

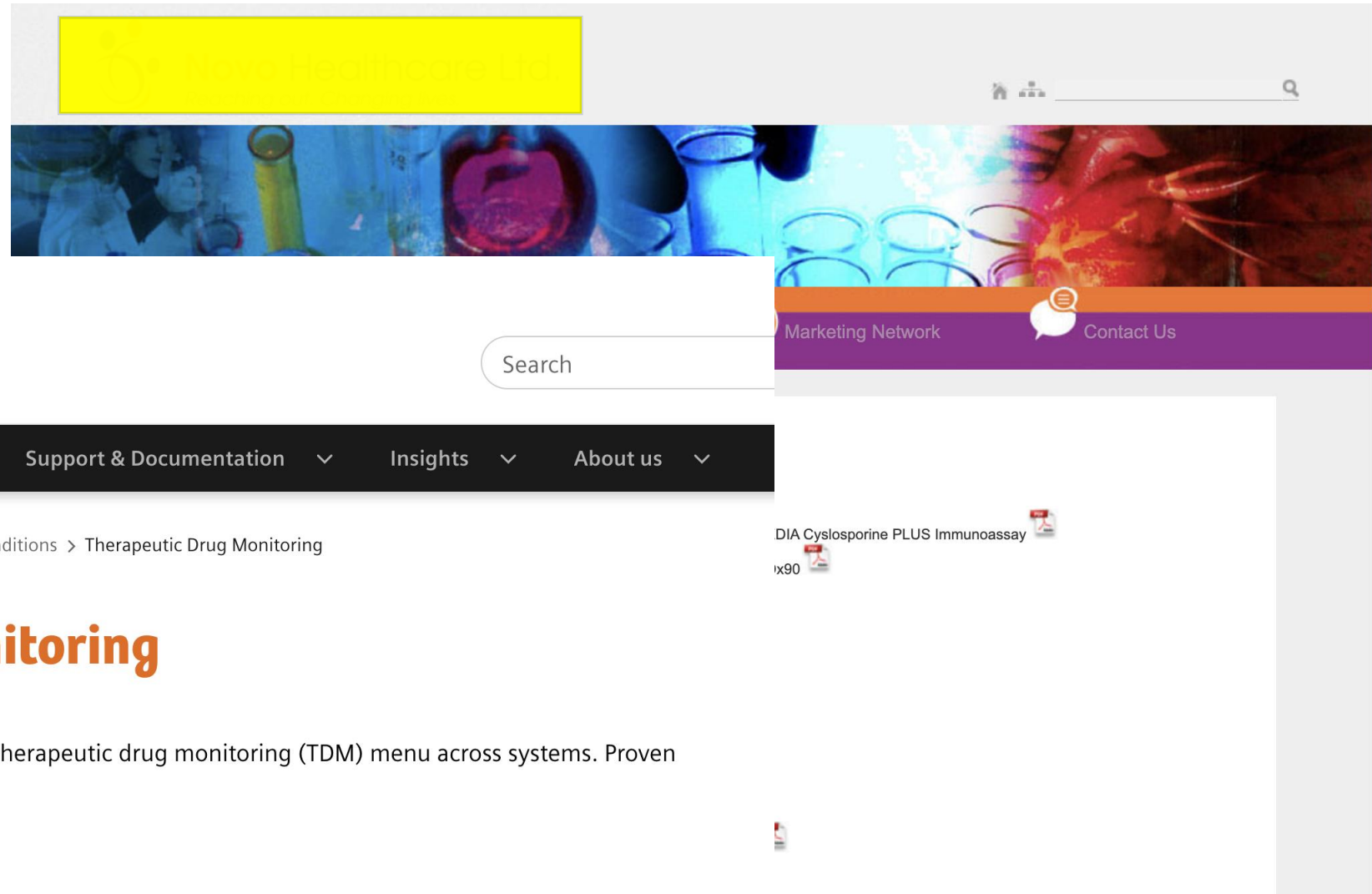
How to set up a TDM Unit

– From lab to clinical

Sumith K Mathew

What is not TDM?

- Simply measuring drug concentrations..



Therapeutic Drug Monitoring

Healthineers delivers a comprehensive therapeutic drug monitoring (TDM) menu across systems. Proven Productivity. Unlimited Possibilities.

Therapeutic Drug Monitoring is not simply measuring drug concentrations

Therapeutic Drug Monitoring

Flow of events



Patient consultation



Sample collection, transport and storage

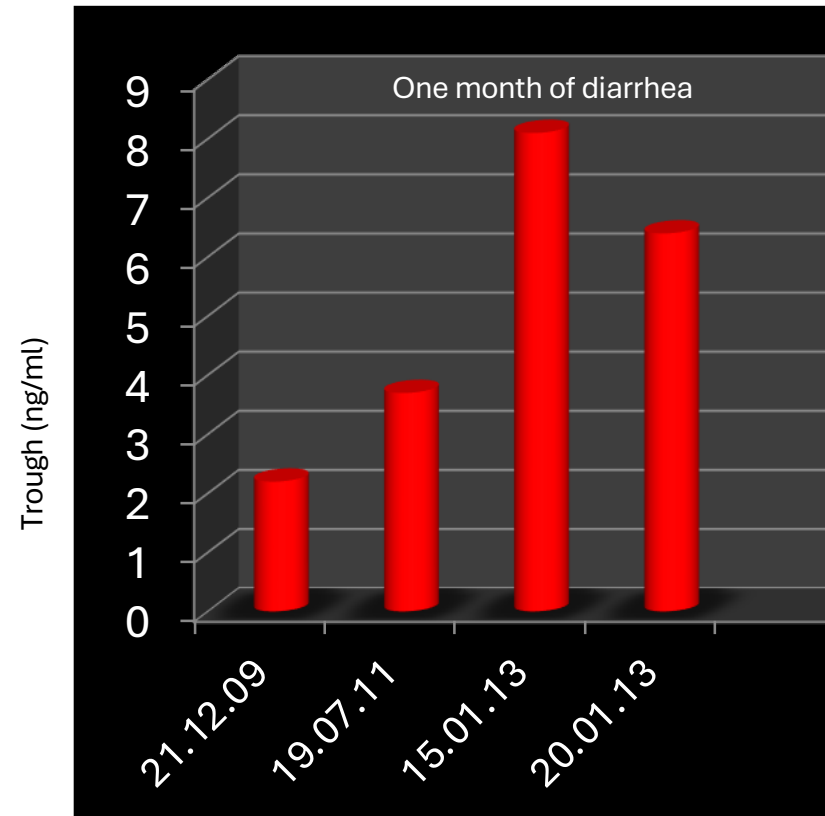


Quantification of analyte



Reporting

1. Patient consultation



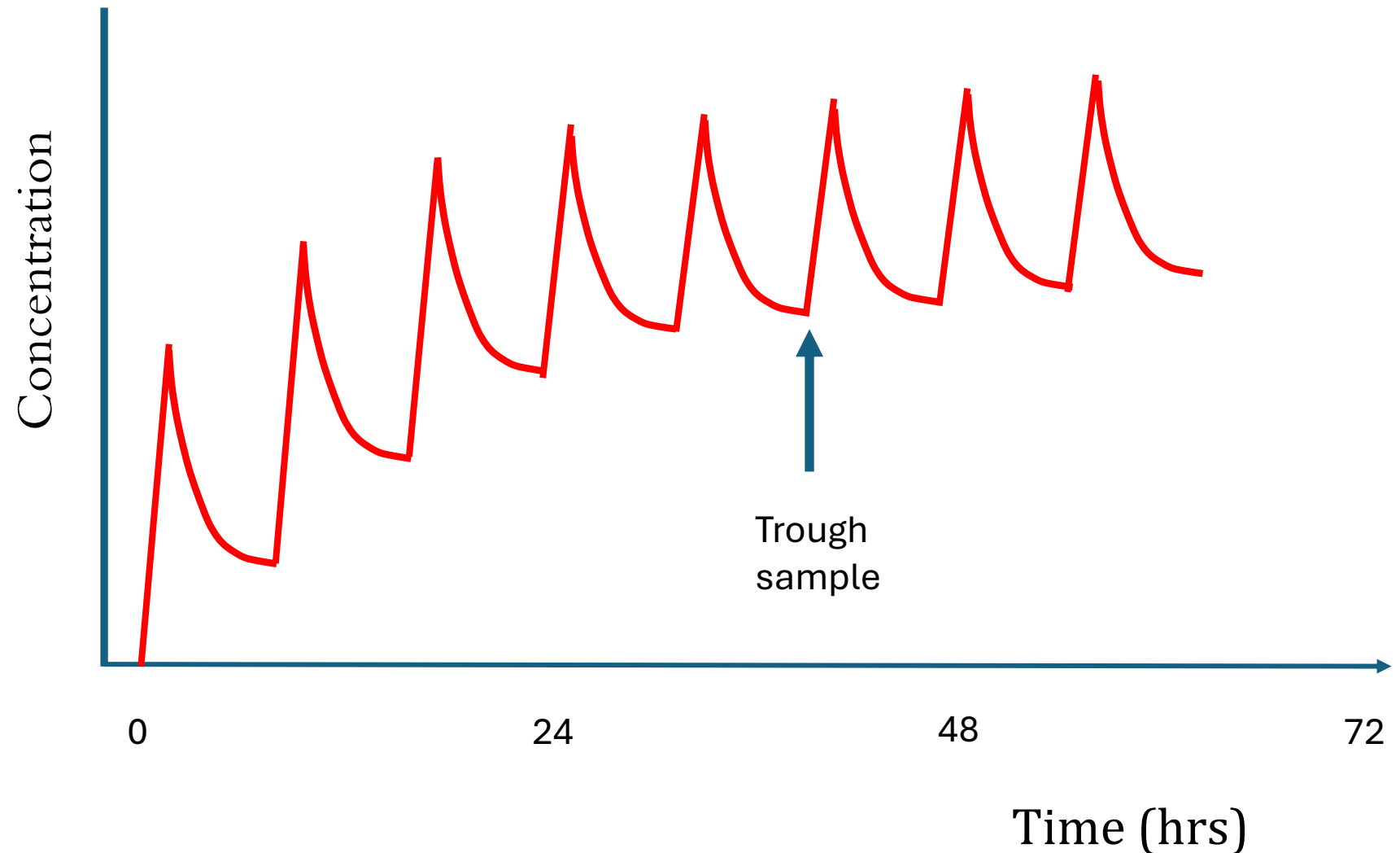
Tacrolimus – diarrhea

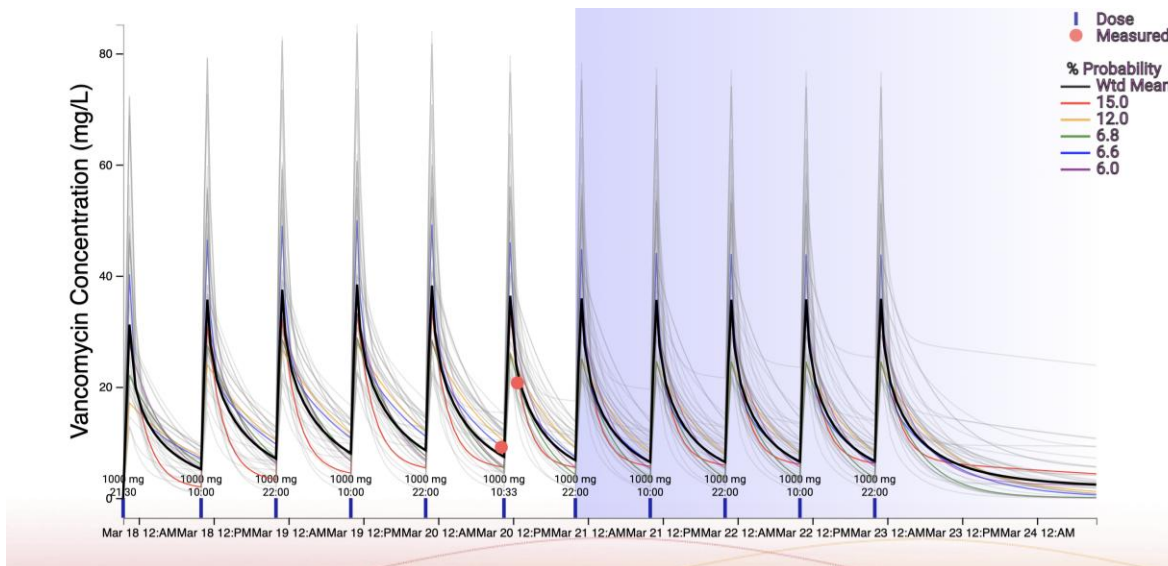
Diarrhea can cause increase in tacrolimus exposure

To ensure steady state conditions

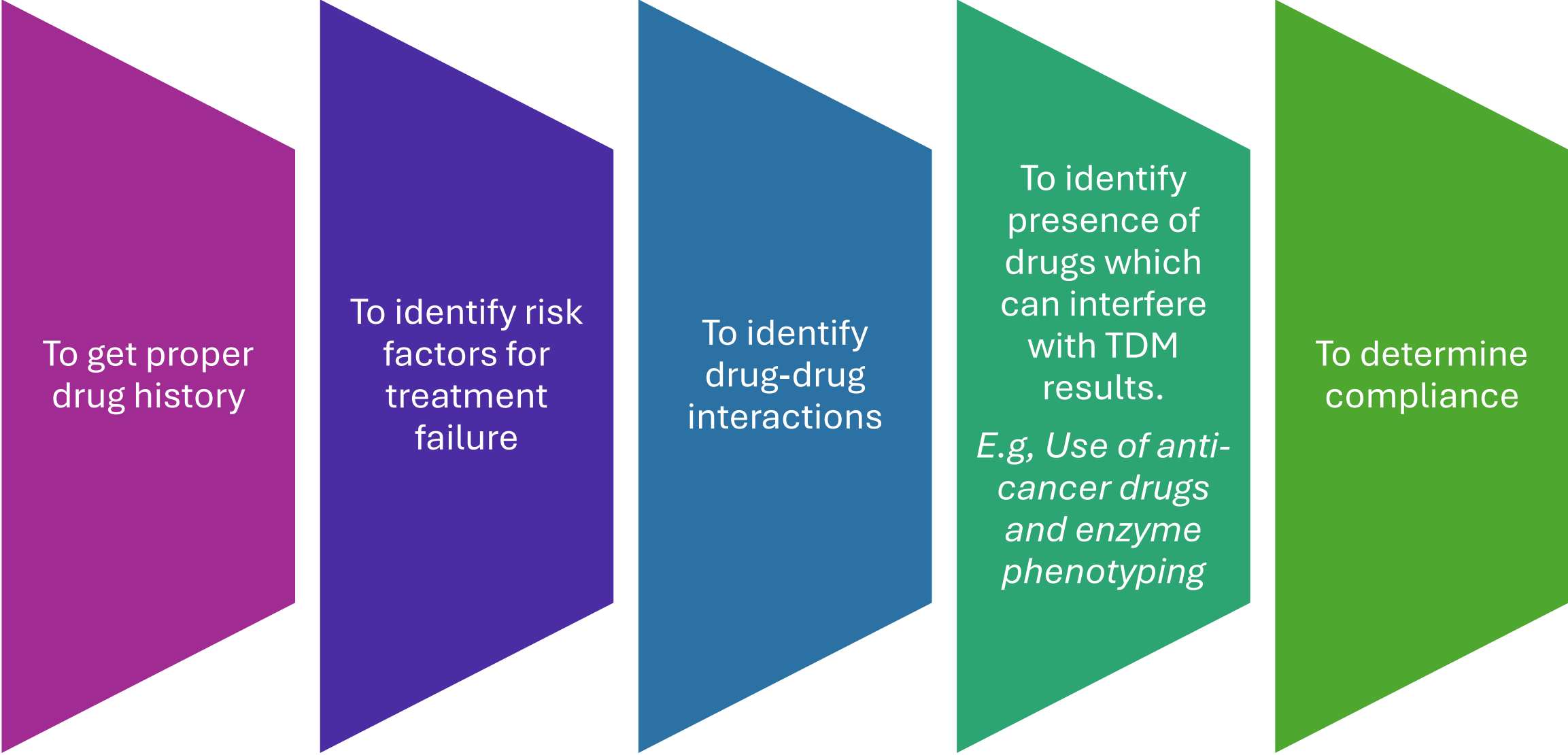
Therapeutic range is defined for trough levels at steady state.

Blood specimen should be collected at trough after attaining steady state.





For Dose- optimization programs



To get proper
drug history

To identify risk
factors for
treatment
failure

To identify
drug-drug
interactions

To identify
presence of
drugs which
can interfere
with TDM
results.

*E.g, Use of anti-
cancer drugs
and enzyme
phenotyping*

To determine
compliance

TDM Patient services: Location

- OP block
 - Very close to Emergency department or Intensive Care unit
 - Laboratory should be easily accessible
- OR
- provision for initial specimen processing and storage.
 - Around 500 sq. feet space + counselling room



Method 2: Patient consultation for TDM

- Use the existing facility and workflow of the hospital.
- Pharmacologist co-ordinate the entire TDM team
- Pros: More convenient for the patient, more convenient for departments ordering TDM procedures.
- Cons: Need to train more manpower

2. Sample collection, transport and storage

Investigation form

CLINICAL PHARMACOLOGY LAB INVESTIGATION FORM			
Name: Age: Sex : M/F Hosp No: Dept/ Unit :	Space for patient sticker		Weight Height (cm)
Investigation Requested:		Ward	
Brand Name of Drug, (if MPA):			
Dose of drug with frequency:	Date & Time of blood Sample	Date & Time of last dose	
Concomitant drugs:			
Name of the Doctor : Phone :	Date:	Date of Transplant, if applicable:	
FORM/PHACL/012/P/01/032022		MATCODE -	

Investigation form

Rifampicin INH specimen collection form

Clinical Pharmacology Unit, CMC, Vellore

Name: _____ Hospital No. _____

Appointment date: ____/____/____ Phone No: _____

Age : _____ Sex : _____ Wt : _____ Ht : _____

Date of specimen collection: _____

Indication for medication: Pulmonary TB/ Others: Specify.....

Comedications: _____

	Rifampicin	Isoniazid	Pyrazinamide
Dose / Frequency			
FDC (Yes/No)			
Date and time of last dose			
Duration since present regimen			

If dose had been adjusted less than 2 months before, collect info on the previous regimen. Any other significant dosing history

Rifampicin			Isoniazid			Pyrazinamide		
Event	Preferred time	Actual time	Event	Preferred time	Actual time	Event	Preferred time	Actual time
Trough								
Dose								
0.5			Trough			Trough		
1			Dose			Dose		
1.5			0.5			0.5		
2			1			1		
2.5			1.5			1.5		
3			2			2		
4			2.5			2.5		
6.5			3			3		
			4			4		
			5.5			5.5		

Do not use tick marks above, all the time-points have to be noted down accurate to the minute

Instructions:

Should come NPO (except water). Bring all the co-medications being taken for all diagnoses. Food to be taken 0.5 hr after Rifampicin dose. Isoniazid and Pyrazinamide to be taken 1.0hr after Rifampicin dose

Sample collection, transport and storage

-
- Time of sample collection
 - Matrix
 - Transit time
 - Maintenance of temperature during transport
 - Stabilizing agent
 - Storage conditions

Analytical Chemistry Laboratory

Methods to assess the specimen concentration of drugs

High Performance Liquid Chromatography

Ultra Fast Liquid Chromatography

Liquid Chromatography – Mass Spectrometry

Spectrophotometer

Immunoassay

Immunoassay

- Advantages:
 - Sensitive
 - Easy to use
 - Short turnaround times
 - Monoclonal antibodies
- Disadvantages
 - Relatively less specific compared to LC-MS/MS
 - Laboratory completely depended on the companies providing the service

LC-MS/MS

- Advantages
 - High specificity
 - High sensitivity
 - High throughput
 - Versatile
 - Gold standard
- Disadvantages
 - Need high technical skills for
 - Relatively longer Turnaround t
 - Documentation
 - Automation



List of support equipment

Microbalance	Ultrasonic cleaner	Pipette	Vacuum manifold
Nitrogen Evaporator	Filtration apparatus	Freezers	Fume cupboard
Mixmate mixer/ Vortex	Vacuum pump	Oven	Biosafety cabinet
Incubator	pH Meter	Centrifuges	Deionized water

Cost of setting up an Analytical Chemistry Laboratory



Equipment

- LC-MS/MS: 1.5 lakhs USD
 - Support equipment: 50,000 USD
 - Consumables: 12,000 USD
-

Manpower:

- **Laboratory:**

- Clinical Pharmacologist:
M.D. Pharmacology (Unit lead)
- Analytical Chemist: Ph.D.
Chemistry (Lab manager)
- Laboratory technicians: B.Sc
Laboratory technicians

- **TDM unit:**

- Clinical Pharmacologist:
M.B.B.S., M.D. Pharmacology
(Unit lead) – prescribing rights
- PharmD faculty (leads TDM
program in respective
departments E.g., Anti-
infectives)
- Nurse
- Phlebotomists
- Secretary

- **Pharmacometrics:**

- M.D. or PharmD

4. Reporting

Pharmacokinetic parameters

Trough

C_{\max}

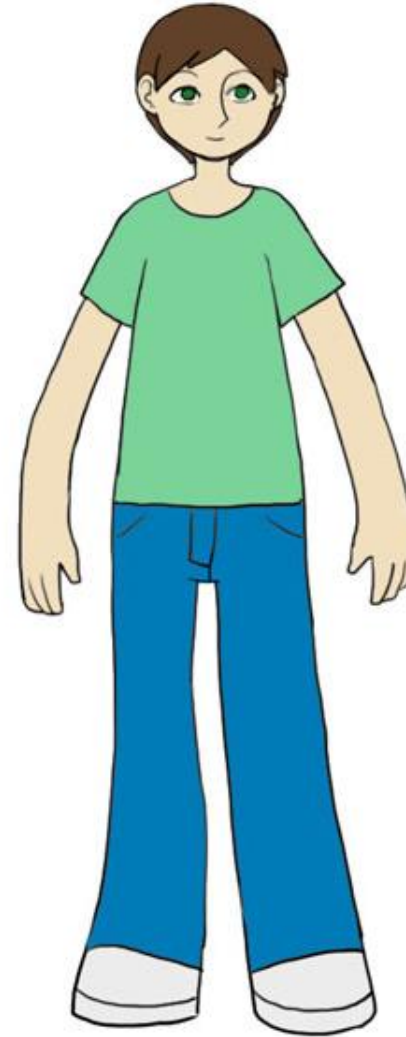
Area under
curve (AUC)

$T > MIC$

C_{\max}/MIC

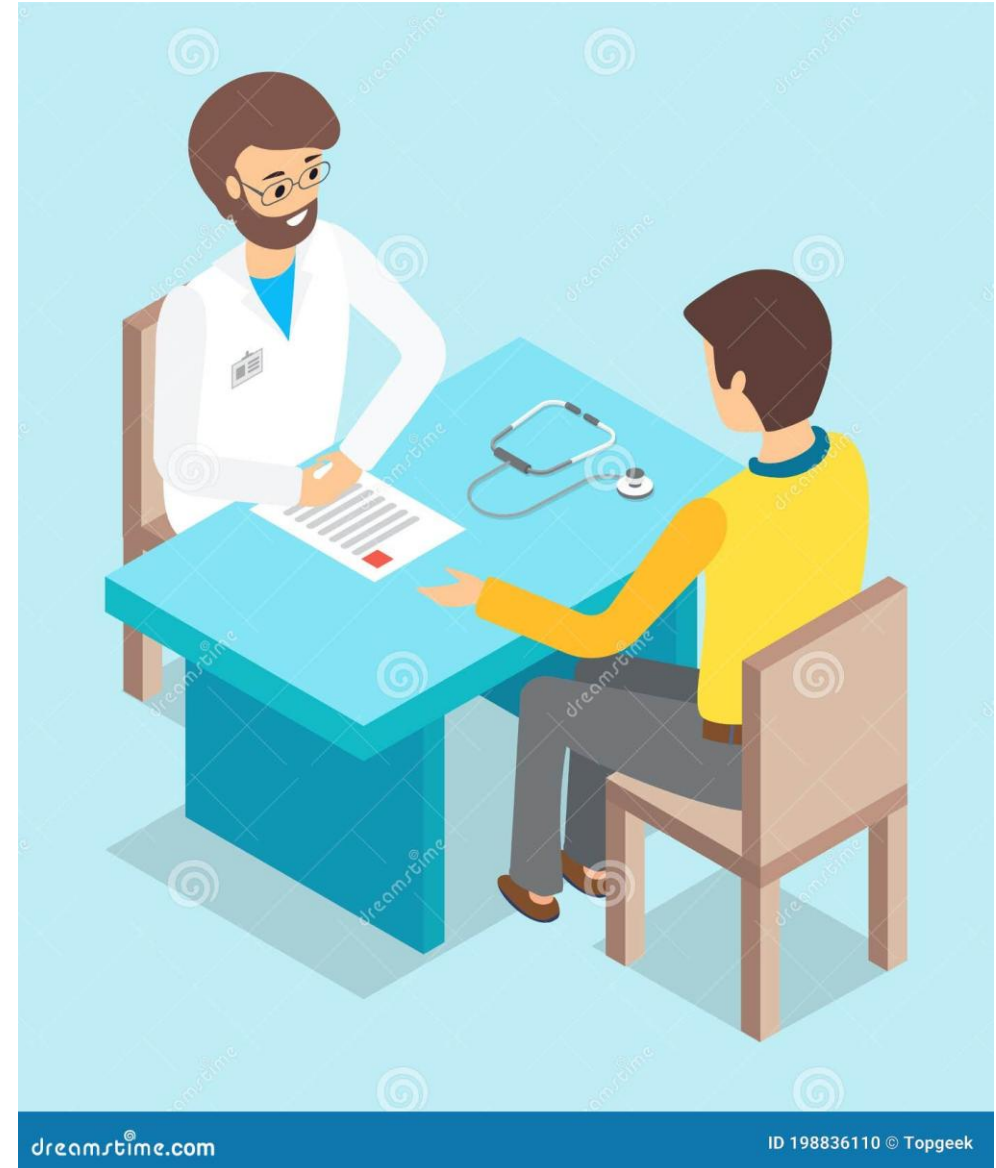
$C_{ss,avg}$

Patient visiting an Outpatient
Department



Doctor

- Sends a referral to PMU mentioning the drug name which needs TDM
- Referral:
 - Describes the patient condition which requires TDM.
 - Tacrolimus TDM



Pharmacologist/ Pharmacist

- Pharmacists collect patient details, discuss with the doctor who sent referral and order an appropriate test.
- Options
 - Tacrolimus trough
 - Tacrolimus random sample
 - Tacrolimus AUC (Bayesian Dose optimization)



Analysis

- Spectrophotometer
- Automated analyzer
- HPLC
- LC-MS/MS



Dose optimization programs

May use

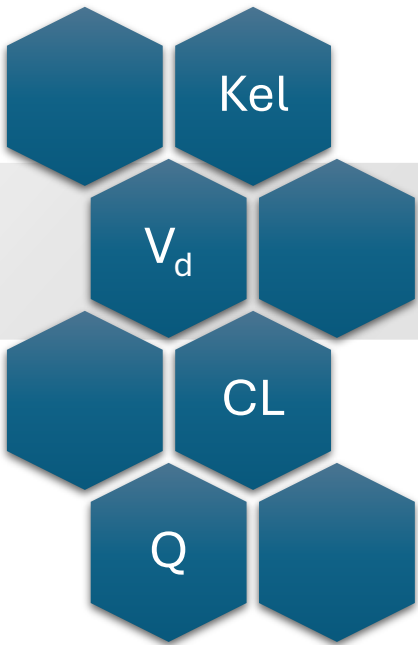


Model
development

Determine
covariates

Population
parameters

Model



Bayesian Prior



Dose
optimization

Individual
parameters

Identify
patient
factors
(covariates)



Bayesian
Posterior

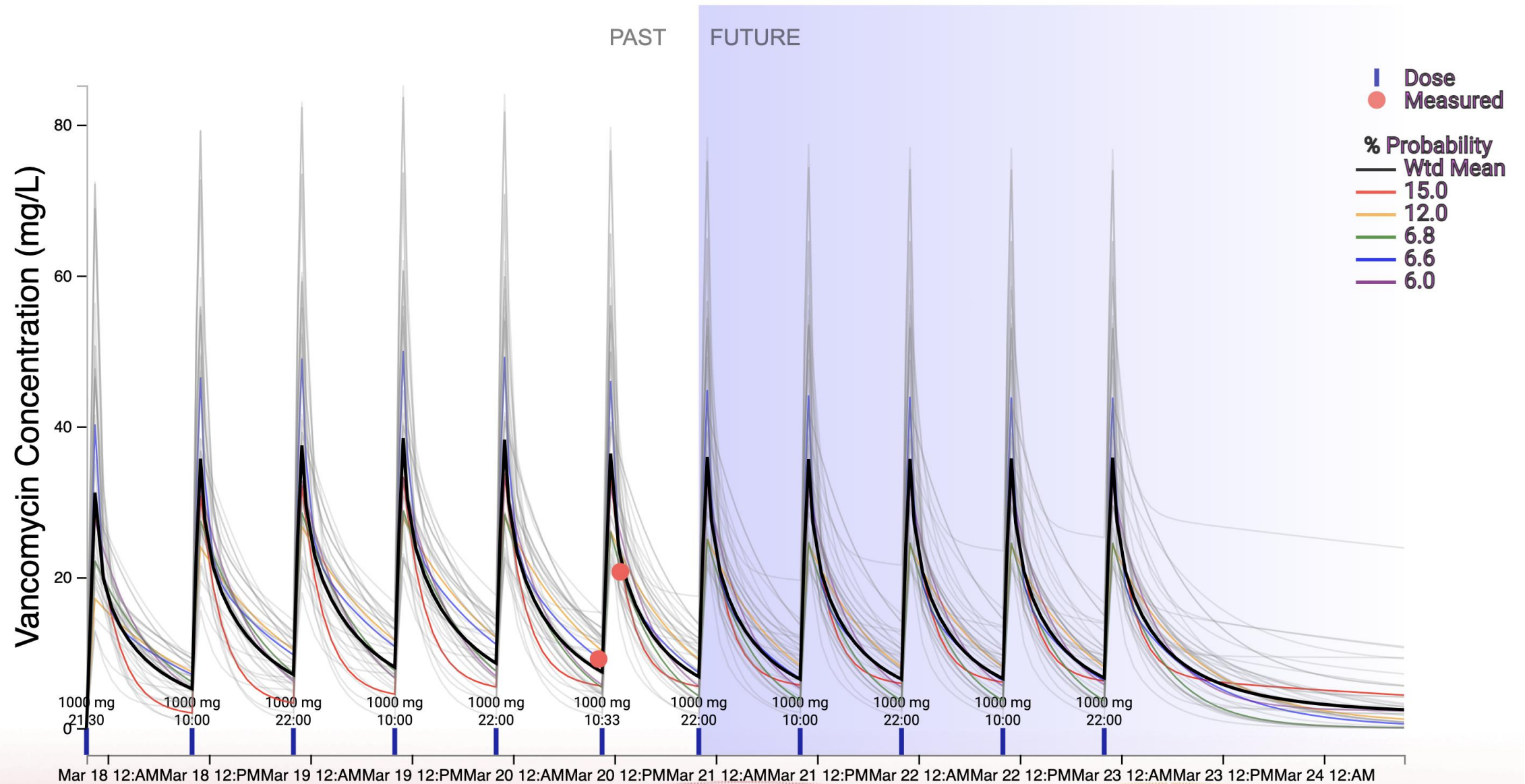
Dose
regimen

Plot

Model Quality

Treatment Summary

AUC



Results

- Discussed among pharmacologists



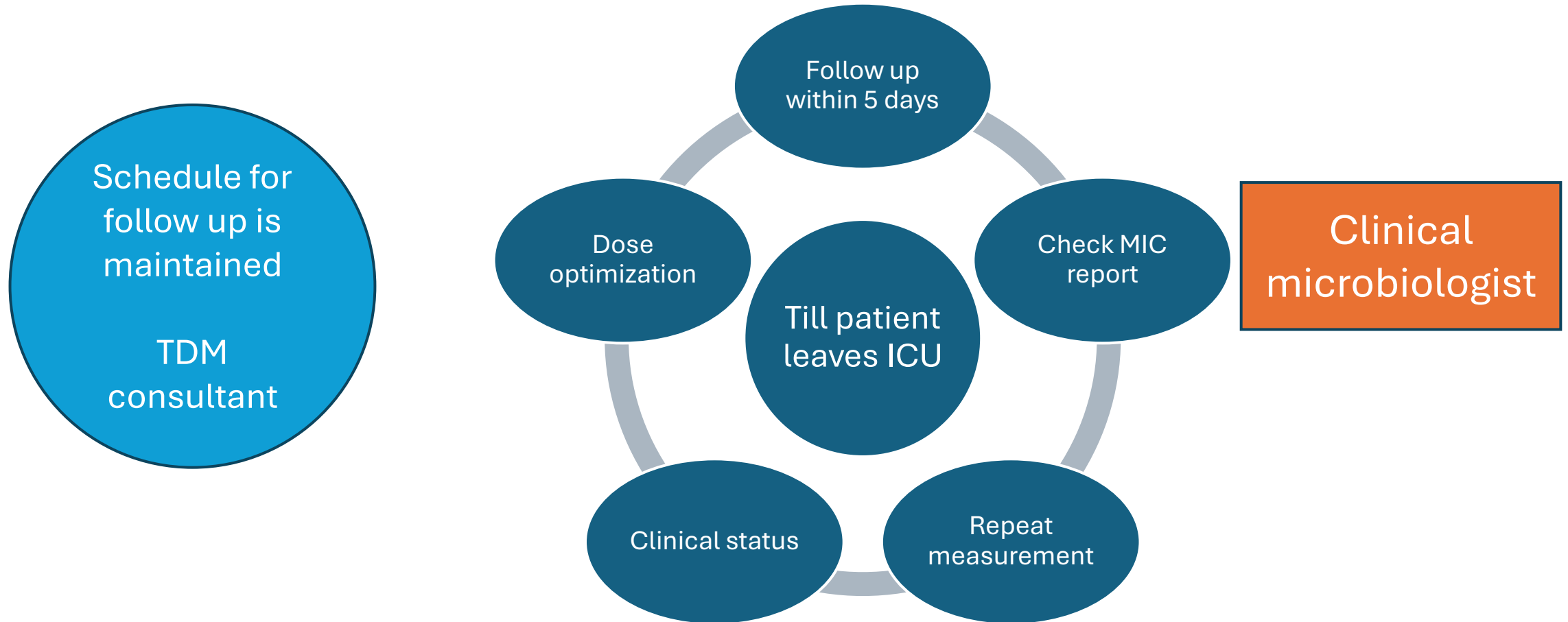
Final report: TDM

- Vancomycin Trough = X mg/L
- Predicted 24-hour Vancomycin AUC = Y mg.h/L
- Predicted AUC/MIC =
- Therapeutic range = 400 - 650
- Suggestions:
 - Monitor serum creatinine frequently (in conditions where s.creatinine fluctuates)
 - Give dose once daily over hours.
 - Follow up TDM: after days

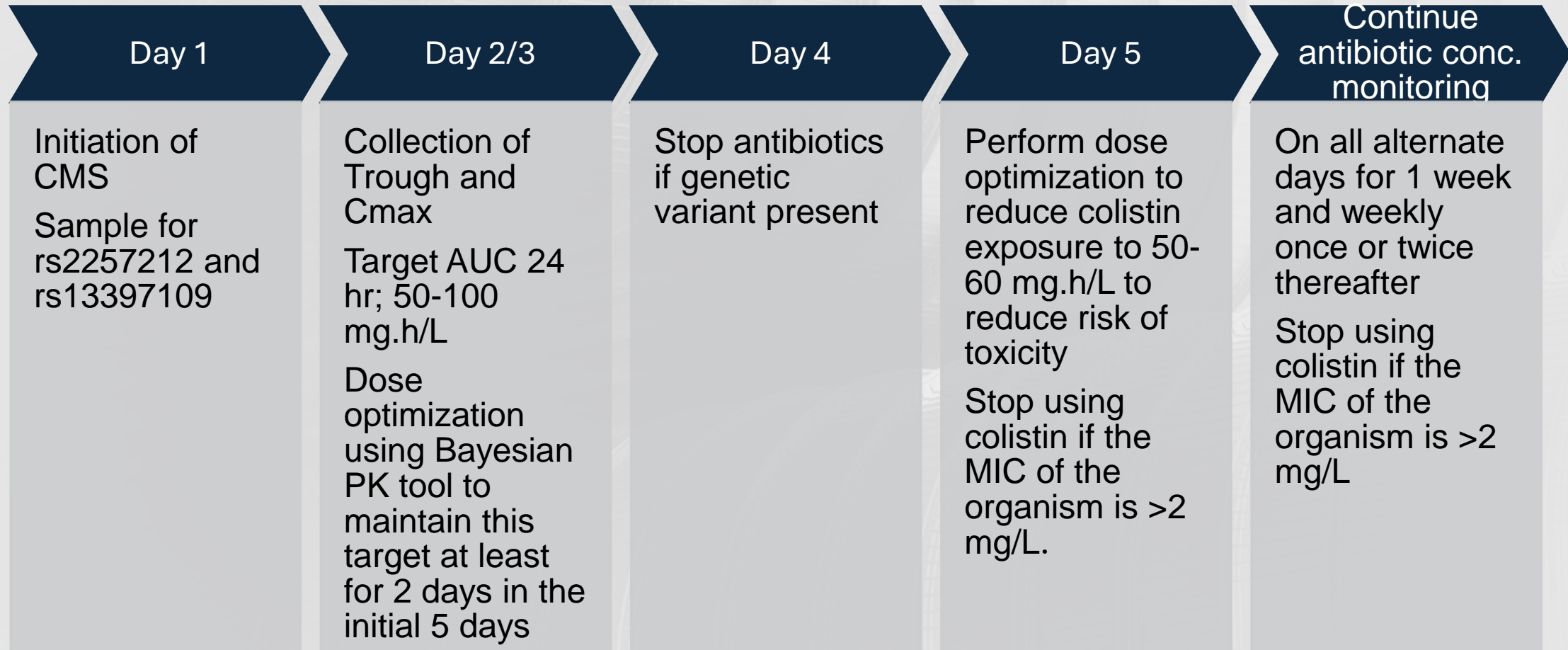
- Typical report format

Signed by M.D. Pharmacologist

Workflow: Critically ill patient follow-up: AMS program



Colistin antibiotic protocol for ICU patients



Three main components of a TDM unit

Analytical
Chemistry

Pharmacometrics

Model-informed
Precision Dosing



Believers Church
Medical College Hospital



Thank you