APPENDIX II

ANALYSIS SETS, STATISTICAL METHODS AND DEFINITIONS

Analysis sets
This refers to the sets of cases whose data are to be included in the analysis.

Six analysis sets were defined:

1. Dialysis patients notification between 2011 and 2021
This analysis set consists of patients commencing dialysis between 2011 and 2021. This analysis set was used for the analysis in Chapter 1, 2 and 3.

Since 1993, the MDTR conducted an annual survey on all dialysis patients to collect data on dialysis and drug treatment, clinical and laboratory measurements. All available data were used to describe the trends in these characteristics. For this analysis in relation to these characteristics, only data from 2011 onwards were used. Remaining missing data in this analysis set was imputed using first available observation carried backward or last observation carried forward. This analysis set was used for the analysis in Chapters 4 to 7.

2. New Dialysis Patients
The number of new dialysis patients was based on the first dialysis treatment of the patients. Patients who convert from one dialysis modality to another (from HD to PD or vice versa) are not counted as new patients. If transplant is the 1st modality and patient's kidney transplant failed and he received dialysis, then for RRT count, the patients will be counted twice. However, if the patients receive transplant between the dialysis, then the dialysis after transplant will be counted if the transplant last for more than 90 days while if it is less than or equal to 90 days, then the dialysis after the transplant will not be counted. This analysis set definition was used in chapters 1, 2 and 5.

3. Peritonitis data
Analysis was confined to chronic PD patients who were on peritoneal dialysis from 2011 to 2021. This analysis set was used for the analysis in Section 6.4.

4. Renal transplant data
This analysis set was confined to patients who had undergone renal transplantation from 2011 to 2021. This analysis set was used for the analysis in Chapter 7.

5. Diabetes Mellitus
Patients are considered to have diabetes mellitus (DM) as the cause of ESRD if the primary cause of ESRD is notified as DM; or as unknown but the comorbid is DM. This is applicable to chapter 2, 3 and 7.

Prior to 2017 when data was submitted in paper form, primary and secondary causes of renal disease were allowed. The National Renal Registry (NRR) office adjudicated discrepancies in the data submitted to determine the primary renal disease (PRD). If the PRD was recorded as unknown and patient has diabetes as the secondary cause or diabetes was included as a co-morbidity, the PRD was amended to diabetes. If there was a discrepancy in PRD reported between centres, one as unknown and the other as diabetes, the PRD was amended to diabetes

In 2017 data collection migrated to eNRR, an online electronic form. From 2017 and 1st February 2021, the system allowed more than one PRD. The determination of PRD was based on the following algorithm:

- If both unknown and diabetes were selected as PRD, diabetes was recorded as the PRD
- If the PRD was recorded as unknown and diabetes was included as a co-morbidity, the PRD was amended to diabetes.
- If there was a discrepancy in PRD reported between centres, the PRD at first notification was used
- If multiple PRDs were entered, the order for PRD determination is as follows:
    i. ADPKD
    ii. Hereditary nephritis, specify
    iii. Glomerulonephritis, specify
    iv. Obstructive uropathy, specify
    v. Drugs / toxic nephropathy
    vi. Diabetes Mellitus
    vii. Hypertension
    viii. Others, specify
    ix. Unknown

Examples:

- If 'Unknown' & 'diabetes' were selected as PRD then PRD is diabetes
- If 'diabetes' & 'ADPKD' were selected as PRD then PRD is ADPKD
- If 'Unknown' was selected as PRD and Comorbidities include diabetes then PRD is diabetes
- If 'Unknown' was selected as PRD and Comorbidities include hypertension then PRD is hypertension Change in PRD is permitted with written request and documentation from the source data providers to NRR

From 2nd February 2021 onwards, only a single entry for PRD is permitted

- If there was a discrepancy in PRD reported between centres, the PRD at first notification was used
- If PRD is unknown and diabetes is included in comorbidity at notification, "Unknown" PRD is maintained
- Change in PRD is permitted with written request and documentation from the source data providers to NRR

Statistical methods

1. Population treatment rates (new treatment or prevalence rates)

Treatment rate is calculated by the ratio of the count of number of new patients or prevalent patients in a given year to the mid-year population of Malaysia in that year, and expressed in per million-population. Results on distribution of treatment rates by state are also expressed in per million-population in the state since states obviously vary in their population sizes.

2. Adjusted Mortality of dialysis patients

Cox proportional hazards model was considered for mortality of the patients adjusted with demographic and laboratory variables. This analysis was used in Chapter 3 and 7.

3. Analysis of trend of intermediate results

For summarizing intermediate results like continuous laboratory data, we have calculated summary statistics like mean, standard deviation, median, lower quartile, upper quartile and the cumulative frequency distribution graph is plotted by year. Cumulative distribution plot shows a listing of the sample values of a variable on the X axis and the proportion of the observations less than or greater than each value on the Y axis. An accompanying table gives the Median (50% of values are above or below it), upper quartile (UQ, 25% of values above and 75% below it), lower quartile (LQ, 75% of values above and 25% below it). Other percentiles can be read directly off

the cumulative distribution plot. The table also shows percent of observations above or below a target value, or with an interval of values; the target value or interval obviously vary with the type of laboratory data. The choice of target value is guided by published clinical practice guidelines, or otherwise they represent consensus of the local dialysis community. This analysis was used in Chapter 4, 5, 6.

4. Centre variation

To compare the variation of the intermediate results between centres, graphs describing intermediate results in each centre are presented. The 95% confidence intervals have been calculated using the normal approximation of the Poisson to show the variation of proportion in centres. Lower quartile and upper quartile are instead plotted in comparison of variation in median among centres. An accompanying table gives the summary statistics like minimum, 5th percentile, lower quartile, median, upper quartile, 95th percentile and maximum value among centres over year. Centres with intermediate results for <10 patients were combined into one composite centre. This analytical method was used in Chapter 4, 5, 6.

5. Cause of Death

As each patient can have more than one reason for death, the main cause of death is selected in the following hierarchy:

i. Covid 19 (Covid-19 is tabulated under infection)
ii. Peritonitis from CAPD (if applicable)
iii. Accident
iv. Cancer
v. Withdrawal of RRT
vi. Died suddenly at home
vii. Gastrointestinal hemorrhage
viii. Infection (besides Covid 19)
ix. Liver disease
x. Lung disease
xi. Cardiovascular disease
xii. Other
xiii. Unknown

The analysis method was used in Chapter 3 and 7.

6. Patient Drop Out

As each PD patient can have more than one reason for drop-out, the main reason of patient drop-out is selected based on the following hierarchy: -

i. Death
ii. Transplant
iii. PD Infections
iv. Inadequate Dialysis
v. Catheter related issues
vi. Social reasons
vii. Others
viii. Unknown

The analysis method was used in Chapter 6.

7. Cause of Graft Failure

As each Transplant patient can have more than one reason for graft failure, the main reason for graft failure is selected based on the following hierarchy:

i. Rejection
ii. Calcineurin toxicity
iii. Other drug toxicity
iv. Ureteric obstruction
v. Infection
vi. Vascular causes
vii. Recurrent/ de novo renal disease
viii. Chronic allograft nephropathy / IFTA
ix. Technical problem
x. Others
xi. Unknown

The analysis method was used in Chapter 7.

Death rate calculation
Annual death rates were calculated by dividing the number of deaths in a year by the estimated mid-year patient population.

Incidence rate ratio
The incidence rate is determined by dividing the number of new cases of a disease or condition in a specific population over a given period of time by the total population. Therefore, incidence rate ratio is the comparison of two groups in terms of incidence rate. Poisson regression model was considered to estimate the independent effect of each factor, expressed as incidence rate ratio. An incidence rate ratio of 3 means that group 2 have the rate 3 times higher than group 1 when group 1 is the reference group.

Standardized mortality rate
The cohort considered for this analysis was patients who were on dialysis in 2019 and new patients in 2020 by modality.

SMR is a ratio between the observed number of death with the expected, based on the age group, diabetic, serum album group, diastolic blood pressure group and hemoglobin group rates in a standard population and the age group, diabetic, serum album group, diastolic blood pressure group and hemoglobin group distribution of the study population. If the ratio is observed: expected death is greater the 1.0, we conclude that there is “excess death” in the study population. SMR was generated using the following formula:

SMR = observed death / expected death

Risk adjusted mortality rate (RAMR)
When the mortality rate is risk adjusted, the information becomes more comparable among the hospitals because the data is adjusted to take into account variations in patients’ severity of renal disease and their risk of mortality. RAMR was generated using the following formula:

RAMR = SMR x AvMR, where AvMR is the average of the overall observed mortality rate

Risk ratio
Risk ratio is the relative measure of the difference in risk between the exposed and unexposed populations in a cohort study. The relative risk is defined as the rate of disease among the exposed divided by the rate of the

disease among the unexposed. A relative risk of 2, means that the exposed group has twice the disease risk as the unexposed group.

Survival analysis
The unadjusted survival probabilities were calculated using the Kaplan-Meier method, in which the probability of surviving more than a given time can be estimated for members of a cohort of patients without accounting for the characteristics of the members of that cohort.

In order to estimate the difference in survival of different subgroups of patients within the cohort, a stratified proportional hazards model (Cox) was used where appropriate. The results from Cox model are interpreted using a hazard ratio. Adjusted survival probabilities are adjusted for age, gender, primary diagnosis and time on RRT. For diabetics compared with non-diabetics, for example, the hazard ratio is the ratio of the estimated hazards for diabetics relative to non-diabetics, where the hazard is the risk of dying at time t given that the individual has survived until this time. The underlying assumption of a proportional hazards model is that the ratio remains constant throughout the period under consideration.

Technique failure is defined as occurrence of death or transfer to another modality of dialysis. Similarly, graft failure is defined as occurrence of death or returned to dialysis.

Patient survival was considered in two ways:
Survival censored for change of modality based on first modality. Duration survival for patients will be calculated from the date commencing the first modality till first modality outcome. Hence duration after the change modality or transplant will not be considered. Death occurring during the first modality will be considered in the analysis since patients will be censored for change of modality before death.

Survival not censored for change of modality based on first modality. Duration survival for patients will be calculated from the date commencing the first modality till 31 Dec 2021 for patients who were still on RRT. For patients who died, duration of survival will be calculated from date commencing the first modality till date of final outcome which is death. All death outcomes whether occurring during first modality or after change in modality will be considered for this analysis.

Survival of incident patients by centre
1-year survival
The cohort considered for this analysis was considered from 2011-2020. Many patients commencing dialysis in 2021 would still not have completed one year.

5-year survival
The cohort considered for this analysis was considered from 2012-2016. This is due to those commence from 2017 onwards still not able to have 5 year survivals analysis.

Funnel plot
This analysis was confined to new dialysis patients from year 2011-2021. The figure is included to assess whether survival probability adjusted to age and diabetes of each centre is likely to be different from the national average. This plot was used in Chapter 3.

Peritonitis rate
The occurrence of peritonitis is expressed as number of episode per patient-month of observation; peritonitis rate in short. Relapse peritonitis is defined as peritonitis caused by the same organism occurring within 6 weeks of diagnosis of previous peritonitis.