# STUDY PROTOCOL

## PROTOCOL TITLE:
Beta-Lactam Therapeutic Drug Monitoring in Singapore

## PROTOCOL NUMBER:
BLAST-2

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# PROTOCOL SIGNATURE PAGE

Protocol Title: Beta-Lactam Therapeutic Drug Monitoring in Singapore

Protocol Number: BLAST-2

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Sponsor Name: Singapore General Hospital Research Grant

Declaration of Investigator

I confirm that I have read the above-mentioned protocol and its attachments. I agree to conduct the described study in compliance with all stipulations of the protocol, regulations and ICH E6 Guideline for Good Clinical Practice (GCP).

Principal Investigator Name: Nathalie Grace Sy Chua

Principal Investigator Signature: _____

Date: 11 November 2020

## 1. BACKGROUND AND RATIONALE

Beta-lactams (penicillins, cephalosporins, carbapenems and aztreonam) are the most commonly prescribed antibiotics [1] as these agents have large therapeutic window, avoiding the need for therapeutic drug monitoring, and are associated with lower adverse effects compared to other antimicrobials. Despite their widespread usage, there are emerging evidence that suggest current licensed beta-lactam doses may be suboptimal and irrelevant to clinical practice, especially in the setting of rising antimicrobial resistance and variable/unpredictable pharmacokinetic changes in specific patient groups [2-8]. Thus, therapeutic drug monitoring (TDM) to optimise and individualise beta-lactam dosing regimens has been suggested [2-6].

Beta-lactam TDM will be increasingly important in the following areas:

1. Use of high dose beta-lactam therapy to treat resistant infections

Antimicrobial resistance is a known public health threat. A national surveillance study in Singapore from 2006-2007 found increased incidence of multi-drug resistant bacteria, including resistance to one of the broadest spectrum antibiotic class, carbapenems [9-11]. Since then, antimicrobial resistance has been noted to be increasing exponentially [12-16]. In fact, carbapenem resistance rates among common Gram-negative bacteria, are reported to be around 10 to 50% locally [13]. Such resistant infections place a significant burden on healthcare, as they increase morbidity, mortality, resource utilisation and costs [17,18]. Globally, it is predicted to cause 300 million premature deaths and cost SGD 150 trillion by 2050 [18].

Optimal treatment for resistant bacterial infections is limited. Currently available alternative antibiotics, such as tigecycline, polymyxin B and aminoglycosides, are often associated with adverse effects such as hepatotoxicity and nephrotoxicity. In addition, pathogens with multi-drug resistance could already be resistant to these agents [19]. Unfortunately, very few novel antibiotics are available in the pipeline and for the newly approved agents (e.g. ceftolazone/tazobactam), resistance is already being reported [20]. These novel agents are also significantly costlier than currently available antibiotics. In such desperate situations, prescribers may need to resort to high dose beta-lactam therapy, often exceeding current licensed recommendations, to achieve beta-lactam levels beyond the elevated minimum inhibitory concentrations (MIC) of the resistant pathogens to ensure maximum bacterial kill and efficacy [3,21]. This implies that doses of beta-lactams used would be at or near the threshold for adverse effects or toxicity and the concept of wide therapeutic window for beta-lactams no longer applies. In order to balance between efficacy and toxicity in such setting, beta-lactam TDM with subsequent dose adjustment would be required to ensure optimal therapy. This will also give prescribers confidence to use such high dose beta-lactam regimens.

2. Use of high dose beta-lactam therapy to treat pathogens with "intermediate" susceptibility

The Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are shifting towards reclassifying pathogens with intermediate beta-lactam susceptibility to susceptible-dose-dependent (SDD) or susceptible, increased exposure, respectively [22,23]. This implies that high dose beta-lactam therapy can still be used to treat pathogens with "intermediate" beta-lactam susceptiblity. Only beta-lactam TDM will enable us to ensure that the high dose beta-lactams dosage regimens are sufficient for such infections while avoiding risks for toxicity. If high dose beta-lactam therapy

could be used with confidence in these situations, we can avoid unnecessary switch to other agents, which may be more broad-spectrum, toxic or expensive. This will allow us to reserve the use of these antibiotics for highly resistant pathogens.

3. Use of pharmacokinetic/pharmacodynamics-guided approach to individualise and optimise beta-lactam therapy

Current "one-size-fits-all" beta-lactam dosing regimens are largely derived from Phase I clinical studies on healthy volunteers. They may be sub-optimal in clinical practice as patients may display variable and unpredictable pharmacokinetics, for example, those who are critically ill [4,5], febrile neutropaenia [8], burns [28], with renal/liver impairment [29], or require dialysis and other extracorporeal therapies [30]. In fact, studies have shown that conventional beta-lactam dosing recommendations were unable to achieve therapeutic targets in at least 35-50% in these patients [4,5,8,30], requiring further dose adjustments guided by beta-lactam TDM [5,28]. Hence, dose individualisation using TDM is increasingly being advocated.

In addition, technology in dialysis is rapidly evolving with new generation filters, dialysis techniques/modes being developed and placed in clinical practice [31]. However, their effects on beta-lactam disposition and clearance are limited (e.g. limited publication available for plasmapheresis, molecular adsorbent recirculating system therapy). More importantly, in Singapore General Hospital, dialysis filters have now switched from low flux to high flux membranes as the default for most patients. Some studies have reported increased clearance with high flux dialysis for small drug molecules, such as beta-lactams, resulting in reduced antimicrobial exposure with conventional renally-adjusted dosing regimens [32] and potentially affect clinical outcomes. Hence, beta-lactam TDM will be increasingly important in these patients. We would also like to elucidate from this study how these changes in dialysis technology would influence our beta-lactam dosing regimens.

Evidence Gap with Beta-lactam TDM:
Beta-lactam TDM is only performed in a few centres worldwide. Outside Japan, no other Asian countries are reported to perform beta-lactam TDM routinely. As there could be pharmacokinetic/pharmacodynamic differences between Asian and Caucasian populations due to differences in ethnicity, clinical practice (e.g. types and settings of dialyser machines/membranes) and resistance patterns of pathogens, we hope this study could provide early insights to generate recommendations most suitable for our local/Asian population and setting.

In addition, therapeutic targets for beta-lactam TDM are not well established, with varying practices world-wide [33]. None the beta-lactam targets have been extensively clinically validated. Beta-lactams exhibit time-dependent bactericidal activity and their pharmacokinetic/pharmacodynamics therapeutic target is characterised by the percentage of the dosing interval for which the unbound beta-lactam concentration is maintained above the MIC (fT>MIC). Based on in vitro and in vivo studies, the targets are 40% of the dosing interval (40% fT>MIC) for carbapenems, 50% (50% fT>MIC) for penicillins and 60-70% (60-70% fT>MIC) for cephalosporins [34-36]. However, clinical observational studies suggest a longer fT>MIC for optimal clinical outcomes (mortality, clinical response, duration of hospital stay) [4,37-39]. In addition, some studies have shown that higher plasma concentrations (fT>4-5×MIC) may be required for maximal bactericidal activity [40-41], optimal tissue penetration [42-44], optimal clinical response and microbial eradication in patients with pneumonia [45] and

prevention of resistance [6,46]. Centres, that perform beta-lactam TDM, have used the targets 100%fT>MIC, 40-70%fT>4-5xMIC (depending on type of beta-lactam) or 100%fT>4-5xMIC [33] but no studies have compared these targets in terms of clinical outcomes achieved. In this study, we plan to evaluate the correlation between beta-lactam target and clinical outcomes and to determine which beta-lactam target is optimal for clinical practice.

To address the gaps in evidence above, we propose a prospective observational study to evaluate the feasibility of beta-lactam TDM in the local setting. Our target population will be adult patients (21 years old and above), admitted to Singapore General Hospital, are receiving beta-lactams for documented or suspected infection and belong to the following group of patients who will most benefit from beta-lactam TDM: i.e. critically ill patients (admitted to intensive care units, intensive care areas, high dependency wards), haematology/oncology patients, burns patients, patients with extracorporeal therapies which will alter beta-lactam pharmacokinetics (e.g. extracorporeal membrane oxygenation, dialysis), patients with resistant infections or deep-seated infections requiring high dose beta-lactam therapy and patients, who are suspected or at risk of developing beta-lactam adverse effects. We will prospectively collect four blood samples over a dosing interval from each patient. The beta-lactam levels will be assayed using liquid chromatography with tandem mass spectrometry. Attending physicians will have the option of knowing the results and whether to accept dose adjustments recommendations by trained infectious disease pharmacist. Proportion of patients attaining therapeutic targets during the first and subsequent TDM will be evaluated. Patients will also be followed up for clinical outcomes such as mortality and clinical response.

## 2. HYPOTHESIS AND OBJECTIVES

We hypothesise that current licensed beta-lactam dosing regimens are suboptimal in at least half our patients: patients with severe sepsis in intensive care units/high dependency wards, burns patients, patients requiring dialysis and other forms of extracorporeal therapy, haematology/oncology patients, and patients with resistant pathogens or deep-seated infections requiring high dose beta-lactam therapy. Hence, beta-lactam TDM would be necessary for these patients to optimise their dosing regimens and improve their clinical outcomes.

Our primary objective is to evaluate proportion of sub-optimal beta-lactam levels in correlation to MIC and the need for dose adjustments

Our secondary objectives include:

1. Correlating the achieved pharmacokinetic/pharmacodynamic therapeutic targets (100%T>MIC, 40-70%T>5xMIC, 100%T>5xMIC) with clinical outcomes (mortality, clinical response, microbial eradication) in the different sub-groups mentioned above
2. Characterising beta-lactam pharmacokinetics (as exploratory analysis) for certain patient populations, with limited beta-lactam pharmacokinetics characterised in primary literature (e.g. those requiring extracorporeal therapy, various types of dialysis), to aid design of empiric dosing regimens suitable for local practice.

## 3. EXPECTED RISKS AND BENEFITS

Expected risks:

Anticipated risks of this study are estimated to not more than that in standard clinical care as no interventions are done to the subject's treatment.

There may be minimal risk associated with blood sampling. Blood samples will be taken from established blood vessel access in order to minimise discomfort from the patients. In the event where blood-sampling is done directly from a vein, it is possible that some bruising or bleeding may occur at the site where the blood is drawn. There is also a rare chance that inflammation or infection may occur at the sites of blood withdrawal.

There may be a risk of breach of confidentiality but the risk is low. Only members of the study team will be involved in the extraction of the clinical information and laboratory results. Identifying data, e.g., name and NRIC number will be kept separately from other clinical information in the database. The database will be password-protected and can only be accessed by members of the study team.

Expected Benefits:
Clinical outcomes in this study will be similar to that of standard clinical care as no interventions are done to the subject's treatment. Attending physicians will have the option of knowing the results and decide on their own discretion whether to make any dose adjustments to optimise beta-lactam therapy, based on the suggestion of an infectious disease trained pharmacist.

Data derived can be used to build pharmacokinetic models and derive subsequent individualised optimal dosing regimen to improve clinical outcomes.

## 4. STUDY POPULATION

### 4.1. List the number and nature of subjects to be enrolled.

Patients will be recruited until 320 assays are performed (based on budget of $40,000, estimated cost of each assay is $125, number of assays = 40,000/125 = 320 assays). This will be roughly equivalent to 80 patients, assuming patients will have 4 assays each. There will be no restriction on race or gender.

### 4.2. Criteria for Recruitment and Recruitment Process

Patients, admitted to intensive care units/intensive care areas/high dependency wards/burs department/haematology department/oncology department/renal department/infectious disease department, and are initiated on beta-lactam therapy will be identified from pharmacy dispensing records and screened for eligibility. Physicians may also refer patients to the study team.

### 4.3. Inclusion Criteria

a) Age ≥21 years old
b) Admitted to Singapore General Hospital
c) Receiving beta-lactams for documented or suspected infection
d) With indication for beta-lactam TDM: critically ill, altered pharmacokinetics (burns, obese, on extracorporeal therapy e.g. dialysis), immunocompromised (haematology/oncology patients), resistant pathogens, deep-seated infections, suspected

or at risk for adverse effects

### 4.4. Exclusion Criteria

a) Pregnancy
b) Expected mortality within 24 hours

## 5. STUDY DESIGN AND PROCEDURES/METHODOLOGY

This is a prospective observational study conducted in Singapore General Hospital from October 2019 to September 2020. Patients will be screened for eligibility using criteria 4.3 and 4.4. If women of childbearing age are eligible, the beta HCG result taken during the potential subject's course of hospitalisation will be used to exclude pregnant women. If no beta HCG result is available, clinical case notes will be referred to confirm non-pregnancy status.

Eligible patients will be approached by their treating physicians to seek their consent to be referred to the study team. Informed consent will be taken directly from the patient by the study team once patient is agreeable to be referred to the study team. For subjects who do not have the mental capacity to exercise rational judgement, primary physician will assess and document their mental capacity using the Documentation of Capacity form and substituted consent will be obtained by the study team from the spouse, parent, guardian, or legally acceptable representative of the subject. Consent for continued participation will be obtained from patient directly when he regains mental capacity to give informed consent.

Blood sampling and data collection will only commence once informed consent has been taken. Subjects may withdraw voluntarily from participation in the study at any time. Once they have withdrawn from the study, all subsequent blood sampling and data collection will be discontinued.

All patients will be followed up until end of beta-lactam therapy, 30 days from commencement of beta-lactam therapy, hospital discharge or mortality, whichever occurs later.

Blood sampling:
For all patients, 4 sets of blood samples (5 mL each) will be obtained via venipuncture or existing cannula access within a dosing interval. We propose to obtain 4 samples for each TDM in this study to generate more robust and accurate drug concentration-time curves for calculation of target attainment and to better characterise patients' pharmacokinetic profiles. For most patients (except those on intermittent extracorporeal therapies), blood samples will be obtained during end of infusion, 1 hour after infusion, 2 hours after infusion and within 30 minutes of the next scheduled dose (i.e. trough level) if beta-lactam is given as short infusion over ≤30 minutes. If beta-lactam is given as extended infusion (e.g. 3-4 hours), blood samples will be obtained at mid-infusion, end of infusion, 1 hour after infusion and within 30 minutes of the next scheduled dose (i.e. trough level). For patients on intermittent extracorporeal therapies (e.g. intermittent dialysis), blood samples will be obtained at end of beta-lactam infusion, at the beginning of dialysis, end of dialysis and within 30 minutes of the next scheduled dose (i.e. trough level).

To ensure therapeutic targets are reached, further blood sampling, according to the schedule above, may be performed after dose adjustments or when there is a change in patient's clinical

status (e.g. change in dialysis settings, change in renal function), which may warrant change in beta-lactam dosing regimen. Blood sampling for TDM will be stopped when beta-lactam has been discontinued, when therapeutic targets are achieved or when patient has been discharged from the hospital.

Assay of beta-lactam levels

All blood samples will be sent to our research laboratory for assay via liquid chromatography-tandem mass spectrometry. All blood samples will be labelled by our study team using subject codes (no patient identifiers will be used).

Beta-lactam TDM and Dose Individualisation

The treating physicians will have the option to know the results of the TDM, once available. An infectious disease-trained pharmacist may make recommendations on dose adjustments based on the TDM results. However, accepting these recommendations will be at the discretion of the treating physicians.

The infectious disease trained pharmacist may use pharmacokinetic software to analyse drug concentration-time profile to guide dose adjustments. If available, dose recommendations will be based on the MIC of the known pathogen, which will be provided by the local microbiology laboratory. Where no pathogen was formally identified, MICs are not available or cultures are pending, the highest MIC (according to the Clinical and Laboratory Standards Institute (CLSI criteria) for susceptible bacteria to the antibiotic will be assumed.

Data Collection

All patients will be followed up from study entry to 30 days from study entry, hospital discharge or mortality, whichever occurs earlier.

Data will be collected from electronic medical records, using a standardised data collection form. These will include:

•patient demographics (unique identifier, age, gender, race, body weight, height, comorbidities including Charlson Comorbidity Index)

•pharmacokinetic-specific data (use of extracorporeal therapy/dialysis and settings, urine output, serum creatinine, albumin)

•clinical data (temperature, blood pressure, heart rate, respiratory rate, mortality, cause of mortality, severity of illness indicators such as APACHE II score and SOFA score, incidence of beta-lactam-related adverse events/side effects as reported by primary physicians, admission and discharge date from hospital and from intensive care unit if applicable)

•laboratory data (albumin, serum creatinine, procalcitonin, CRP, total white count)

•infection-related data (site and type of infection, pathogens isolated and their susceptibility results and reported minimum inhibitory concentrations)

•drug-related data (beta-lactam dosing regimens including any change to dosing regimens, concurrent antibiotic use history and their dosing regimens, presence of any drug which may interact with beta-lactams or interfere with beta-lactam assay results)

•beta-lactam assays levels, attainment of therapeutic targets and whether dose adjustments were made

Data will be stored in a password-protected database and only study team members will have access to data. Identifiers will be stored separately from collected data. Data collection forms will not contain identifiers (e.g. NRIC, name, date of birth). All hardcopy data collection forms and consent forms will be stored under lock and key in the cupboard at Blk 8 Level 2 of

Pharmacy department in Singapore General Hospital.

Based on SingHealth Cluster Research Data Management Policy – Clinical Trial and Clinical Research, research data will be retained in a secured storage facility (mentioned in section R1(i) for a minimum of 7 years after completion of research study or date of publication of the research using the research data, whichever is later. The data collected will be also stored and used for future research.

## 6. SAFETY MEASUREMENTS

### 6.1. Definitions

Serious adverse event (SAE) in relation to human biomedical research, means any untoward medical occurrence as a result of any human biomedical research which:

- results in or contributes to death
- is life-threatening
- requires in-patient hospitalisation or prolongation of existing hospitalisation
- results in or contributes to persistent or significant disability/incapacity or
- results in or contributes to a congenital anomaly/birth defect
- results in such other events as may be prescribed

Adverse event (AE) in relation to human biomedical research means any untoward medical occurrence as a result of any human biomedical research which is NOT serious. Adverse event can be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease possibly/ probably/ definitely associated with the participant in the human biomedical research.

### 6.2. Collecting, Recording and Reporting of Adverse Events and Serious Adverse Events to CIRB

Reporting of adverse events involves the Principal Investigator submitting to CIRB the SAE Reporting Form to CIRB within the stipulated timeframe. The Principal Investigator is responsible for informing the institution representative, the chairman medical board (when required by the institution for local SAE resulting in death), sponsor or regulatory bodies as required and appropriate.

Reporting timeline to CIRB:

- Local unexpected SAE resulting in death that are related events should be reported immediately - within 24 hours of the Principal Investigator becoming aware of the event.
- Local unexpected, life-threatening SAE that are related events should be reported as soon as possible but no later than 7 calendar days after the Principal Investigator is aware of the event, followed by a full report within 8 additional calendar days.
- Local unexpected, not life-threatening SAE that are related events, should be reported no later than 15 calendar days after the Principal Investigator is aware of the event.
- An increase in the rate of occurrence of Local expected SAE that are related events,

which is judged to be clinically important, should be reported within 15 calendar days after the Principal Investigator is aware of the event.

- Local unexpected AE that are related events should be reported at least annually (together with Study Status Report for annual review).
- Non-local unexpected SAE that are fatal or life threatening and related should be reported not later than 30 calendar days after the Principal Investigator is aware of the event.

### 6.3. Safety Monitoring Plan

This is an observational study; hence no clinical safety monitoring is required.

### 6.4. Complaint Handling

As stated in the informed consent form, patients can complain to the site PI or CIRB. If CIRB receives any complaints, CIRB will inform the site PI.

## 7. DATA ANALYSIS

### 7.1. Data Quality Assurance

The quality and accuracy of the data collected will be reviewed once every 3 months by the investigators.

A standardised data collection form will be used. All investigators need to have a good understanding on how to fill up the form accurately. The transcribing of the information from the data collection form to the electronic database will also be reviewed and checked regularly by the investigators.

### 7.2. Data Entry and Storage

Data will be stored in a password-protected electronic database and only study team members will have access to data. Identifiers will be stored separately from collected data. Data collection forms will not contain identifiers (e.g. NRIC, name, date of birth). All hardcopy data collection forms and consent forms will be stored under lock and key in the cupboard at Blk 8 Level 2 of Pharmacy department in Singapore General Hospital. Only the PI and designated study members have access to the locked cupboard.

Based on SingHealth Cluster Research Data Management Policy – Clinical Trial and Clinical Research, research data will be retained in a secured storage facility (mentioned in section R1(i) for a minimum of 7 years after completion of research study or date of publication of the research using the research data, whichever is later. The data collected will be also stored and used for future research.

## 8. SAMPLE SIZE AND STATISTICAL METHODS

### 8.1. Determination of Sample Size

Patients will be recruited until 320 assays are performed (based on budget of $40,000, estimated cost of each assay is $125, number of assays = 40,000/125 = 320 assays). This will be roughly equivalent to 80 patients, assuming patients will have 4 assays each.

### 8.2. Statistical and Analytical Plans

Our primary outcome will be attainment of beta-lactam therapeutic targets: 100%fT>MIC, 40-70%fT>5xMIC, 100%fT>5xMIC. Proportion of patients, who achieve beta-lactam therapeutic targets, during the first and subsequent TDM will be determined. For the group of patients, who require dose adjustments, after the 1st TDM and need further TDM, the proportion of patients who require dose increment and dose reduction, the number of TDM performed to achieve therapeutic target and the mean/median time required to achieve therapeutic target will also be evaluated.

Correlation of primary outcomes will be made to the following secondary outcomes.

a. Mortality at the end of therapy and within 30-day mortality.
b. Days to defervescence
c. Days to resolution of white blood cell count, pro-calcitonin and C-reactive protein.

Any incidence of adverse effects related to beta-lactam therapy will also be reported and evaluated in correlation to beta-lactam levels.

For univariate analyses with binomial outcomes (e.g. mortality), Chi-square test or Fisher's exact test will be performed where appropriate. For univariate analyses with time-dependent outcomes (e.g. days to defervescence, days to resolution of inflammatory markers), Kaplan-Meier analysis will be performed. For univariate analyses with continuous outcome variables (e.g. APACHE II score, SOFA score), Student's t-test and Mann-Whitney-U test will be performed for parametric and non-parametric data respectively. Multivariate analyses will then be performed to include potential confounders such as APACHE II score, SOFA score, Charlson comorbidity index, use of beta-lactam as culture-directed therapy, presence of multi-drug resistant infection, and presence of concurrent infections requiring additional antibiotics. Logistic regression will be used for binomial outcomes (mortality) while Cox regression will be used for time-dependent outcomes (days to defervescence, days to resolution of inflammatory markers).

To evaluate population pharmacokinetics in various patient groups, a specialised pharmacokinetic software will be used to develop population pharmacokinetic models. Model simulation will then be performed to design empiric dosing recommendations to guide local practice.

## 9. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator(s)/institution(s) will permit study-related monitoring, audits and/or IRB review and regulatory inspection(s), providing direct access to source data/document.

## 10. QUALITY CONTROL AND QUALITY ASSURANCE

Standardised data collection form will be used to ensure accuracy of data collected. The investigators will evaluate data quality every 3 months.

## 11. ETHICAL CONSIDERATIONS

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the Good Clinical Practice and the applicable regulatory requirements.

This final Study Protocol, including the final version of the Participant Information and Consent Form, must be approved in writing by the Centralised Institutional Review Board (CIRB), prior to enrolment of any patient into the study.

The principle investigator is responsible for informing the CIRB of any amendments to the protocol or other study-related documents, as per local requirement.

### 11.1. Informed Consent

Patients eligible for the study will be first approached by their treating physicians for consent to be referred to the study team.

For critically ill patients who are unable to give consent, documentation of mental capacity will be made by primary physician and consent from patients' spouse, parent, guardian or LAR will sought before study team approach them. Informed consent will be obtained from the spouse, parent, guardian or LAR using the substituted consent form. Once patient has regained capacity to give informed consent, their consent for continued participation will be obtained using the continued participation consent form.

Informed consent will then be taken by a designated member of the study team in a quiet area at an appropriate time when the patient or his / her spouse, parent, guardian or LAR will not be interrupted by other healthcare workers, patients or visitors. The objectives, study procedures, risk and benefits will be explained and any questions will be answered.

Informed consent will be obtained from English-speaking patients and/or his/her representatives only.
All informed consents will be held in the presence of a witness. All patients will be given sufficient time to make a decision.

While obtaining and documenting informed consent, the study team members will comply with the SGGCP guidelines and to the ethical principles that have their origin in the Declaration of Helsinki.

### 11.2. Confidentiality of Data and Patient Records

Informed consent process will be done at patient bedside. If more privacy is warranted, consent

will be taken in a single room or treatment/counseling room.

All blood samples will be labelled by a subject code by the study team (i.e. no patient identifier will be used).

Data will be stored in a password-protected electronic database and only study team members will have access to data. Identifiers will be stored separately from collected data. Data collection forms will not contain identifiers (e.g. NRIC, name, date of birth). All hardcopy data collection forms and consent forms will be stored under lock and key in the cupboard at Blk 8 Level 2 of Pharmacy department in Singapore General Hospital. Only the PI and designated study members have access to the locked cupboard.

## 12. RETENTION OF STUDY DOCUMENTS

Based on SingHealth Cluster Research Data Management Policy – Clinical Trial and Clinical Research, research data will be retained in a secured storage facility (mentioned in section R1(i) for a minimum of 7 years after completion of research study or date of publication of the research using the research data, whichever is later.

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