



CLINICAL PHARMACOLOGY STUDY CONDUCT TUTORIAL

The Clinical Pharmacology Quality
Assurance Revision Team

IMPAACT ANNUAL MEETING 2018

 **University at Buffalo** The State University of New York



Background

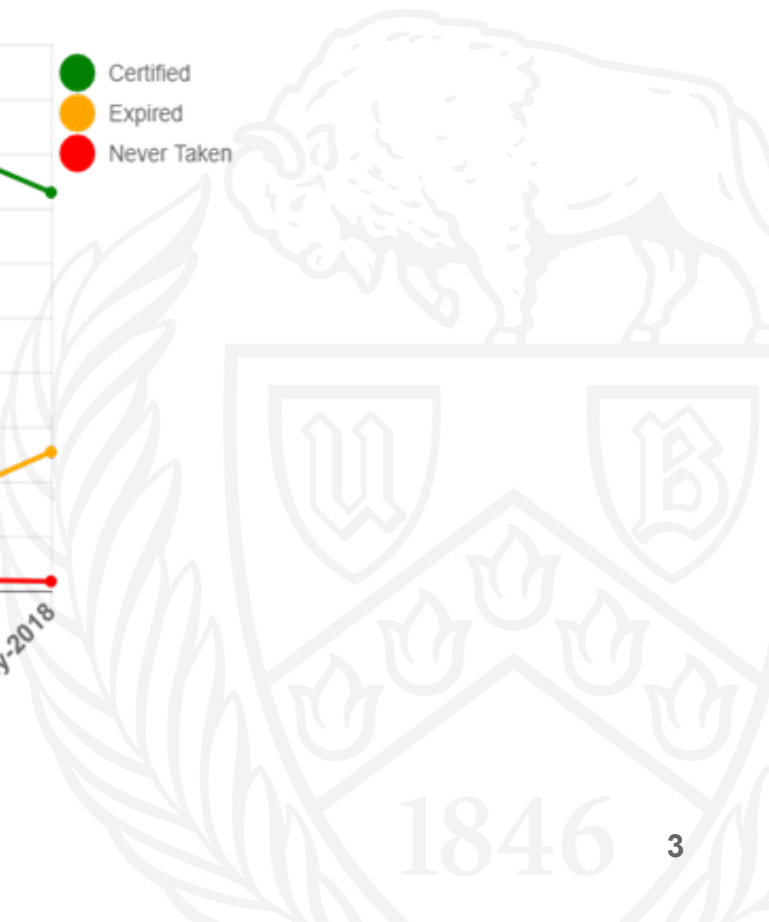
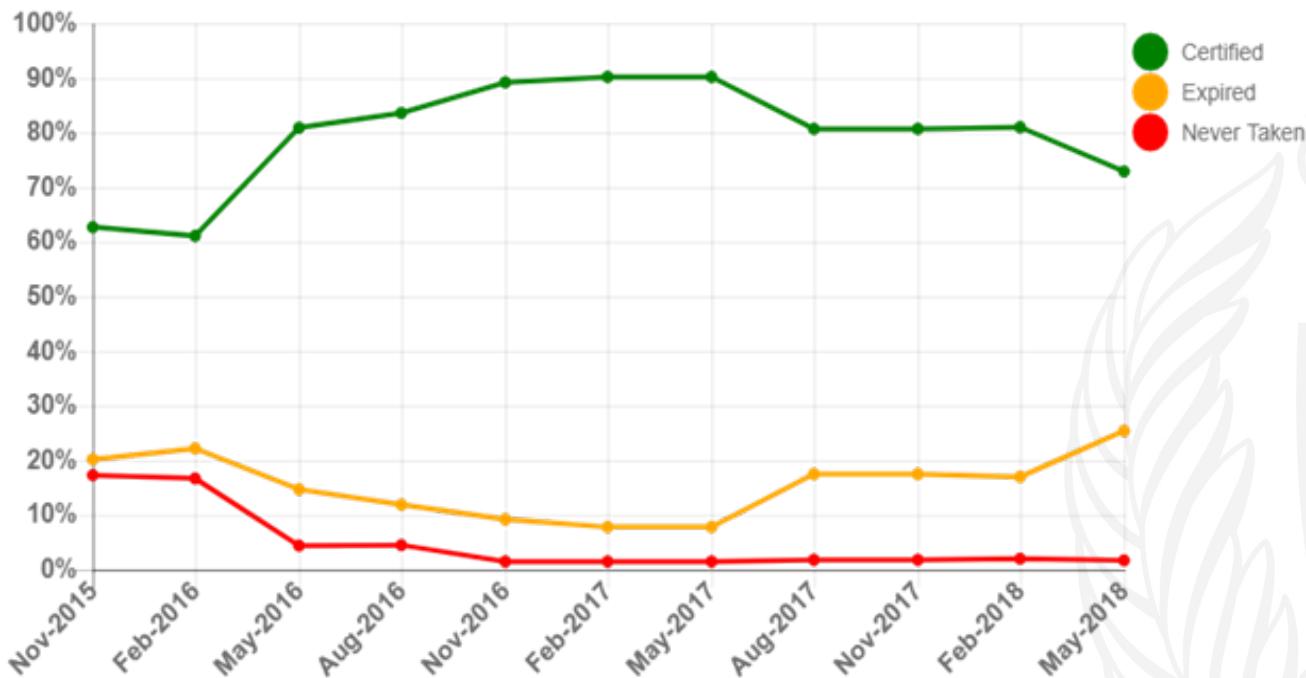
- In 2003 the clinical pharmacology tutorial was introduced and was located on the ACTG portal
- In 2006 PQA and FSTRF published that use of the tutorial resulted in a 13% drop in errors related to pharmacology data and specimen collection/handling*
- In 2007 ACTG and IMPAACT networks made participation 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)

* DiFrancesco R, Rosenkranz SL, Craft J, Morse GD. (2006). Tutorial reduces protocol deviations in multicenter ACTG trials with pharmacology endpoints. HIV Clin Trials. 2006 Jul-Aug;7(4):203-9.

PMID: 17065032

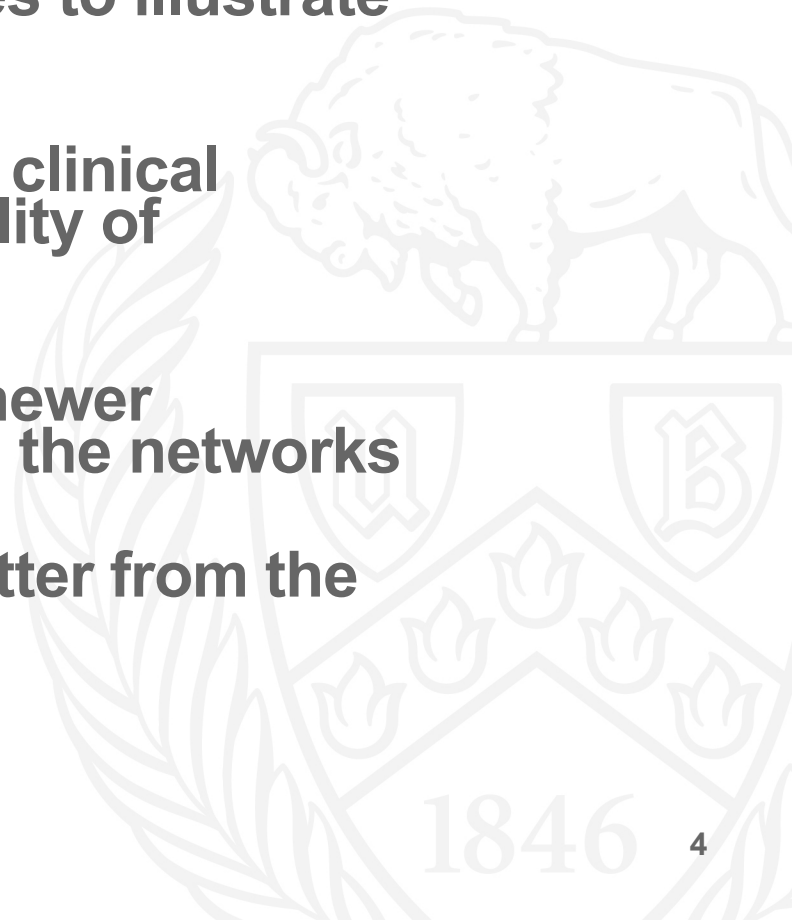
May 2018 IMPAACT Certification Report

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**

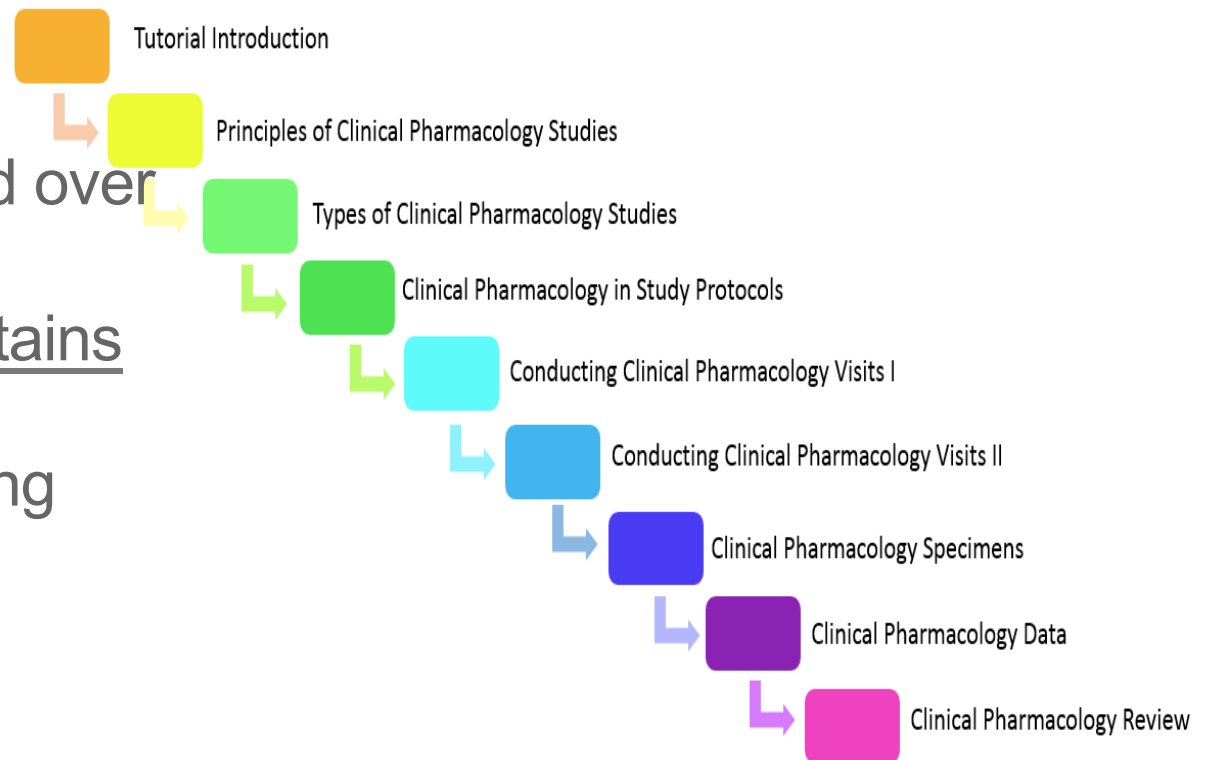


New Tutorial Overview

- 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



Welcome to the

Clinical Pharmacology Tutorial

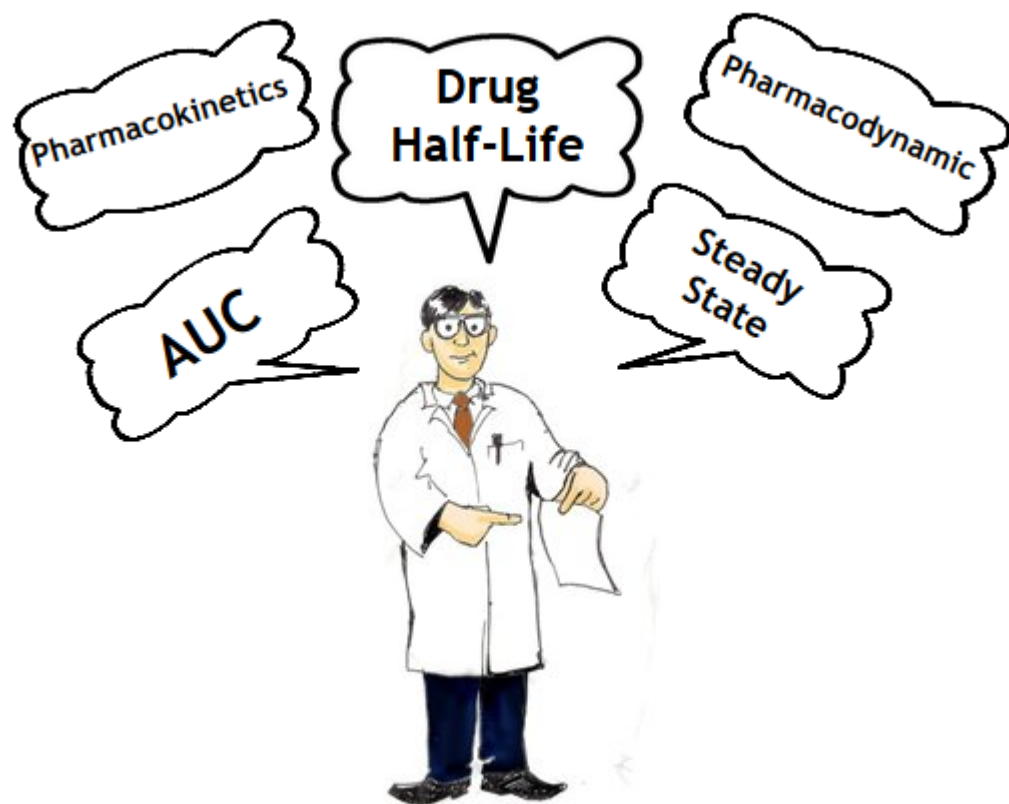
An online tutorial to ...

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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

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Principles of Clinical Pharmacology Studies

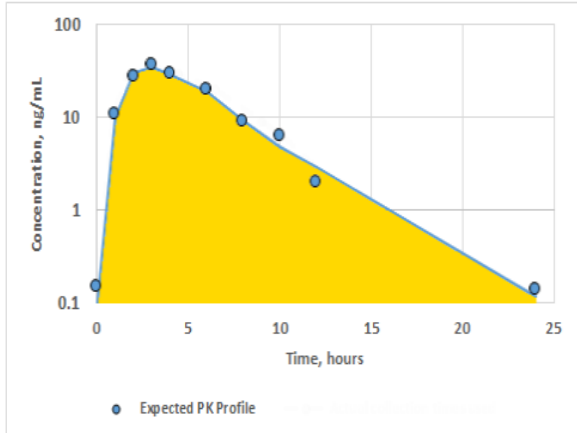



Area Under the Curve


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



Time (hours)	Concentration (ng/mL)
0	0.1
1	10
2	30
3	40
4	35
5	25
7	15
10	8
12	3
24	0.1


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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





Clinical Pharmacology Tutorial

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Clinical Trial Studies and Pharmacology

Clinical Pharmacology Research

Key clinical pharmacology research outcomes in a clinical trial may be applied in a variety of ways:

Directions: Click each graphic to see how research outcomes may be applied.

				
Support an application for drug marketing or be included in prescribing information.	Determine the appropriate dosing for specific sub-groups of participants such as infants and children, pregnant women, or ethnic groups.	Determine if drug-drug or drug-food interactions are likely to occur.	Assess the adherence of participants to study medications.	Determine if more extensive research in a specific area is needed.


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New Tutorial Module 4

Clinical Pharmacology Study Protocols

- Clinical Pharmacologist's role
- Pharmacology Objectives
- Protocol Document & PK
- Resources and Tools

Clinical Pharmacology Tutorial

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Clinical Pharmacology Study Protocols


Protocol Pharmacologist

When pharmacology research is part of a clinical trial, a protocol pharmacologist(s) will be part of the study team.

PRE-STUDY Works with the study team to develop and finalize the protocol by providing key information, study design content, sampling information for pharmacology specimens, outcome measurements for data analysis and other integrated protocol recommendations.

STUDY

POST-STUDY



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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.

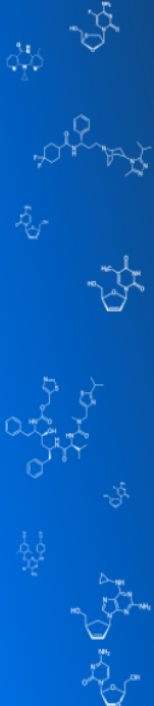


New Tutorial Module 5

Conducting Clinical Pharmacology Visits I

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




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Conducting Clinical Pharmacology Visits I

Impact of Incorrect Dosing Upon Study Results

If the answer was "yes" to any of the prior slide questions, the concentration results of the specimens will be affected.

Directions: Click on each box on the left of the graph to compare PK results to the results obtained when the improper dosing or dosing schedule occurred.



Has not taken the last three doses

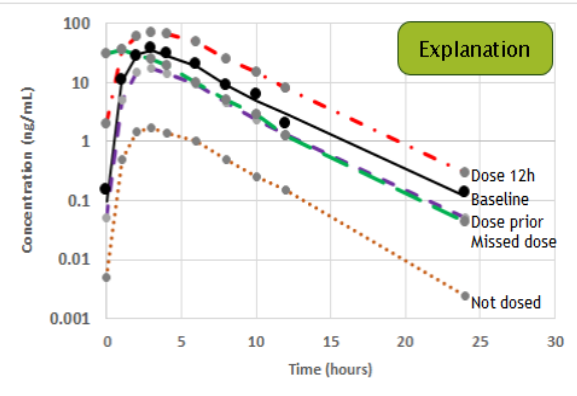
Missed one of their last three doses

Took their dose prior to arrival

QD dosing not switched to AM

Show all above on one graph

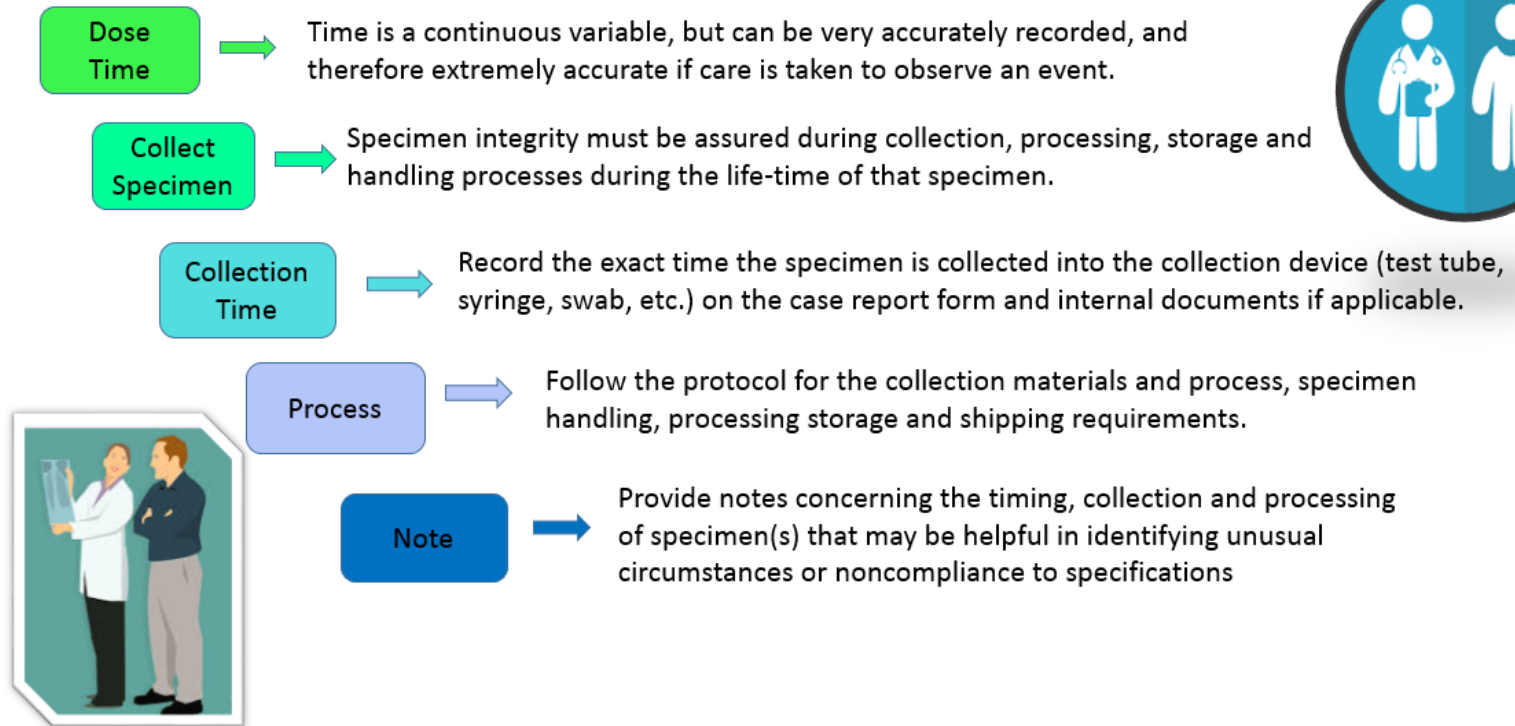





Explanation

New tutorial Module 6

Conducting Clinical Pharmacology Visits II






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.

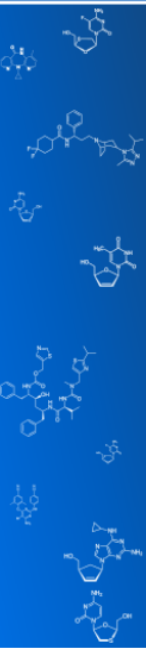
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Clinical Pharmacology Tutorial

Conducting Clinical Pharmacology Visits II



Dose Time

From LPC

→

Use spray dried K₂EDTA collection tubes (e.g. BD367861).


Week 2, 6, 12 specimens are collected 2 hours after morning dose of drug

"After the morning dose of drug..."


How do you determine the accurate 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.


Directions: Click on the graphic to determine its dose time.



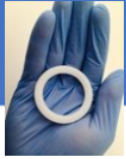
Dose Time = participant swallows the pill




Dose Time = IV bolus is given intravenously or subcutaneously



Dose Time = IV delivery begins and ends



Dose Time = delivery system is put in place (vaginally, rectally, placed on skin, etc)


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New Tutorial Module 6

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"

Clinical Pharmacology Tutorial

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Conducting Clinical Pharmacology Visits II

Specimen Collection Times

From LPC →


Use spray dried K₂EDTA collection tubes (e.g. BD367861).

Week 2, 6, 12 specimens are collected 2 hours after morning dose of drug

- **Remember:** Time is a continuous variable, but can be an extremely accurate variable if care is taken to observe an event and document/record the true time of that event.
- 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.

The collection time is when:

Directions: Click on each graphic for details of collection times.



The blood specimen is filling a tube.

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New Tutorial Module 6




Conducting Clinical Pharmacology Visits II

Specimen collection

From LPC →

EDTA blood 4 mL	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
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Clinical Pharmacology Tutorial


Conducting Clinical Pharmacology Visits II

From LPC →

EDTA blood 4 mL	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
-----------------------	-------------------------------------------------------------------------------------------------------------------------------------------------------

Collect Specimen(s)

- 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 pharmacologspecimenles per the protocol and direction from other informational documents, such as an LPC.



Specimen container specifications interactive activity

Directions: Click on terms below to see specimen specifications of the picture to the right

Vessel


Volume

Additive/Anticoagulant

Specimen collection vessel:
Specified collection tube

Specimen collection volume:
5.0 mL

Specimen additive/anticoagulant:
EDTA


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New Tutorial Module 7

Clinical Pharmacology Specimens

Clinical Pharmacology Tutorial

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Clinical Pharmacology specimens

Types of Pharmacology Specimens

Directions: Click on the triangles of the compartmental pyramid to the right to reveal some types of pharmacology specimens collected in clinical research trials.

Drug metabolites can be excreted in **urine**.

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

Tissues 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)

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

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Clinical Pharmacology specimens

Matrix Directions: Click each matrix to show the next step.

Primary example: *BLD (blood)*

↓

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

centrifuge

↓

Derivative example: *SER (Serum)*

centrifuge

↓

Derivative example: *PL₁ (Plasma)*

↓

Additives example: *85% phosphoric acid*

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

Matrix	Drug
Storage	Container(s)




Directions: Click below for examples of LDMS codes



New Tutorial Module 7

Clinical Pharmacology Specimens

Clinical Pharmacology Tutorial

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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.



```

            graph LR
            A[Collection] --> B[Labeling]
            B --> C[Transfer]
            C --> D[Shipment]
            D --> E[Receipt]
            E --> F[Analysis]
            F --> G[Reporting Results]
            
```

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.

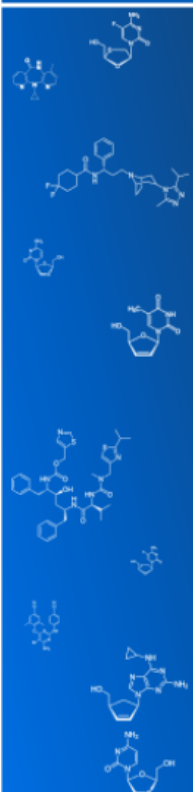
Outcomes data entered by the Pharmacology Specialty Laboratory (PSL) have known errors associated with their measurement.



These measured or estimated variables are known as **DEPENDENT** variables.

New Tutorial Module 8

Pharmacology Data




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Clinical 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:

eCRF



LDMS[®]



- Incorrect dose information
- Missing data
- PID errors




- Date/Time discrepancies
- Mislabeled specimens

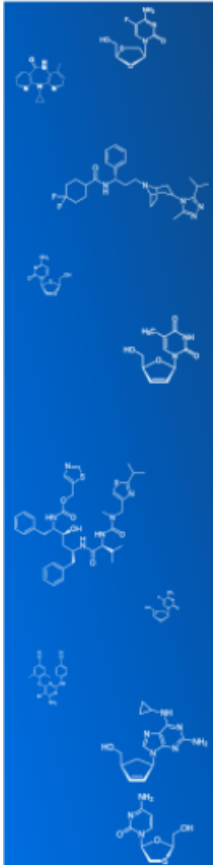
New tutorial Module 8



Pharmacology Data

Clinical Pharmacology Tutorial

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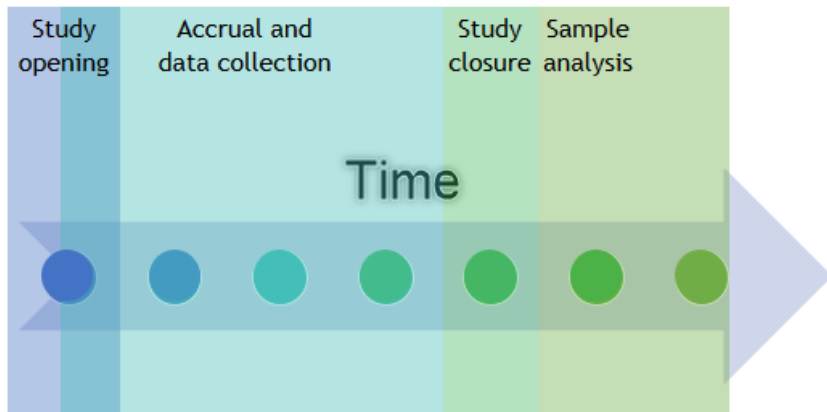






Clinical Pharmacology Data  

The Right Data at the Right Time

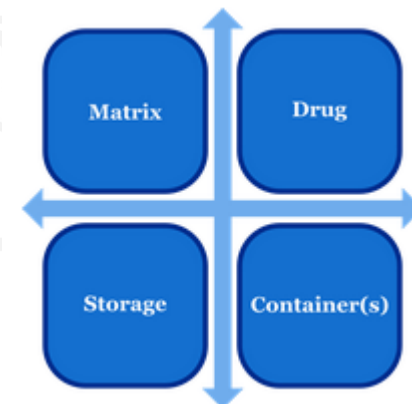
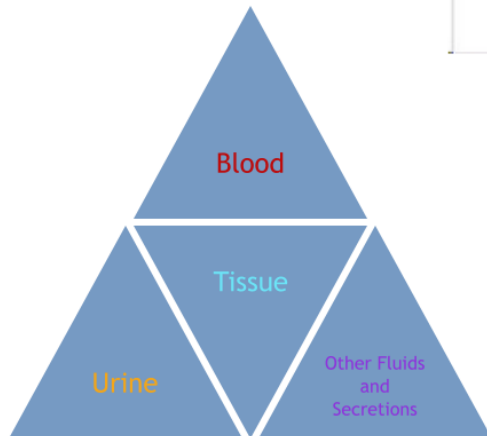
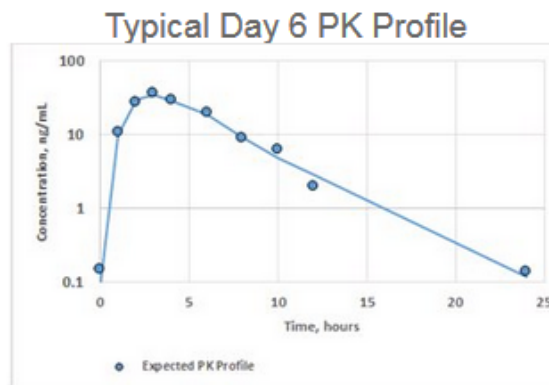
Pharmacology sample analyses are sometimes batched and analyzed at the end of the study. The time needed to accrue all participants to the study and close the study varies, but can often be years. At this time, the samples are analyzed and the results entered into the LDMS.



Directions: Click the circles on the time line to see the phases of a study.

New tutorial Module 9

Clinical Pharmacology Review



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....

