CLINICAL PHARMACOLOGY STUDY CONDUCT TUTORIAL

The Clinical Pharmacology Quality Assurance Revision Team

IMPAACT ANNUAL MEETING 2018
Background

• In 2003 the clinical pharmacology tutorial was introduced and was located on the ACTG portal

• In 2006 PQA and FSTRF published that use of the tutorial resulted in a 13% drop in errors related to pharmacology data and specimen collection/handling*

• In 2007 ACTG and IMPAACT networks made participation a site requirement

• In 2008, the tutorial was relocated to CPQA website maintained by Frontier Science, with on-demand reporting made available for network leadership

• In 2018, a new overhauled version of the tutorial will be made available on the DAIDS LMS (anticipated in Fall )

May 2018 IMPAACT Certification Report

Note: Individual site queries are made by CPQA to assure high adherence for Network sites
New Clinical Pharmacology Tutorial Goals

- Create interactive learning slides to illustrate principles and examples
- Develop cognitive aptitudes for clinical researchers to improve the quality of pharmacology study conduct
- Broaden scope to incorporate newer pharmacology strategies within the networks
- Retain the pertinent subject matter from the current tutorial
New Tutorial Overview

- DAIDS LMS
- Nine Modules
- Can be completed over a few days

Each Module contains
- Objectives
- Interactive Learning Slides
- Summary
- Quiz Questions
New Tutorial Module 1

Clinical Pharmacology Tutorial Introduction

- Goals
- Overview
- Instructions
- Technical settings
New Tutorial Module 2

Principles of Clinical Pharmacology Studies

This module strives to illustrate many of the concepts network pharmacologists use when designing the clinical study pharmacology objectives and reporting the outcomes derived from the data analyses.
New Tutorial Module 2

Principles of Clinical Pharmacology Studies

- Pharmacokinetics
- Its measurements based on Time and Concentration
- Steady State and adherence to study medication
- Adherence

Clinical Pharmacology Tutorial

Area Under the Curve

Certain PK analyses are highly dependent on estimation of total drug exposure. Total drug exposure is estimated by calculating the area under the curve (AUC).

Directions: Click the button to view the area under the curve on the graph.

AUC
New Tutorial Module 3
Clinical Trial Studies and Pharmacology

- Clinical Trial Research
- Pharmacology measures in clinical trials.
- Typical pharmacology study designs & intended outcomes
- Examples of sampling strategies for specific study designs
New Tutorial Module 4

Clinical Pharmacology Study Protocols

- Clinical Pharmacologist’s role
- Pharmacology Objectives
- Protocol Document & PK
- Resources and Tools
New tutorial Module 5

Conducting Clinical Pharmacology Visits I

- Planning
- Preparation
- Execution

- Counsel
  - The study participant should be completely informed of the study details that will impact their stay and their participation.

- Collect Data
  - Accurate collection of historical dosing information is vital to evaluating if the study participant was compliant with their doses required for the study protocol.

- Assess for Adherence
  - Participant contact through counseling and assessment are critical preliminary steps to assure that the participant has been adherent to their medications and the protocol requirements.

- Directions
  - Multiple documents and tools exist to direct parts of the clinical pharmacology conduct, such as: Protocol, Laboratory Processing Chart and Manual of Operations.
New Tutorial Module 5

Conducting Clinical Pharmacology Visits I

Section 1 provides an overview of the key concepts and actions to consider when preparing for the participant visit.
New tutorial Module 6

Conducting Clinical Pharmacology Visits II

- **Dose Time**: Time is a continuous variable, but can be very accurately recorded, and therefore extremely accurate if care is taken to observe an event.

- **Collect Specimen**: Specimen integrity must be assured during collection, processing, storage and handling processes during the life-time of that specimen.

- **Collection Time**: Record the exact time the specimen is collected into the collection device (test tube, syringe, swab, etc.) on the case report form and internal documents if applicable.

- **Process**: Follow the protocol for the collection materials and process, specimen handling, processing storage and shipping requirements.

- **Note**: Provide notes concerning the timing, collection and processing of specimen(s) that may be helpful in identifying unusual circumstances or noncompliance to specifications.
New Tutorial Module 6

Conducting Clinical Pharmacology Visits II

Section 2 provides essential concepts to assure that the time of medication dose and specimen collection are accurately recorded. To the right is an interactive slide defining dose-times for various dosage routes.

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Conducting Clinical Pharmacology Visits II

Recording the ACTUAL collection time is critical and various routes of administration must be considered.

Collection Time- dose time = time used for “X” for concentration “Y”
New Tutorial Module 6

Conducting Clinical Pharmacology Visits II

Specimen collection

**Collect Specimen(s)**

- Use spray dried K$_2$EDTA collection tubes (e.g., BD367861).
- Week 2, 6, 12 specimens are collected 2 hours after morning dose of drug.

- Specimen integrity must be assured during collection, processing, storage and handling processes during the life-time of that specimen.
- CPLs expend significant resources to determine specimen and processing specifications that assure the reported drug concentration accurately reflects the biofluid or tissue concentration at the time the specimen is collected.
- Therefore, collect pharmacology specimens per the protocol and direction from other informational documents, such as an LPC.

Specimen container specifications:
- Vessel: Specified collection tube
- Volume: 5.0 mL
- Specimen additive/anticoagulant: EDTA
Clinical Pharmacology Tutorial

**Types of Pharmacology Specimens**

- **Blood**: Distributes a drug to many areas of the body. Examples of blood pharmacology specimens are:
  - Whole blood
  - Dried blood spots
  - Plasma or serum
  - Peripheral blood mononuclear cells

  *Cells are technically tissue*

- **Tissue**: Are secondary compartments where a drug arrives via the circulatory or transdermal systems. Tissue is most often the targeted site of treatment. Examples of anatomical objects comprised of tissues include:
  - Organs
  - Epithelial
  - Skin
  - Hair (dead tissue)

- **Urine**: Drug metabolites can be excreted in urine.

- **Other fluids and secretions**: Include saliva, rectal and vaginal fluids, semen, cerebral spinal fluid. These fluids are collected for a variety of rationales where the achieved concentration of a drug is thought to be important.
New Tutorial Module 7
Clinical Pharmacology Specimens

Clinical Pharmacology Tutorial

Matrix

Primary example: BLD (blood)

Additive example: HPN (Heparin)
EDTA (EDTA)
NON (None-no additive)

Derivative example: DBS (Dried Blood Spot)

Directions: Click each matrix to show the next step.

Centrifuge

Derivative example: SER (Serum)

Derivative example: PL (Plasma)

Additives example: 85% phosphoric acid

Matrix
Drug
Storage
Container(s)

Directions: Click below for examples of LDMS codes

Plasma from K2 or K3 EDTA whole blood

BLD/EDT/PL

Dried blood spot from K2 or K3 EDTA whole blood

BLD/EDT/DBS
**New Tutorial Module 7**

**Clinical Pharmacology Specimens**

**Specimen Identity**

Maintaining proper specimen identity seems to be simple enough. However, in light of the many other complex steps that occur in the study conduct, this simple step is often thwarted. The chain of identity, once broken, cannot be resolved without some assumptions. Assumptions are not acceptable for confirming identity.

Clearly, the need for double and triple confirmation at all stages of the process cannot be emphasized enough.
New Tutorial Module 8

Pharmacology Data

**Clinical Data**

- Dates, times, drugs, yes/no, gender, and others are variables that are known, exact, or pure fact.

- When data are recorded on CRFs and subsequently used in outcome analysis, they are assumed to be known and exact.

- In statistical analyses, these variables are known as INDEPENDENT VARIABLES and are associated with NO ERROR.

**Laboratory Data**

- Laboratory assessments such as viral load and drug concentrations are variables that are ESTIMATED, or have ERROR associated with numbers.

- Outcomes data entered by the Pharmacology Specialty Laboratory (PSL) have known errors associated with their measurement.

- These measured or estimated variables are known as DEPENDENT variables.
New Tutorial Module 8
Pharmacology Data

Managing CP Specimen-Related Data

Both the CRF and LDMS data must match exactly for the purposes of bringing together the endpoint laboratory measurement with the pharmacology-related clinical information. Apart, they are often meaningless.

The mismatching of data is the most frequent cause behind critical queries. The sooner a mismatch is queried, the more likely the issue will be easily resolved.

Click the items below to see common causes that result in queries for their respective formats:

- Incorrect dose information
- Missing data
- PID errors

- Date/Time discrepancies
- Mislabeled specimens
New tutorial Module 8
Pharmacology Data

Clinical Pharmacology Tutorial

Clinical Pharmacology Data

The Right Data at the Right Time

Pharmacology sample analyses are sometimes batched and analyzed at the end of the study. The time needed to accrue all participants to the study and close the study varies, but can often be years. At this time, the samples are analyzed and the results entered into the LDMS.

Directions: Click the circles on the time line to see the phases of a study.
New tutorial Module 9

Clinical Pharmacology Review

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Certification and Learning

- Re-certification is required every two years
- Tutorial available to all sites and laboratories for training and teaching purposes
QUESTIONS, SUGGESTIONS, AND CONCERNS....