

# **HOW TO SET UP ANTIFUNGAL TDM SERVICE**

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# DISCLAIMER

- NO FINANCIAL DISCLOSURES
- NO CONFLICT OF INTERESTS

# OBJECTIVE

- PROCESS OF TDM
- KEY STAKEHOLDERS IN ANTIFUNGAL TDM
- FEASIBILITY AND UTILITY OF ANTIFUNGAL TDM
- PROTOCOL FOR ANTIFUNGAL TDM
- THE SINGAPORE GENERAL HOSPITAL EXPERIENCE

# FOR TDM TO BE USEFUL

- LARGE INTERINDIVIDUAL VARIABILITY IN PHARMACOKINETICS
- ESTABLISHED RELATIONSHIP BETWEEN DRUG CONCENTRATION AND ITS EFFECT (EFFICACY OR ADVERSE EFFECT)
- DEFINED TARGET RANGE (THERAPEUTIC WINDOW)
- NO OTHER MEANS TO MEASURE PATIENT RESPONSE DIRECTLY



# FOR SUCCESSFUL IMPLEMENTATION OF ANTIFUNGAL TDM SERVICE

Knowledge on the population pharmacokinetics and covariates



Knowledge on the pharmacodynamics (breakpoints)



Validation in clinical trials of defined breakpoints

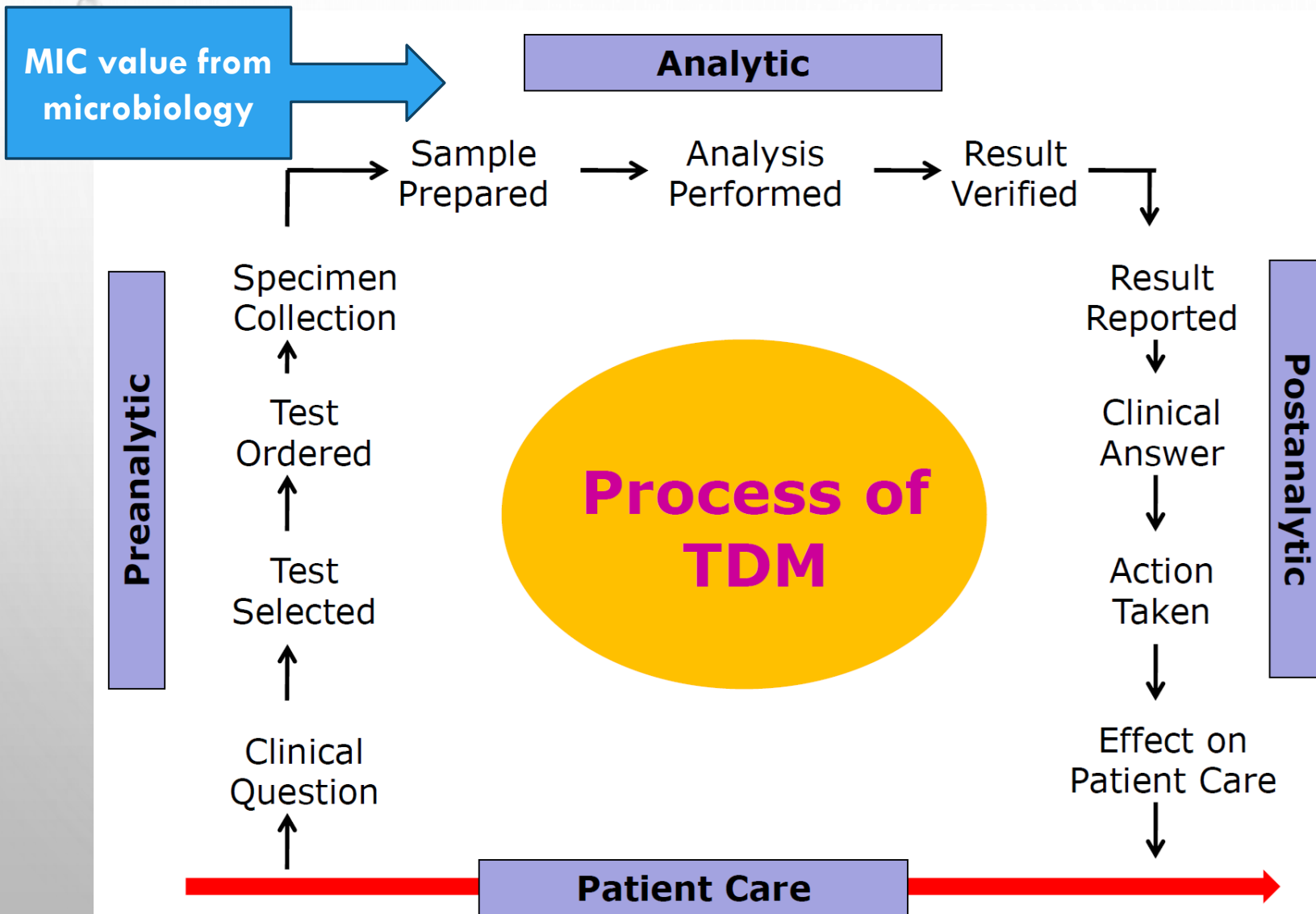


Translation to other populations and pathogens with confirmation  
in similar trial design



Safeguarding all requirements in daily practice for execution of  
TDM (pre-analytical, analytical, post-analytical aspects)

# THE PROCESS OF THERAPEUTIC DRUG MONITORING



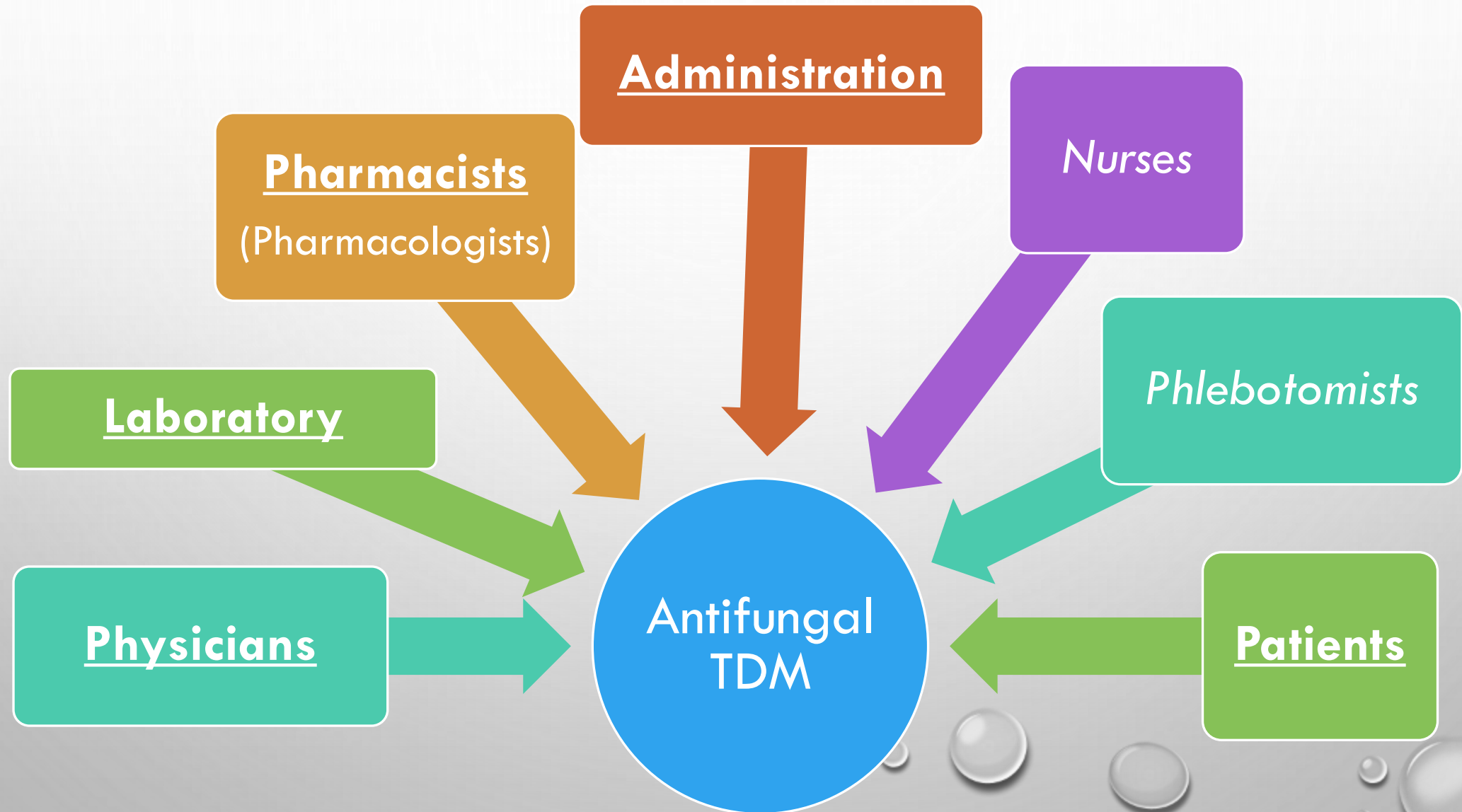
Why is this important?

TDM is a **MULTIDISCIPLINARY** process (Identify and engage all stakeholders)

Pre-empt issues arising from each step when designing the workflow



# KEY STAKEHOLDERS IN ANTIFUNGAL TDM



# FIND PHYSICIAN CHAMPIONS

Physicians

- PRESCRIBE THE MOST ANTIFUNGALS
  - **INFECTIOUS DISEASES**
  - **HAEMOTOLOGY, ONCOLOGY**
  - **TRANSPLANT**
  - **RHEUMATOLOGY, IMMUNOLOGY**
- HAVE SUFFICIENT AUTHORITY WITHIN THE INSTITUTION (E.G. HEAD OF DEPARTMENTS)



# ENGAGE LABORATORY

Laboratory

- UNDERSTAND THEIR **CAPACITY, RESOURCES AND WORKFLOWS**
  - COMPETING PRIORITIES
- SELECT **ASSAY** TO USE (HPLC VS LC MS/MS)
  - AVAILABILITY OF TEST KITS LOCALLY
- ADDITIONAL **PERSONNEL** REQUIRED TO RUN TESTS (HPLC VS LC MS/MS)
- **SUSTAINABILITY AND CONTINGENCY PLANNING**
  - FREQUENCY OF ASSAYS
  - MACHINE BREAKDOWN, STAFF ON URGENT LEAVE
  - DISCREPANT RESULTS
- **DON'T FORGET MICROBIOLOGY LAB**

# IDENTIFY PHARMACY ADVOCATES

**Pharmacists**  
(Pharmacologists)

- MOST WELL VERSED IN ANTIFUNGALS
  - **INFECTIOUS DISEASE / ANTIMICROBIAL STEWARDSHIP**
  - HAEMATOLOGY/ONCOLOGY
  - TRANSPLANT
  - CRITICAL CARE
  - RHEUMATOLOGY/IMMUNOLOGY
- ROLE OF PHARMACISTS IN ANTIFUNGAL TDM TO BE DISCUSSED IN ANOTHER PRESENTATION

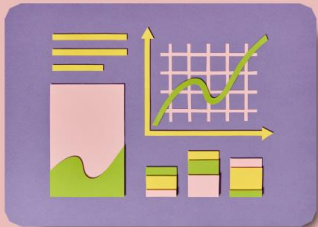
# ADMINISTRATION APPROVAL AND SUPPORT

Administration

- WORKPLAN PROPOSAL
  - FUNDING
  - EQUIPMENT, TEST KITS
  - MANPOWER, ADDITIONAL TRAINING
- BILLING AND SUBSIDIES
  - PROJECT DEMAND, OPERATION COSTS
  - ESTIMATE COST TO PATIENTS
- GOVERNMENT SUPPORT IF APPLICABLE

# CONVINCING STAKEHOLDERS

- **EVIDENCE ON FEASIBILITY AND UTILITY OF ANTIFUNGAL TDM**
- BE PREPARED TO READ A LOT OF LITERATURE



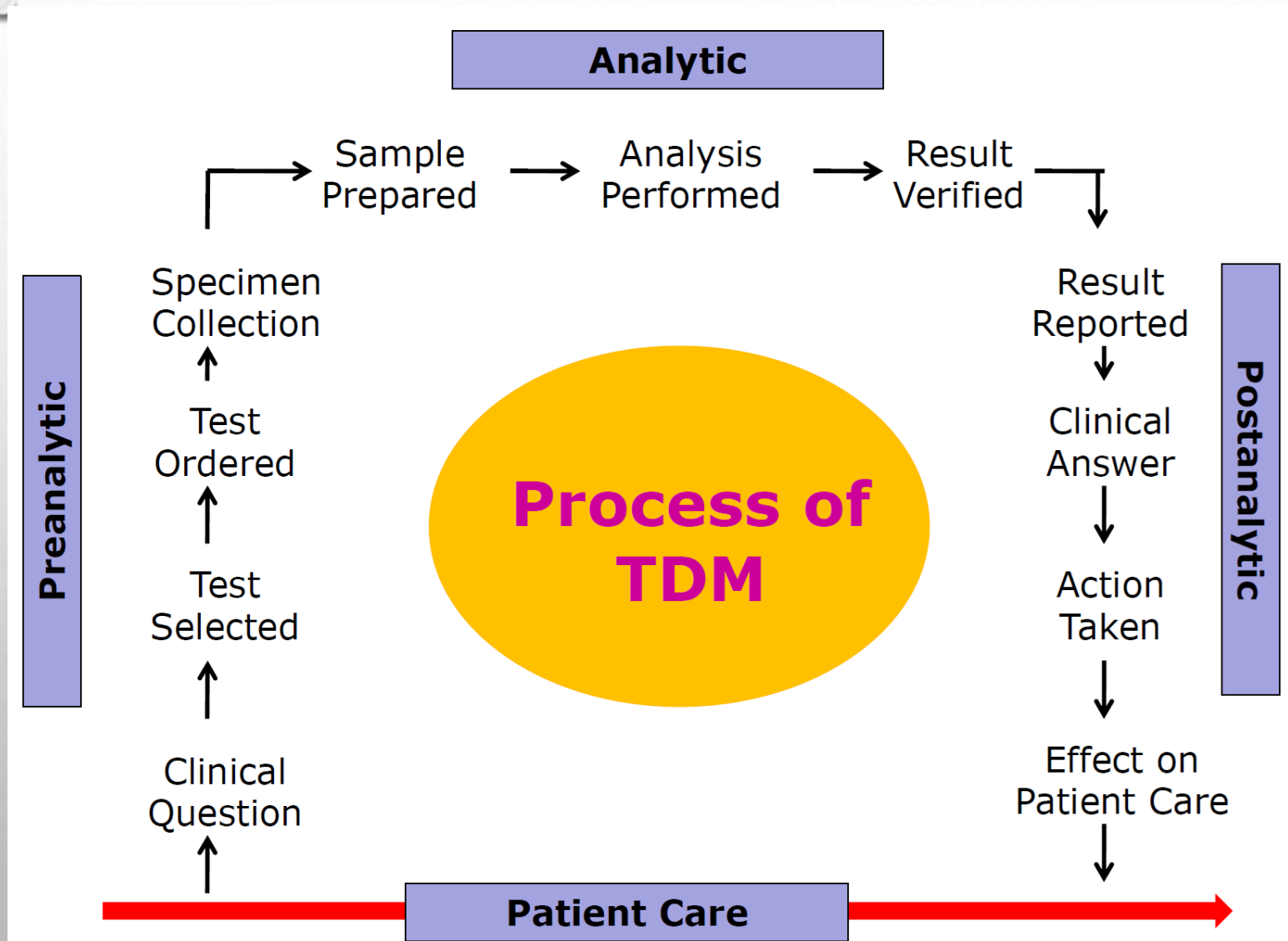


# **FEASIBILITY AND UTILITY OF ANTIFUNGAL TDM**

- PUBLISHED STUDIES FROM OTHER COUNTRIES
- GUIDELINES
- COST-EFFECTIVENESS STUDIES (IF AVAILABLE)
- LOCAL DATA
  - DRUG USE EVALUATION
  - LOCAL SURVEY TO ESTABLISH NEED FOR TDM AND POSSIBLE BARRIERS
  - PILOT STUDY: HAEMATOLOGY, TRANSPLANT OR ICU



# DESIGNING ANTIFUNGAL TDM PROTOCOL





# DESIGNING ANTIFUNGAL TDM PROTOCOL

## PRE-ANALYTIC PHASE

- **CLINICAL QUESTION: WHY IS TDM REQUESTED?**

Pre analytical  
phase

Clinical question

Test selected

Test ordered

Specimen collected

# THE CLINICAL QUESTION: JUSTIFICATION FOR ANTIFUNGAL TDM

**Table 3.** Clinical circumstances that may favour the use of TDM

Context	Example	Comment
Pharmacokinetic variability	children, neonates, elderly, obese, organ dysfunction, critical illness haemodialysis, haemofiltration, extracorporeal membrane oxygenation, cardiopulmonary bypass	pharmacokinetics of many antifungal agents very poorly defined in special populations
Changing pharmacokinetics	physiological instability, critical illness, diarrhoea, iv-to-oral switch	
Interacting drugs	antacids, histamine antagonists, proton pump inhibitors and itraconazole capsules; agents known to decrease concentrations of triazoles	drug–drug interactions well defined and documented for many antifungal compounds
Compliance		compliance may be a significant issue for longer-term consolidation therapy or secondary prophylaxis
Poor prognosis disease	extensive or bulky infection, lesions contiguous with critical structures (mediastinum), CNS disease; multifocal or disseminated infection	
Persistent and/or significant underlying immunological defects	prophylaxis versus established disease	

# DESIGNING ANTIFUNGAL TDM PROTOCOL

## PRE-ANALYTIC PHASE

- CLINICAL QUESTION: WHY IS TDM REQUESTED?
- PEAK VS TROUGH VS RANDOM
- PRE-STEADY STATE VS STEADY-STATE
- NUMBER OF SAMPLES
- BLOOD VS TISSUES/FLUIDS
- ACCURATE SAMPLE COLLECTION
  - CHALLENGES WITH INPATIENT VS OUTPATIENT SETTING
  - DOCUMENTED ADMINISTRATION AND SAMPLING TIME

Pre analytical  
phase

Clinical question

Test selected

Test ordered

Specimen collected

# DESIGNING ANTIFUNGAL TDM PROTOCOL

## ANALYTIC PHASE

- **WHAT ASSAY TO USE?**

- ACCURACY, PRECISION, RELIABILITY, SENSITIVITY
- VALIDATED METHOD/ACCREDITED FACILITY
- TURN AROUND TIME
- ASSAY INTERFERENCE
- AVAILABLE EXPERTISE

Analytical  
phase

Sample prepared

Analysis performed

Results verified

# WHAT ASSAY TO USE

**Table 4.** Advantages, disadvantages and examples of methods for determining drug levels in serum

Method	Advantages	Disadvantages
Bioassay	cheap; simple to perform	subject to interference from other drugs, including other antifungals; may measure combined activity of parent and metabolites (e.g. itraconazole)
HPLC with ultraviolet fluorescence detection	technology widely available; commercially available assays; can quantify multiple drugs in single sample	subject to interference from miscellaneous substances; run times maybe slow
Liquid chromatography – mass spectrometry	very sensitive and specific; can quantify multiple drugs in single sample	expensive; not widely available



# DESIGNING ANTIFUNGAL TDM PROTOCOL

## ANALYTIC PHASE

- WHAT ASSAY TO USE?
  - ACCURACY, PRECISION, RELIABILITY, SENSITIVITY
  - VALIDATED METHOD/ACCREDITED FACILITY
  - TURN AROUND TIME
  - ASSAY INTERFERENCE
  - AVAILABLE EXPERTISE
- TOTAL VS FREE DRUG CONCENTRATION
- INTERNAL CHECKS BEFORE RELEASE OF RESULTS
- FREQUENCY OF ASSAY (DAILY, TWICE WEEKLY ETC)
- BATCH PROCESSING: PROPER STORAGE OF SAMPLES

Analytical  
phase

Sample prepared

Analysis performed

Results verified



# DESIGNING ANTIFUNGAL TDM PROTOCOL

## POST-ANALYTIC PHASE (PART 1)

- WHO REPORTS THE RESULTS?
- WHO INTERPRETS THE RESULTS?
- HOW TO REPORT RESULTS?
  - REFERENCE RANGE → IMPLICATIONS
  - CLEAR REMARKS
  - CITATION OF LITERATURE?
- USE MODEL-INFORMED PRECISION DOSING?
  - SUITABILITY OF MODEL - VALIDATED TO LOCAL POPULATION?  
(HAEM VS ICU, ASIAN VS NON-ASIAN)
  - USER-INTERFACE
  - COMPATIBILITY WITH HOSPITAL SYSTEM
  - COST

Post analytical  
phase

Results reported

Clinical answer

Action taken

Effect on patient  
care

# DESIGNING ANTIFUNGAL TDM PROTOCOL

## POST-ANALYTIC PHASE (PART 2)

- DOCUMENTATION OF RECOMMENDATIONS
- FOLLOW UP MONITORING
- IF WITHIN THERAPEUTIC RANGE, SHOULD TDM BE REPEATED?
- HOW OFTEN TO MONITOR?
- WHEN TO REPEAT LEVELS?
- WHEN TO STOP MONITORING?
- WHEN TO RESUME MONITORING?
- TRACKING OUTCOMES AND KEY PERFORMANCE INDEX?

Post analytical  
phase

Results reported

Clinical answer

Action taken

Effect on patient  
care

# PROTOCOLS, GUIDELINES, TRAINING AND EDUCATION

- SET UP PROTOCOLS/GUIDELINES AND DISSEMINATE TO ALL STAKEHOLDERS FOR APPROVAL
  - EMPIRIC DOSING RECOMMENDATIONS
  - INTERPRETATION OF RESULTS
  - DOSE ADJUSTMENT RECOMMENDATIONS
- TRAIN ALL PERSONNELS INVOLVED
- ENSURE ADHERENCE TO GUIDELINES
- EVALUATE THE SERVICE PERIODICALLY



# **THE GOAL OF TDM IS TO MINIMISE NEED FOR FURTHER TDM (IDEAL GOAL)**

- DON'T PERFORM TDM FOR THE SAKE OF DOING TDM
- USE EXISTING TDM DATA TO DESIGN LOCAL EMPIRIC DOSING REGIMENS FOR VARIOUS SUBPOPULATIONS
  - PHARMACOKINETIC MODELLING
  - BAYESIAN FEEDBACK FORECASTING
- TDM IS THEN USED TO CONFIRM THE EMPIRIC DOSING IS RIGHT (VS USING TDM AS TOOL TO ADJUST DOSING REGIMEN)
- GET THE DOSE RIGHT FROM THE START TO AVOID DELAYED EFFICACY <sup>24</sup>

# TRACKING OUTCOMES OF ANTIFUNGAL TDM SERVICE

- **PROCESS INDICATORS:**

- NUMBER OF PATIENTS OR NUMBER OF SAMPLES PROCESSED
- TIME SPENT PER TDM CASE
- NUMBER OF TDM-DRIVEN DOSE ADJUSTMENTS OR INTERVENTIONS (ACCEPTANCE RATE FOR INTERVENTIONS)

- **OUTCOME INDICATORS:**

- HOW MANY PATIENTS REACH TDM TARGET
- HOW MANY TDM PER PATIENT TO REACH TARGET/ TIME TAKEN TO REACH TARGET
- HOW MANY ACHIEVED THERAPEUTIC RANGE WITHIN 1<sup>ST</sup> TDM, 2<sup>ND</sup> TDM
- ?POTENTIAL COST-SAVINGS

- **EFFICACY OUTCOMES:**

- CLINICAL RESPONSE, COMPLETION OF THERAPY VS
- TREATMENT FAILURE/ RELAPSE/ RECURRENCE

- **SAFETY OUTCOMES:**

- SIDE EFFECTS DUE TO SUPRATHERAPEUTIC LEVELS



# The Singapore General Hospital Experience in Azole TDM



Singapore  
General Hospital  
SingHealth



Singapore  
General Hospital



Changi  
General Hospital



Sengkang  
General Hospital



KK Women's and  
Children's Hospital



National Cancer  
Centre Singapore



National Dental  
Centre Singapore



National Heart  
Centre Singapore



National  
Neuroscience Institute



Singapore National  
Eye Centre



SingHealth  
Community Hospitals



Polyclinics  
SingHealth



# HOW AZOLE TDM BEGAN IN SGH

- ORIGINALLY, AZOLE TDM WAS PERFORMED OVERSEAS
  - TURN AROUND TIME: SEVERAL WEEKS
  - LOGISTICS OF SENDING SAMPLES OVERSEAS
  - COSTS

**RECOGNISED THE CLINICAL NEED AND DEMAND FOR AZOLE TDM**



# HOW AZOLE TDM BEGAN IN SGH

- **STARTED AS A RESEARCH STUDY BY INFECTIOUS DISEASE PHARMACISTS**
  - SCREENED AND RECRUITED PATIENTS
  - INTERPRETED AND REPORTED RESULTS (WITH DOSE ADJUSTMENT RECOMMENDATIONS)
- **CHAMPIONED BY INFECTIOUS DISEASE AND HAEMATOLOGY PHYSICIANS**
  - PATIENTS RECRUITED FROM HAEMATOLOGY WARDS
  - HAEMATOLOGY PHARMACISTS WERE ALSO COLLABORATORS
- **HPLC ASSAY DEVELOPED AND VALIDATED BY PHARMACY RESEARCH LABORATORY** (ITRACONAZOLE, VORICONAZOLE, POSACONAZOLE)
- **BUILDING CAPACITY + ECONOMIES OF SCALE:** ALSO ACCEPTED REQUESTS FROM OTHER HOSPITALS IN SINGAPORE (AND OVERSEAS)

# Azole TDM: From Benchtop to Bedside

> J Glob Antimicrob Resist. 2020 Jun;21:427-433. doi: 10.1016/j.jgar.2019.12.004. Epub 2019 Dec 14.

## The utility of voriconazole therapeutic drug monitoring in a multi-racial cohort in Southeast Asia

Peijun Yvonne Zhou<sup>1</sup>, Tze Peng Lim<sup>1</sup>, Si Lin Sarah Tang<sup>1</sup>, Yixin Liew<sup>1</sup>, Sy Grace Nathalie Chua<sup>1</sup>,  
Li Ling Cheryl Lim<sup>1</sup>, Hui Ling Winnie Lee<sup>1</sup>, Si Xuan Tan<sup>1</sup>, Oi Fah Lai<sup>2</sup>, Thuan Tong Tan<sup>3</sup>,  
Gee Chuan Wong<sup>4</sup>, Lay Hoon Andrea Kwa<sup>5</sup>

# Azole TDM: From Benchtop to Bedside

➤ *J Infect.* 2021 Jun;82(6):e18-e21. doi: 10.1016/j.jinf.2021.03.021. Epub 2021 Mar 29.

## Therapeutic drug monitoring is necessary for patients receiving posaconazole tablet

Peijun Yvonne Zhou<sup>1</sup>, Tze Peng Lim<sup>1</sup>, Si Lin Sarah Tang<sup>1</sup>, Jia Le Lim<sup>1</sup>, Yixin Liew<sup>1</sup>,  
Nathalie Grace Chua<sup>1</sup>, Li Ling Cheryl Lim<sup>1</sup>, Hui Ling Winnie Lee<sup>1</sup>, Oi Fah Lai<sup>1</sup>, Thuan Tong Tan<sup>1</sup>,  
Gee Chuan Wong<sup>1</sup>, Lay Hoon Andrea Kwa<sup>2</sup>

Affiliations + expand

PMID: 33794263 DOI: [10.1016/j.jinf.2021.03.021](https://doi.org/10.1016/j.jinf.2021.03.021)

# HANDING OVER TO BIOCHEMISTRY LABORATORY

Lab Section Category	Clinical Biochemistry <a href="#">View write-up</a>
Specimen Required	3 mL plain blood in red top tube (no gel) Blood sample should be taken just before the next dose for assessment of trough level.
Method	High Performance Liquid Chromatography
Reference Interval / Value	Therapeutic Range:  1.0 - 5.0 mg/L Trough levels of >1.0 mg/L are associated with treatment success. (Antimicrob Chemother 2014; 69(5): 1162 - 1176)
Turnaround Time	Mean = 3 days, Range: 2 - 5 days

<https://www.sgh.com.sg/patient-care/specialties-services/voriconazole-serum>

# HANDING OVER TO BIOCHEMISTRY LABORATORY

Day(s) Test Set up	Tuesday and Friday
Remarks	<p>Patient Preparation: Patient should abstain from the following at least 3 days prior to and during blood sample collection:</p> <ul style="list-style-type: none"><li>- where medically possible, drugs such as Levofloxacin, Valsartan, Clindamycin, Fosamprenavir, Pyrimethamine, Piperacillin, Sulfamethoxazole, Tazobactam, Trimethoprim and Flecainide</li></ul> <p>The list of drugs have been selected on the basis of potential significance to test measurement and are not necessarily all-inclusive.</p> <p>Please contact the Clinical Biochemistry Laboratory for assistance if necessary.</p>



# Azole TDM: Disseminating Information

- **ROADSHOWS TO**
  - ID PHYSICIANS
  - HAEMATOLOGY DEPARTMENT
  - PHARMACISTS
- **EDUCATION ON HOW TO INTERPRET LEVELS AND TITRATE**
  - ID PHYSICIANS AND PHARMACISTS –  
MAIN CONTACT FOR DOSE  
TITRATION



# Azole TDM: Disseminating Information

 Learning Corner



## Voriconazole TDM

Wondering how to conduct voriconazole TDM?

Click on the PDF below for some educational materials and guidance!

Alternatively, approach any of the ASU pharmacists for advice.

# CURRENT STATE OF AZOLE TDM IN SINGAPORE

- SINGAPORE GENERAL HOSPITAL REMAINS THE **ONLY CENTRE** TO PERFORM AZOLE TDM IN SINGAPORE (ITRACONAZOLE, VORICONAZOLE, POSACONAZOLE)
- ISAVUCONAZOLE TDM – ONLY PERFORMED BY PHARMACY RESEARCH LABORATORY IN SINGAPORE GENERAL HOSPITAL

# Azole TDM: From Benchtop to Bedside

Comment > [Int J Antimicrob Agents. 2023 May;61\(5\):106748.](#)

doi: 10.1016/j.ijantimicag.2023.106748. Epub 2023 Feb 8.

## Isavuconazole dosing in Asian patients with invasive mould infections: is there a role for therapeutic drug monitoring?

Yvonne Fu Zi Chan <sup>1</sup>, Yvonne Peijun Zhou <sup>2</sup>, Ban Hock Tan <sup>3</sup>, Candice Yuen Yue Chan <sup>3</sup>, Benjamin Pei Zhi Cherng <sup>3</sup>, Yii Ean Teh <sup>3</sup>, Gee Chuan Wong <sup>4</sup>, Andrea Lay Hoon Kwa <sup>2</sup>, Tze Peng Lim <sup>2</sup>, Kelvin Kau Kiat Goh <sup>2</sup>, Farah Iffah Binte Zulkifli <sup>2</sup>, Jasmine Shimin Chung <sup>3</sup>

# OTHER TIPS

- IT'S A TEAM EFFORT! (IT TAKES A VILLAGE TO GROW A TDM SERVICE!)
- TAKE CHANCES
- PREPARE TO GET REJECTED AND TRY AGAIN
  - SOMETIMES IT'S ABOUT TIMING
- PRE-EMPT ALL POSSIBLE QUESTIONS AND COUNTER-ARGUMENTS (KNOW YOUR STAKEHOLDERS WELL)
- FIND THE PATH OF LEAST RESISTANCE
- EXPLORE WIN-WIN SOLUTIONS FOR ALL STAKEHOLDERS
- THINK OUTSIDE THE BOX
- PREPARE FOR HICCUPS DURING IMPLEMENTATION



# THANK YOU!

**FOR QUESTIONS:**

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