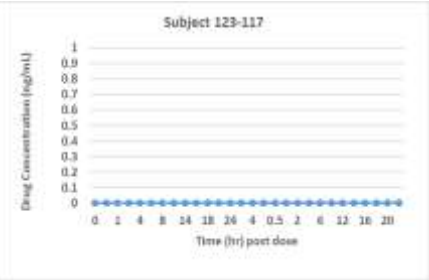
Section 1 - Study report submitted to FDA

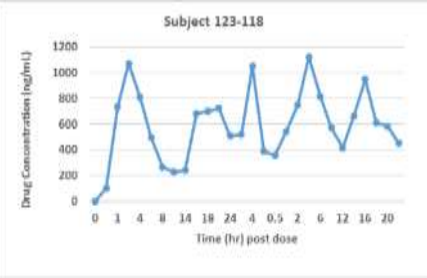
FDA

Subject ID	Cohort	Dietary condition	Bottles dispensed	Treatment description
123-050	Lead in	Fed	11236/12345	Placebo/Placebo
123-115	Lead in	Fasted	11334/14233	Creseltamivir/Placebo
123-117	Lead in	Fed	13134/14524	Creseltamivir/Creseltamivir
123-118	Lead in	Fed	11876/11880	Creseltamivir/Creseltamivir









Medicines & Healthcare products Regulatory Agency

Section 2 - Inspection consult

FDA

- **How do you select sites to inspect?**
  - Consider high enrollers, adverse events (or lack thereof), inspection history, previous findings

- **What inspection instructions do you convey?**
  - Access randomization schedule in IWRS
  - Determine treatment allocation and identity in IWRS
  - Verify dietary conditions
  - Check dosing logs at the site(s)

Medicines & Healthcare products Regulatory Agency

Section 3 - Inspection findings

FDA

- **What are possible explanations that the ORA investigator's findings don't support your initial concerns?**
  - No available randomization schedule or blinding codes on site because the study involved IWRS

Subject ID	Cohort	Bottles dispensed	**Identity?**
123-050	Lead in	11236/12345	?
123-115	Lead in	11334/14233	?
123-117	Lead in	13134/14524	?
123-118	Lead in	11876/11880	?

Medicines & Healthcare products Regulatory Agency

Section 3 - Inspection findings

FDA

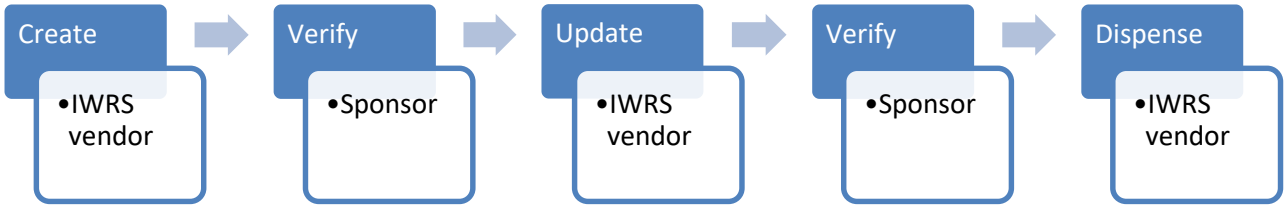
- **eCRF provides important information which helps put the IWRS trail into perspective**

Protocol ABCD2015 – Serious Medicine, LLC; Dr. Wayne Jones, MD: Site 123
Folder: Day 1; Form: Randomization and vital signs; Generated on: July 1, 2015, 08:05:45; Data signed: (WJones), 1 JUL 2015, 13:10:36

Cohort	Lead-in
Randomization date	1JUL2015
Subject number	123-050
Visit date	1JUL2015
Pulse rate (beats/min)	54
Systolic blood pressure (mmHg)	121
Diastolic blood pressure (mmHg)	77
Respiratory rate (breaths/min)	16
Dietary condition	Fed
Time of meal	12:00:10
Bottle number	11236 and 12345
Time of first dose	12:30:00

Section 4 - Post-Inspection Correspondence from the Sponsor

- **How can the IWRS audit trail be used by a regulatory agency to reconstruct the study?**
  - Verify:
    - Subject numbers
    - Bottles dispensed
    - Dates and signatures
  - From CRO + IWRS vendor contract:



Section 4 Post-Inspection Correspondence from the Sponsor

- IWRS audit trail mirrors the vendor contract

ACTIV	DATE	OPERATOR	BOTTLE	1=TST 2=PBO
CREATE	**4/17/2015** 8:05	**JD; Clinical research solutions, Inc.**	11236	**2**
CREATE	4/17/2015 8:10	JD; Clinical research solutions, Inc.	12345	**2**
VERIFY	**6/13/2015** 8:05	**PS; PK Enterprises, LLC.**	11236	2
VERIFY	6/13/2015 8:06	PS; PK Enterprises, LLC.	12345	2
UPDATE	**6/30/2015** 8:05	RA; Clinical research solutions, Inc.	11236	1
UPDATE	6/30/2015 8:06	RA; Clinical research solutions, Inc.	12345	1
VERIFY	**6/30/2015** 8:31	PS; PK Enterprises, LLC.	11236	1
VERIFY	6/30/2015 8:32	PS; PK Enterprises, LLC.	12345	1
DISPENSE	**7/1/2015** 12:00	RA; Clinical research solutions, Inc.	11236	**1**
DISPENSE	7/1/2015 12:00	RA; Clinical research solutions, Inc.	12345	**1**

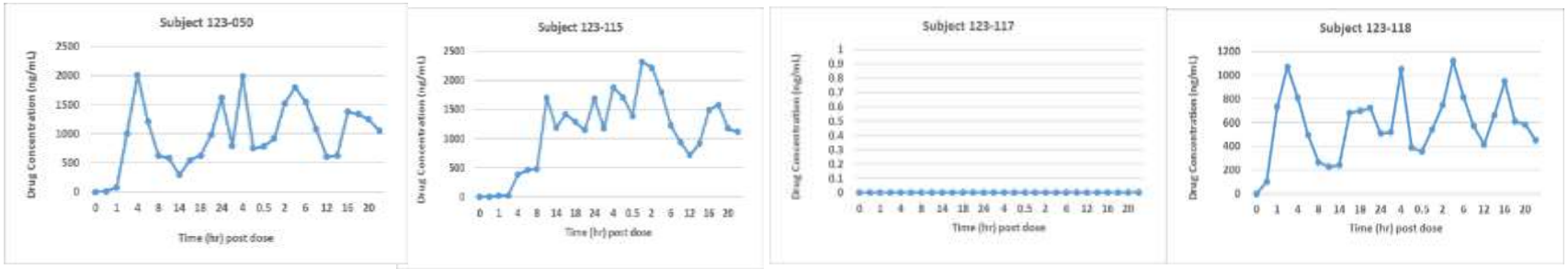
Medicines and Healthcare products Regulatory Agency

Section 4 - Post-Inspection Correspondence from the Sponsor

FDA

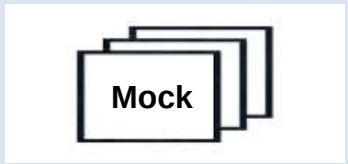
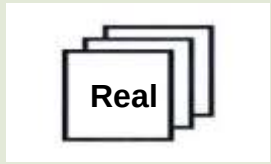
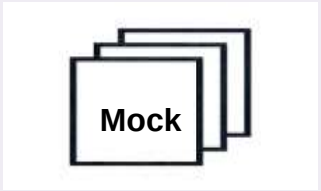
- Second randomization schedule from the sponsor matches PK data and IWRS information

Subject ID	Cohort	Bottles dispensed	Second randomization
123-050	Lead in	11236/12345	Creseltamivir/Creseltamivir
123-115	Lead in	11334/14233	Creseltamivir/Creseltamivir
123-117	Lead in	13134/14524	Placebo/Placebo
123-118	Lead in	11876/11880	Creseltamivir/Creseltamivir



Section 4 - Post-Inspection Correspondence from the Sponsor

- **In your opinion, what caused the data discrepancies?**
  - IWRS vendor used a mock randomization schedule to design study platform
  - Sponsor inadvertently submitted mock schedule to FDA
  - IWRS audit trails confirmed the real randomization schedule was uploaded pre-study

Planning and Design	Pre-study	FDA submission
		

Section 4 - Post-Inspection Correspondence from the Sponsor

- **Did the sponsor successfully mitigate the inspectional findings?**
  - Yes
- **Are the study data reliable for further Agency review?**
  - Yes

Questions


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Part 2 - Audit Trail Case Study

Section 4 - Post-Inspection Correspondence from the Sponsor

At this point, you are concerned with the inspectional findings and cannot ensure the integrity of the study data. You decide to issue an Information Request (IR) letter to the study sponsor. The Sponsor replies to your request and gives a series of supporting documents including a contract from the IWRS vendor, IWRS audit trail, and a revised randomization schedule. The Sponsor assures you that the provided documents will explain all data discrepancies.

Table 3 - IWRS contract between vendor Clinical Research Solutions (CRS), Inc. and Study Sponsor PK Enterprises, LLC.

Deliverables	Author	Approvers	Provided To:
Provide mock schedule	Sponsor	• Sponsor	• CRS manager
Develop IWRS for study	CRS manager	• CRS IRT Project Manager	• CRS IRT Project Manager
Verify IWRS structure	Sponsor	• Sponsor	• Sponsor
Investigator Meeting Slides	CRS IRT Project Manager	• Sponsor or CRS Clinical Team	• CRS Clinical Team • Sponsor
User Training Materials	CRS IRT Project Manager	• CRS Project Manager • CRS Clinical Project Manager • Sponsor	• CRS manager • Sponsor • CRS Clinical Team
Translated User Training Materials	CRS IRT Project Manager	• N/A	• CRS RSG • Sponsor • CRS Clinical Team
Communication Plan	CRS IRT Project Manager	• CRS IRT Project Manager • Sponsor	• CRS RSG • Sponsor • CRS Clinical Team
IP Inventory Release	Sponsor	• Sponsor	• CRS IRT Project Manager
IP Inventory Update Form	CRS IRT Project Manager	• CRS IRT Project Manager	• CRS IRT Project Manager
Verify IP Inventory Update Form	Sponsor	• CRS Project Manager • CRS Clinical Project Manager	• CRS Project Manager • CRS Clinical Project Manager • Sponsor
Live system	CRS IRT Project	• CRS Project Manager • CRS Clinical Project Manager • Sponsor	• CRS Project Manager • CRS Clinical Project Manager

Table 4 - IWRS audit trail obtained from Clinical Research Solutions, Inc. Provided by the Study Sponsor.

ACTIV	ACTIV ID	DATE	OPERATOR	COMMENT	BOTTLE	1=TST 2=PBO
CREATE	[Id]=N'27560ADA-2C6B-11E5-8652-005056854EDA	4/17/2015 8:05	JD; Clinical research solutions, Inc.	style="create"	11236	2
CREATE	[Id]=N'27560ADA-2C6B-11E5-8652-005056854EDA	4/17/2015 8:10	JD; Clinical solutions, Inc.	style="create"	12345	2
CREATE	[Id]=N'27560ADA-2C6B-11E5-8652-005056854EDA	4/17/2015 9:45	JD; Clinical solutions, Inc.	style="create"	13455	1
CREATE	[Id]=N'27560ADA-2C6B-11E5-8652-005056854EDA	4/17/2015 10:05	JD; Clinical solutions, Inc.	style="create"	12222	1
CREATE	[Id]=N'27560ADA-2C6B-11E5-8652-005056854EDA	4/17/2015 10:16	JD; Clinical solutions, Inc.	style="create"	14567	2
CREATE	[Id]=N'27560ADA-2C6B-11E5-8652-005056854EDA	4/17/2015 10:32	JD; Clinical solutions, Inc.	style="create"	76543	1
CREATE	[Id]=N'27560ADA-2C6B-11E5-8652-005056854EDA	4/17/2015 10:33	JD; Clinical solutions, Inc.	style="create"	76980	2
CREATE	[Id]=N'27560ADA-2C6B-11E5-8652-0050568	4/17/2015 10:34	JD; Clinical solutions, Inc.	style="create"	11334	1
CREATE	[Id]=N'634AB3C1-2C6B-11E5-138-792-005056854EDA'	4/17/2015 11:05	JD; Clinical solutions, Inc.	style="create"	14233	2
CREATE	[Id]=N'634AB3C1-2C6B-11E5-138-792-005056854EDA'	4/17/2015 11:08	JD; Clinical solutions, Inc.	style="create"	11920	2
CREATE	[Id]=N'634AB3C1-2C6B-11E5-138-792-005056854EDA'	4/17/2015 11:10	JD; Clinical solutions, Inc.	style="create"	11223	1
CREATE	[Id]=N'634AB3C1-2C6B-11E5-138-792-005056854EDA'	4/17/2015 11:12	JD; Clinical solutions, Inc.	style="create"	11224	1
CREATE	[Id]=N'634AB3C1-2C6B-11E5-138-792-005056854EDA'	4/17/2015 11:13	JD; Clinical solutions, Inc.	style="create"	11225	2
CREATE	[Id]=N'634AB3C1-2C6B-11E5-138-792-005056854EDA'	4/17/2015 11:15	JD; Clinical solutions, Inc.	style="create"	13134	1
CREATE	[Id]=N'634AB3C1-2C6B-11E5-138-792-005056854EDA'	4/17/2015 11:18	JD; Clinical solutions, Inc.	style="create"	14524	1
CREATE	[Id]=N'634AB3C1-2C6B-11E5-138-792-005056854EDA'	4/17/2015 11:19	JD; Clinical solutions, Inc.	style="create"	11876	1
CREATE	[Id]=N'634AB3C1-2C6B-11E5-138-792-005056854EDA'	4/17/2015 11:21	JD; Clinical solutions, Inc.	style="create"	11880	1
VERIFY	[Id]=N'634AB3C1-2C6B-11E5-138-792-005056854EDA'	6/13/2015 8:05	PS; PK Enterprises, LLC.	FileOID="verify"	11236	2
VERIFY	[Id]=N'634AB3C1-2C6B-11E5-138-792-005056854EDA'	6/13/2015 8:06	PS; PK Enterprises, LLC.	FileOID="verify"	12345	2

VERIFY	[Id]=N'634AB3C1-2C6B-11E5-138-792-005056854EDA'	6/13/2015 8:07	PS; PK Enterprises, LLC.	FileOID="verify"	13455	1
VERIFY	[Id]=N'634AB3C1-2C6B-11E5-138-792-005056854EDA'	6/13/2015 8:15	PS; PK Enterprises, LLC.	FileOID="verify"	12222	1
VERIFY	[Id]=N'634AB3C1-2C6B-11E5-138-792-005056854EDA'	6/13/2015 8:16	PS; PK Enterprises, LLC.	FileOID="verify"	14567	2
VERIFY	[Id]=N'634AB3C1-2C6B-11E5-138-792-005056854EDA'	6/13/2015 8:17	PS; PK Enterprises, LLC.	FileOID="verify"	76543	1
VERIFY	[Id]=N'634AB3C1-2C6B-11E5-138-792-005056854EDA'	6/13/2015 8:18	PS; PK Enterprises, LLC.	FileOID="verify"	76980	2
VERIFY	[Id]=N'634AB3C1-2C6B-11E5-138-792-005056854EDA'	6/13/2015 8:19	PS; PK Enterprises, LLC.	FileOID="verify"	11334	1
VERIFY	[Id]=N'634AB3C1-2C6B-11E5-138-792-005056854EDA'	6/13/2015 8:20	PS; PK Enterprises, LLC.	FileOID="verify"	14233	2
VERIFY	[Id]=N'634AB3C1-2C6B-11E5-138-792-005056854EDA'	6/13/2015 8:21	PS; PK Enterprises, LLC.	FileOID="verify"	11920	2
VERIFY	[Id]=N'634AB3C1-2C6B-11E5-138-792-005056854EDA'	6/13/2015 8:22	PS; PK Enterprises, LLC.	FileOID="verify"	11223	1
VERIFY	[Id]=N'634AB3C1-2C6B-11E5-138-792-005056854EDA'	6/13/2015 8:25	PS; PK Enterprises, LLC.	FileOID="verify"	11224	1
VERIFY	[Id]=N'634AB3C1-2C6B-11E5-138-792-005056854EDA'	6/13/2015 8:26	PS; PK Enterprises, LLC.	FileOID="verify"	11225	2
VERIFY	[Id]=N'634AB3C1-2C6B-11E5-138-792-005056854EDA'	6/13/2015 8:28	PS; PK Enterprises, LLC.	FileOID="verify"	13134	1
VERIFY	[Id]=N'634AB3C1-2C6B-11E5-138-792-005056854EDA'	6/13/2015 8:29	PS; PK Enterprises, LLC.	FileOID="verify"	14524	1
VERIFY	[Id]=N'634AB3C1-2C6B-11E5-138-792-005056854EDA'	6/13/2015 8:35	PS; PK Enterprises, LLC.	FileOID="verify"	11876	1
VERIFY	[Id]=N'634AB3C1-2C6B-11E5-138-792-005056854EDA'	6/13/2015 8:36	PS; PK Enterprises, LLC.	FileOID="verify"	11880	1

UPDATE	[Id]=N'27560ADA-2C6B-11E5-8652-005056854EDA	6/30/2015 8:05	RA; Clinical research solutions, Inc.	style="update"	11236	1
UPDATE	[Id]=N'27560ADA-2C6B-11E5-8652-005056854EDA	6/30/2015 8:06	RA; Clinical research solutions, Inc.	style="update"	12345	1
UPDATE	[Id]=N'27560ADA-2C6B-11E5-8652-005056854EDA	6/30/2015 8:07	RA; Clinical research solutions, Inc.	style="update"	13455	1
UPDATE	[Id]=N'27560ADA-2C6B-11E5-8652-005056854EDA	6/30/2015 8:08	RA; Clinical research solutions, Inc.	style="update"	12222	2
UPDATE	[Id]=N'27560ADA-2C6B-11E5-8652-005056854EDA	6/30/2015 8:09	RA; Clinical research solutions, Inc.	style="update"	14567	2
UPDATE	[Id]=N'27560ADA-2C6B-11E5-8652-005056854EDA	6/30/2015 8:10	RA; Clinical research solutions, Inc.	style="update"	76543	2
UPDATE	[Id]=N'27560ADA-2C6B-11E5-8652-005056854EDA	6/30/2015 8:11	RA; Clinical research solutions, Inc.	style="update"	76980	1
UPDATE	[Id]=N'27560ADA-2C6B-11E5-8652-0050568	6/30/2015 8:12	RA; Clinical research solutions, Inc.	style="update"	11334	1
UPDATE	[Id]=N'634AB3C1-2C6B-11E5-138-792-005056854EDA'	6/30/2015 8:13	RA; Clinical research solutions, Inc.	style="update"	14233	1
UPDATE	[Id]=N'634AB3C1-2C6B-11E5-138-792-005056854EDA'	6/30/2015 8:14	RA; Clinical research solutions, Inc.	style="update"	11920	1
UPDATE	[Id]=N'634AB3C1-2C6B-11E5-138-792-005056854EDA'	6/30/2015 8:15	RA; Clinical research solutions, Inc.	style="update"	11223	2
UPDATE	[Id]=N'634AB3C1-2C6B-11E5-138-792-005056854EDA'	6/30/2015 8:16	RA; Clinical research solutions, Inc.	style="update"	11224	1
UPDATE	[Id]=N'634AB3C1-2C6B-11E5-138-792-005056854EDA'	6/30/2015 8:17	RA; Clinical research solutions, Inc.	style="update"	11225	1
UPDATE	[Id]=N'634AB3C1-2C6B-11E5-138-792-005056854EDA'	6/30/2015 8:18	RA; Clinical research solutions, Inc.	style="update"	13134	2
UPDATE	[Id]=N'634AB3C1-2C6B-11E5-138-792-005056854EDA'	6/30/2015 8:19	RA; Clinical research solutions, Inc.	style="update"	14524	2

UPDATE	[Id]=N'634AB3C1-2C6B-11E5-138-792-005056854EDA'	6/30/2015 8:20	RA; Clinical research solutions, Inc.	style="update"	11876	1
UPDATE	[Id]=N'634AB3C1-2C6B-11E5-138-792-005056854EDA'	6/30/2015 8:21	RA; Clinical research solutions, Inc.	style="update"	11880	1
VERIFY	[Id]=N'27560ADA-2C6B-11E5-8652-005056854EDA	6/30/2015 8:31	PS; PK Enterprises, LLC.	style="verify"	11236	1
VERIFY	[Id]=N'27560ADA-2C6B-11E5-8652-005056854EDA	6/30/2015 8:32	PS; PK Enterprises, LLC.	style="verify"	12345	1
VERIFY	[Id]=N'27560ADA-2C6B-11E5-8652-005056854EDA	6/30/2015 8:33	PS; PK Enterprises, LLC.	style="verify"	13455	1
VERIFY	[Id]=N'27560ADA-2C6B-11E5-8652-005056854EDA	6/30/2015 8:34	PS; PK Enterprises, LLC.	style="verify"	12222	2
VERIFY	[Id]=N'27560ADA-2C6B-11E5-8652-005056854EDA	6/30/2015 8:35	PS; PK Enterprises, LLC.	style="verify"	14567	2
VERIFY	[Id]=N'27560ADA-2C6B-11E5-8652-005056854EDA	6/30/2015 8:36	PS; PK Enterprises, LLC.	style="verify"	76543	2
VERIFY	[Id]=N'27560ADA-2C6B-11E5-8652-005056854EDA	6/30/2015 8:37	PS; PK Enterprises, LLC.	style="verify"	76980	1
VERIFY	[Id]=N'27560ADA-2C6B-11E5-8652-0050568	6/30/2015 8:38	PS; PK Enterprises, LLC.	style="verify"	11334	1
VERIFY	[Id]=N'634AB3C1-2C6B-11E5-138-792-005056854EDA'	6/30/2015 8:39	PS; PK Enterprises, LLC.	style="verify"	14233	1
VERIFY	[Id]=N'634AB3C1-2C6B-11E5-138-792-005056854EDA'	6/30/2015 8:40	PS; PK Enterprises, LLC.	style="verify"	11920	1
VERIFY	[Id]=N'634AB3C1-2C6B-11E5-138-792-005056854EDA'	6/30/2015 8:41	PS; PK Enterprises, LLC.	style="verify"	11223	2
VERIFY	[Id]=N'634AB3C1-2C6B-11E5-138-792-005056854EDA'	6/30/2015 8:42	PS; PK Enterprises, LLC.	style="verify"	11224	1
VERIFY	[Id]=N'634AB3C1-2C6B-11E5-138-792-005056854EDA'	6/30/2015 8:43	PS; PK Enterprises, LLC.	style="verify"	11225	1

VERIFY	[Id]=N'634AB3C1-2C6B-11E5-138-792-005056854EDA'	6/30/2015 8:44	PS; PK Enterprises, LLC.	style="verify"	13134	2
VERIFY	[Id]=N'634AB3C1-2C6B-11E5-138-792-005056854EDA'	6/30/2015 8:45	PS; PK Enterprises, LLC.	style="verify"	14524	2
VERIFY	[Id]=N'634AB3C1-2C6B-11E5-138-792-005056854EDA'	6/30/2015 8:46	PS; PK Enterprises, LLC.	style="verify"	11876	1
VERIFY	[Id]=N'634AB3C1-2C6B-11E5-138-792-005056854EDA'	6/30/2015 8:47	PS; PK Enterprises, LLC.	style="verify"	11880	1
DISPENSE	[Id]=N'27560ADA-2C6B-11E5-8652-005056854EDA	7/1/2015 12:00	RA; Clinical research solutions, Inc.	style="dispense"	11236	1
DISPENSE	[Id]=N'27560ADA-2C6B-11E5-8652-005056854EDA	7/1/2015 12:00	RA; Clinical research solutions, Inc.	style="dispense"	12345	1

Table 5 - Excerpt from revised randomization schedule submitted post-inspection by the sponsor.

Subject ID	Cohort	Dietary condition	Bottles dispensed	Treatment description
123-050	Lead in	Fed	11236/12345	Creseltamivir/Creseltamivir
123-115	Lead in	Fasted	11334/14233	Creseltamivir/Creseltamivir
123-117	Lead in	Fed	13134/14524	Placebo/Placebo
123-118	Lead in	Fed	11876/11880	Creseltamivir/Creseltamivir
124-119	Lead in	Fed	93455/92222	Placebo/Placebo
124-120	Lead in	Fasted	94567/96543	Creseltamivir/Creseltamivir
124-121	Lead in	Fasted	91345/91346	Creseltamivir/Creseltamivir
124-122	Lead in	Fasted	91347/91349	Placebo/Placebo
124-101	Lead in	Fed	91356/91398	Creseltamivir/Creseltamivir
124-102	Lead in	Fed	92345/92346	Placebo/Placebo
124-103	Lead in	Fasted	92456/92457	Creseltamivir/Creseltamivir
124-104	Lead in	Fed	92567/92678	Creseltamivir/Creseltamivir
124-105	Lead in	Fasted	92889/92998	Creseltamivir/Creseltamivir
124-106	Lead in	Fasted	94245/94256	Placebo/Placebo
124-107	Lead in	Fed	94267/94678	Creseltamivir/Creseltamivir
124-108	Lead in	Fed	95256/25267	Creseltamivir/Creseltamivir
124-109	Lead in	Fed	96268/96269	Creseltamivir/Creseltamivir
124-110	Lead in	Fasted	97289/97278	Placebo/Placebo
124-111	Lead in	Fasted	98134/98145	Creseltamivir/Creseltamivir
124-112	Lead in	Fed	91345/91467	Creseltamivir/Creseltamivir
124-113	Lead in	Fasted	92345/92789	Placebo/Placebo
201-101	Expanded	Fed	94356/94357	Creseltamivir/Creseltamivir
201-102	Expanded	Fed	94456/94567	Creseltamivir/Creseltamivir
201-103	Expanded	Fasted	94678/94789	Placebo/Placebo
201-104	Expanded	Fed	94987/94765	Placebo/Placebo
201-105	Expanded	Fasted	94123/94234	Placebo/Placebo
201-106	Expanded	Fasted	95123/95345	Creseltamivir/Creseltamivir
201-107	Expanded	Fed	95567/95789	Creseltamivir/Creseltamivir
201-108	Expanded	Fed	96123/96789	Creseltamivir/Creseltamivir
201-109	Expanded	Fed	97374/97902	Creseltamivir/Creseltamivir

Section 4 Questions

1. **How can the IWRS audit trail be used by a regulatory agency to reconstruct the study?**
2. **In your opinion, what caused the data discrepancies?**
3. **Did the sponsor successfully mitigate the inspectional findings?**
4. **Are the study data reliable for further Agency review?**