PRIMARY END POINTS ANALYSIS IN PIVOTAL SUBMISSION STUDIES – FROM A STATISTICAL PROGRAMMER'S PERSPECTIVE

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AGENDA

PRIMARY END POINTS ANALYSIS IN PIVOTAL SUBMISSION STUDIES – FROM A STATISTICAL PROGRAMMER'S PERSPECTIVE

- Introduction
- Skills
  - Analytical skills
  - Technical skills
- HIV efficacy end points
  - Virology
  - Snapshot
  - Mutation
  - Resistance
- Good programming practices
- Summary

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INTRODUCTION

- Clinical statistical programmer translates research data into mathematical indicators by utilizing their analytical and technical skills
- Key role in ***pivotal*** submission studies
- Dynamic skill set required in evolving clinical research industry

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SKILLS

- ANALYTICAL
- TECHNICAL

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ANALYTICAL SKILLS

- Data visualization
- Protocol/ SAP/Regulatory guidance documents coherent construal
- Scenario creation
- Algorithm generation

TECHNICAL SKILLS

- DATA/PROC Step Programming
- Functions
- Data Conversion
- Output Delivery System
- Macro Programming
- Statistical Techniques

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TECHNICAL SKILLS

- CDISC Expertise
- XPT files
- DEFINE.XML
- Pinnacle 21 Report
- Analysis Results Metadata (ARM)
- Executable code
- Technical writing
- eCRT package

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HIV EFFICACY END POINTS

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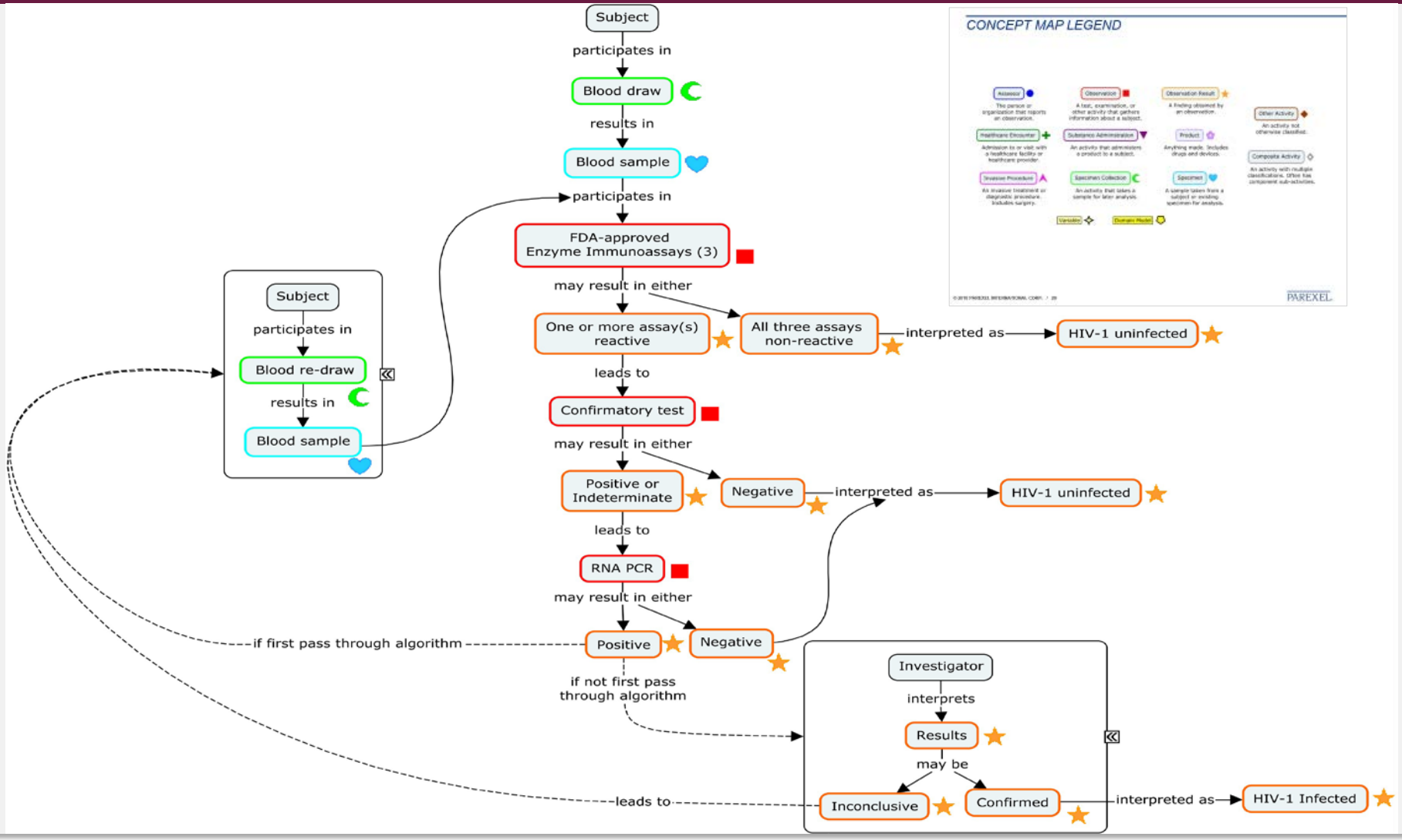
HIV DIAGNOSIS

CONCEPT MAP OF HIV DIAGNOSIS ALGORITHM



Source: CDISC Therapeutic Area Data Standards User Guide for Virology

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VIRAL LOAD DETECTION EXAMPLE

Row	STUDYID	DOMAIN	USUBJID	SPDEVID	MBSEQ	MBREFID	MBTESTCD	MBTEST	MBTSTDTL	MBORRES	MBORRESU	MBSTRESC	MBSTRESN	MBSTRESU	MBLOINC	MBSPEC	MBMETHOD	MBLLOQ	VISITNUM	VISIT	MBDTC
1	ABC	MB	ABC-001	RT-qPCR01	1	001-02	HIV1RNA	HIV-1 RNA	VIRAL LOAD	496700	copies/mL	496700	496700	copies/mL	70241-5	PLASMA	QUANTITATIVE REVERSE TRANSCRIPTASE POLYMERASE CHAIN REACTION	20	2	WEEK 1	2016-05-19
2	ABC	MB	ABC-001	RT-qPCR01	2	001-03	HIV1RNA	HIV-1 RNA	VIRAL LOAD	19400	copies/mL	19400	19400	copies/mL	70241-5	PLASMA	QUANTITATIVE REVERSE TRANSCRIPTASE POLYMERASE CHAIN REACTION	20	3	WEEK 4	2016-06-10
3	ABC	MB	ABC-001	RT-qPCR02	3	001-04	HIV1RNA	HIV-1 RNA	VIRAL LOAD	79	copies/mL	79	79	copies/mL	70241-5	PLASMA	QUANTITATIVE REVERSE TRANSCRIPTASE POLYMERASE CHAIN REACTION	20	4	WEEK 24	2016-11-08
4	ABC	MB	ABC-001	RT-qPCR02	4	001-05	HIV1RNA	HIV-1 RNA	VIRAL LOAD	TARGET DETECTED, BELOW LLOQ		TARGET DETECTED, BELOW LLOQ				PLASMA	QUANTITATIVE REVERSE TRANSCRIPTASE POLYMERASE CHAIN REACTION	20	5	WEEK 48	2017-04-06
5	ABC	MB	ABC-001	RT-qPCR03	5	001-06	HIV1RNA	HIV-1 RNA	VIRAL LOAD	TARGET NOT DETECTED		TARGET NOT DETECTED				PLASMA	QUANTITATIVE REVERSE TRANSCRIPTASE POLYMERASE CHAIN REACTION	20	6	WEEK 72	2017-10-13

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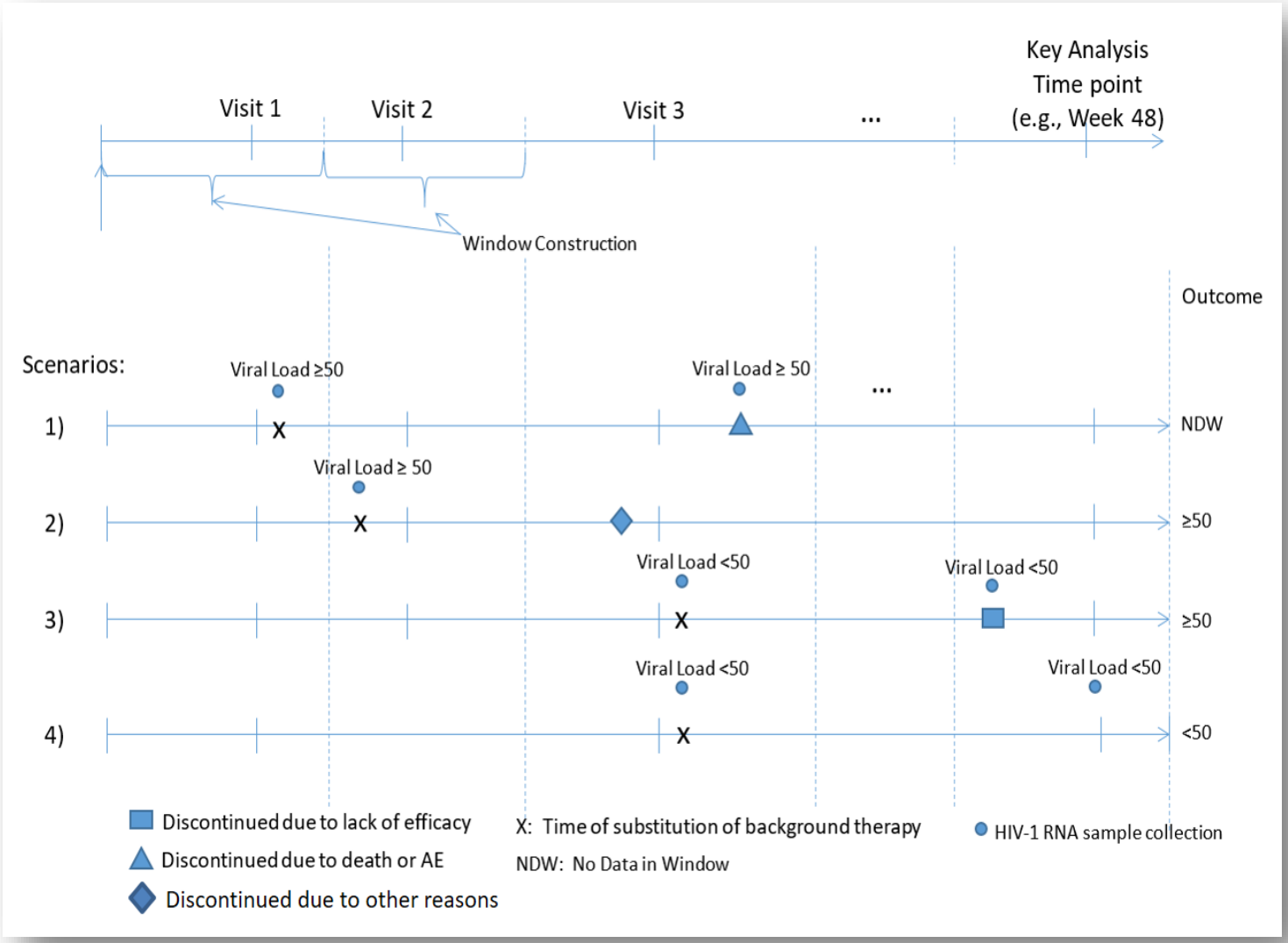
FDA SNAPSHOT ANALYSIS SCENARIOS



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MUTATION

- A mutation is deemed to be present if the encoded amino acid varies from the amino acid that would have been encoded by the wild-type

- In below example table, row 9 shows a case where there was a mixed population of viruses with respect to the same location: those with either a change to F (Phe) or a change to V (Val), as indicated in PFORRES and PFSTRESC.

- Mutations might lead to drug resistance.

Row	USUBJID	NHOID	PFTESTCD	PFTEST	PFGENLOC	PFGENRI	PFGENTYP	PFREFSEQ	PFORRES	PFORREF	PFSTRESC
1	HIV01-101	HIV-1	GENVAR	Genetic Variation	60	REVERSE TRANSCRIPTASE	PROTEIN	CONSENSUS B	I	V	p.(Val60Ile)
2	HIV01-101	HIV-1	GENVAR	Genetic Variation	67	REVERSE TRANSCRIPTASE	PROTEIN	CONSENSUS B	N	D	p.(Asp67Asn)
3	HIV01-101	HIV-1	GENVAR	Genetic Variation	69	REVERSE TRANSCRIPTASE	PROTEIN	CONSENSUS B	N	T	p.(Thr69Asn)
4	HIV01-101	HIV-1	GENVAR	Genetic Variation	70	REVERSE TRANSCRIPTASE	PROTEIN	CONSENSUS B	R	K	p.(Lys70Arg)
5	HIV01-101	HIV-1	GENVAR	Genetic Variation	122	REVERSE TRANSCRIPTASE	PROTEIN	CONSENSUS B	E	K	p.(Lys122Glu)
6	HIV01-101	HIV-1	GENVAR	Genetic Variation	139	REVERSE TRANSCRIPTASE	PROTEIN	CONSENSUS B	K	T	p.(Thr139Lys)
7	HIV01-101	HIV-1	GENVAR	Genetic Variation	184	REVERSE TRANSCRIPTASE	PROTEIN	CONSENSUS B	V	M	p.(Met184Val)
8	HIV01-101	HIV-1	GENVAR	Genetic Variation	200	REVERSE TRANSCRIPTASE	PROTEIN	CONSENSUS B	A	T	p.(Thr200Ala)
9	HIV01-101	HIV-1	GENVAR	Genetic Variation	215	REVERSE TRANSCRIPTASE	PROTEIN	CONSENSUS B	FV	T	p.(Thr215Phe^Val)
10	HIV01-101	HIV-1	GENVAR	Genetic Variation	219	REVERSE TRANSCRIPTASE	PROTEIN	CONSENSUS B	C	K	p.(Lys219Cys)
11	HIV01-101	HIV-1	GENVAR	Genetic Variation	334	REVERSE TRANSCRIPTASE	PROTEIN	CONSENSUS B	H	Q	p.(Gln334His)
12	HIV01-101	HIV-1	GENVAR	Genetic Variation	335	REVERSE TRANSCRIPTASE	PROTEIN	CONSENSUS B	D	G	p.(Gly335Asp)

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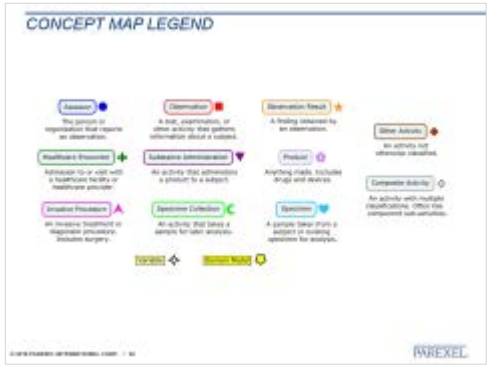
DRUG RESISTANCE

CONCEPT MAP OF DRUG SENSITIVITY TESTING



Subject
participates in
Sample collection
has
method
results in
Sample
may be
may participate in
Final specimen
results in
viral culture for amplification
participates in
Drug resistance assessment
is either
Genotype testing
Phenotype testing
has
gives
method
pyrosequencing
allele specific RT-PCR
may be
next generation sequencing (deep)
Sanger sequencing
Results
have
values
represented as
nucleotide or amino acid changes
PF Domain
stored in
such as
Inhibitory concentration assay
Cell culture replication assay
gives
Results
have
values
represented as
quantification of infectious units/ fold shift in drug suseptibility
gives
Results
have
values
represented as
50% Inhibitory Concentration (IC50)
calculated by
Software
stored in
MS Domain

Source: CDISC Therapeutic Area Data Standards User Guide for Virology

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GOOD PROGRAMMING PRACTICES

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GOOD PROGRAMMING PRACTICES (GPP)

- GPP for smooth submission
  - Header and Revision History
  - Comments and Documentation
  - Defensive programming
  - Periodical review of Pinnacle 21 report
  - DEFINE.XML review

SUMMARY

- It is imperative that statistical programmers possess the required technical and analytical skills to do efficient programing for efficacy end points
- Conceptual understanding is critical for implementation of efficacy analysis
- Good programming practices help in smooth submission of studies

REFERENCES

- https://wiki.cdisc.org/display/TAHIV/TAUG-HIV
- CDISC: Therapeutic Area Data Standards User Guide for Virology Version 2.0 Provisional
- Kirk Paul Lafler, Paper PA-111, SESUG 2016: What's Hot – Skills for SAS® Professionals
- https://www.phusewiki.org/wiki/index.php?title=Good_Programming_Practice_Guidance

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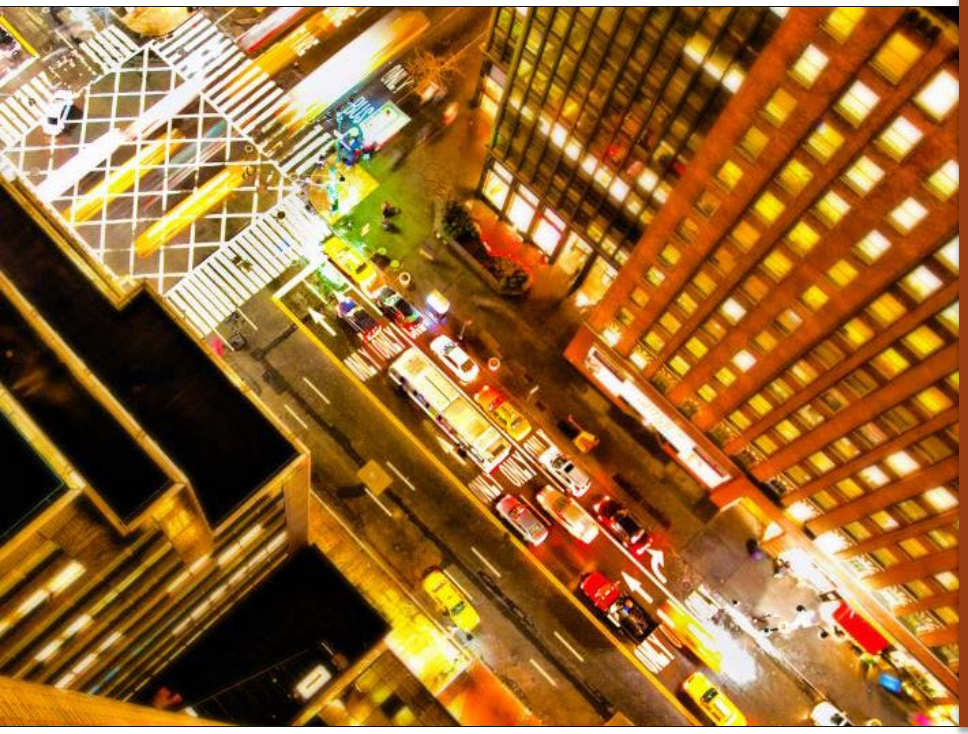
QUESTIONS



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THANK YOU

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