Boehringer Ingelheim

Protocol for non-interventional studies based on existing data

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Research question and objectives:	Primary objective: to assess the association between the annual rate of eGFR change with CV/renal events and all-cause mortality, adjusting for age, sex, CV medical history and baseline eGFR and/or UACR value. Secondary objective: to assess the association between eGFR and/or UACR change and myocardial infarction (MI), stroke, congestive heart failure (CHF), end-stage renal disease (ESRD) and other renal events over time
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In case of PASS, add: <**Signature of EU-QPPV:>**	Not applicable
Date:	04 May, 2020

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1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

CHF	Congestive Heart Failure
CKD	Chronic Kidney Disease
CV	Cardiovascular
DPC	Diagnosis Procedures Combination
ECI	Elixhauser's Comorbidity Index
eGFR	estimated Glomerular Filtration Rate
EMR	Electronic Medical Record
ESRD	End-Stage Renal Disease
UACR	Urine Albumin to Creatinine Ratio
HCEI	Health, Clinic, and Education Information Evaluation Institute
HR	Hazard Ratio
ICD-10	International Classification of Diseases Tenth Revision
MDV	Medical Data Vision
MI	Myocardial Infarction
RWD	Kyoto Real World Data Company
T2DM	Type 2 Diabetes Mellitus

3. RESPONSIBLE PARTIES

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4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product:			
Name of active ingredient:			
Protocol date: 04 May, 2020	**Study number: 1245.0225**	**Version/Revision:** Version 1.0	**Version/Revision date:** Not Applicable
Title of study:	Association of eGFR slope and cardiovascular/renal events or all-cause deaths in Japanese database		
Rationale and background:	The association between eGFR slope and cardiovascular events have been evaluated in countries outside of Japan, but there has been no study to evaluate the relationship between the slope of eGFR values with CV events and all-cause mortality using Japanese administrative claims or electronic medical record (EMR) data.		
Research question and objectives:	Primary objective: to assess the association between the annual rate of eGFR change with CV/renal events and all-cause mortality, adjusting for age, sex, CV medical history and baseline eGFR and/or UACR value. Secondary objective: to assess the association between eGFR and/or UACR change and myocardial infarction (MI), stroke, congestive heart failure (CHF), end-stage renal disease (ESRD) and other renal events over time		
Study design:	Longitudinal, observational, cohort study using existing database. ~~A schematic drawing of the design is as follows.~~		
Population:	Inclusion criteria: Patients must be of or above age 3 on the index date, and must have continuous enrolment during baseline of 1 year prior to the index eGFR date, and must have at least 3 eGFR values between January 1, 2014 to December 31, 2016. Exclusion criteria: Patients are excluded if dialysis or renal failure codes are present in the eGFR selection period or if diagnosed with cardiovascular or renal outcome events in the baseline period are present.		
Variables:	Primary outcomes include all cause and cardiovascular mortality. Secondary outcomes are cardiovascular outcomes (myocardial infarction, congestive heart failure, stroke) and renal outcomes (end stage renal disease, dialysis procedure or kidney transplant or acute kidney failure.		
Data sources:	Medical Data Vision and Kyoto RWD company database will be used.		
Study size:	This is an exploratory study with no hypothesis testing. In the pre-analysis, there were 36,262 patients in MDV database who had at least four eGFR values in the baseline period (Jan 1, 2013 to Dec 31, 2015) with at least one claim every year. If we require patients to have additional two eGFR in the follow up period (index date = last eGFR value in baseline period), approximately 20% reduction in sample size to 30,434 patients was observed.		

Data analysis:	1. Patients' background: descriptive statistics will be provided on the age, sex, presence of medical history Elixhause comorbidity index score and prescription of CV related medication by class during the baseline period. Sex, medical history, and CV related medication will be described as percentages to all eligible patients. 2. Slope of eGFR: descriptive analysis will be provided on the annual decline of eGFR overall (mean, 95% CI) and stratified by patients experiencing cardiovascular/renal and in-hospital mortality. The least square regression method will be used to calculate the slope and its 80%CI. Based on the slope all patients will be categorized into six groups: ① eGFR slope = -1.00 ~ 1.00 ml/min/1.73m^2/year (reference) ② eGFR slope = < - 5.00 (rapid decliner) ③ eGFR slope = - 3.00 ~ -5.00 ④ eGFR slope = -1.00 ~ -3.00 ⑤ eGFR slope = 1.00 ~ 3.00 ⑥ eGFR slope = >3.00 (rapid improver) Instant health data (IHD) is used to create cohort. R version 3.6.2 and SAS version 9.4 are used for statistical analysis.
Milestones:	Start of Data Analysis: 08~~9~~ May 2020 End of Data Analysis: 01 June 2020 Study Report: 01 July 2020

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
<1>	DD Month YYYY	<Text>	<Text>	<Text>
<2>	DD Month YYYY	<Text>	<Text>	<Text>
<n>	DD Month YYYY	<Text>	<Text>	<Text>

6. MILESTONES

Milestone	**Planned Date**
Start of data analysis	09 May 2020
End of data analysis	01 June 2020
Final report of study results:	01 July 2020

7. RATIONALE AND BACKGROUND

Chronic Kidney Disease (CKD) is associated with progression to renal failure, dialysis, and associated with substantial morbidity, mortality, and economic burden (1). There have been several studies to show that decrease in estimated glomerular filtration rate (eGFR) is an independent risk factor for cardiovascular (CV) and all cause death (2).
Matsushita et al collected eGFR and urine albumin-to-creatinine ratio (UACR) values from 14 studies with 730,577 person-years, and seven studies with eGFR values and urinary dipstick results from 4,732,110 person-years of follow-up (2). Cox proportional hazard models were used to estimate the hazard ratios (HRs) for CV and all-cause mortality associated with eGFR and albumiinuria, adjusting for age, sex, CV disease history, systolic blood pressure, diabetes, total serum cholesterol, and smoking status. Adjusted HRs for all-cause mortality at eGFR 60, 45, and 15 (versus 95) ml/min/1.73 m^2 were 1.18 (95% CI: 1.05-1.32), 1.57 (1.39-1.78), and 3.14 (2.39-4.13), respectively. Adjusted HRs for CV mortality were 1.20 (1.15-1.26), 1.63 (1.50-1.77), and 2.22 (1.97-2.51), thus showing both mortality outcomes were associated with decreased eGFR.
In another study, Pottelbergh et al evaluated the relationship between an eGFR slope over a 5-year period and incident cardiovascular events in the following 5 years. By dividing patients with at least 4 eGFR values in the baseline period into 6 categories based on the steepness and direction of the slope, he calculated the hazard of incident CV outcome occurrence in the follow-up period vs. a control group with slope between -1 to 1 ml/min/year. Negative eGFR slopes of at least 3 mL/min/year was found to have higher risk of CV events (3).
To the best of our knowledge, there has been no study to evaluate the relationship between the slope of eGFR values with CV events and all-cause mortality using Japanese administrative claims or electronic medical record (EMR) data.

8. RESEARCH QUESTION AND OBJECTIVES

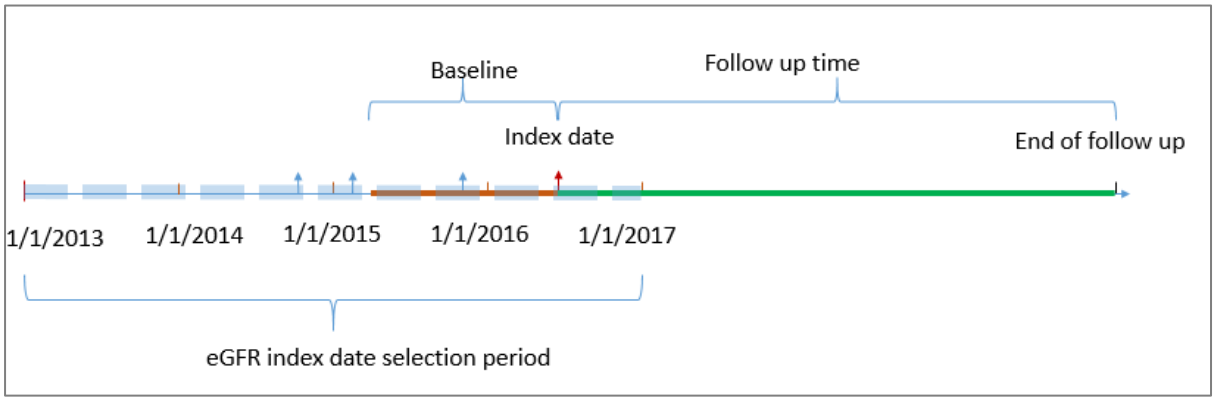
Research question
To examine if CV/ renal events and all-cause death are related to eGFR.

Objectives
Primary objective: to assess the association between the annual rate of eGFR change with CV/renal events and all-cause mortality, adjusting for age, sex, CV medical history and baseline eGFR and/or UACR value.
Secondary objective: to assess the association between eGFR and/or UACR change and myocardial infarction (MI), stroke, congestive heart failure (CHF), end-stage renal disease (ESRD) and other renal events over time.

9. RESEARCH METHODS

9.1 STUDY DESIGN

Study design
Longitudinal, observational, cohort study using existing database. A schematic drawing of the design is as follows.



Definitions:
1. eGFR selection period: January 1, 2013 to December 31, 2016
2. Index date: the date of last eGFR measurement in the eGFR selection period
3. Baseline period: one year period prior to index date.
4. Index eGFR value: the value of eGFR on the index date
5. Follow-up period: from the index date to minimum date between the death date and the end of last claim.

9.2 SETTING

Inclusion criteria:
Patients must be or have:
1. Age ≥ 3 year old on the index date (age 3-15 defined as pediatric population, 16-max defined as adult population)
2. Patient must have continuous enrolment during baseline
3. Continuous enrollment in MDV: having less than 180 days (6months) gap in inpatient or outpatients visits At least 3 eGFR values recorded in the eGFR selection period with at least 1 year apart from the first eGFR value and last index eGFR value.

Exclusion criteria:
1. Patients with procedure codes of dialysis (J038, C102-2, J042, C102, C155, K635-3) or International Classification of Diseases Tenth Revision (ICD-10) code of renal failure (N17.0-17.9, N18.4-18.6) in the eGFR selection period.
2. Patients with diagnosis of cardiovascular and renal outcome events in the baseline period.

Additional cohort for sub-analysis

A) Type 2 Diabetes Mellitus (T2DM) cohort: patients meeting all of above criteria, and having at least one diagnosis code of T2DM coded as E11 (Type 2 diabetes mellitus) or E14 (Unspecified diabetes mellitus) by ICD-10 at least once during the baseline period
B) Patients meeting all inclusion/exclusion criteria, but not meeting the sub-analysis cohort definition above.
C) Pediatric patient (age 3 to 15 on the index date) sub-analysis

9.3 VARIABLES

9.3.1 Exposures

Not applicable

9.3.2 Outcomes

9.3.2.1 Primary outcomes

1. All-cause in-hospital death: defined as any in-hospital death as indicated in the Format 1 of Diagnosis Procedures Combination (DPC) claims.
2. CV in-hospital death: defined as any in-hospital death with the primary cause of hospitalization (main diagnosis, most resource healthcare consuming, and hospitalization triggering diagnosis) categorized as CV related disease by ICD-10 classification as follows: diseases of heart (ICD–10 codes I00–I09, I11, I13, I20–I51); essential hypertension and hypertensive renal disease (I10, I12, I15) or cerebrovascular diseases (I60–169)

9.3.2.2 Secondary outcomes

1. All cause hospitalization
2. Hospitalization due to CV and renal events listed below. These will be treated as individual outcome as well as composites. CV composite outcome includes MI or CHF or any of strokes. Renal composite outcome includes ESRD or dialysis procedure or kidney transplant or acute kidney failure.
    1) MI (I21, I22 by ICD-10 code)
    2) CHF (I50 by ICD-10 code)
    3) any type of stroke (I60, I61, I62, I63, I64 by ICD-10 code)
    4) ESRD (N18.5 by ICD-10 code for MDV, N18.0 for Kyoto RWD data)
    5) Dialysis Procedure (J038, C102-2, J042, C102, C155, K635-3 by procedure code)
    6) Kidney Transplant (Z94.0, T86.1, K780-2 by procedure code)
    7) Acute Kidney Failure (N17 by ICD-10 code)

Based on an internal study using RWD database containing both claims and EMR physician ordering diagnosis, the positive predictive value of in-hospital death, MI, CHF, stroke and ESRD, ranged between 80.3% for MI and 96.7% for CHF. (CTMS 1245.209)

9.3.2.3 Further outcomes

Exploratory Outcomes:

1. Decline from normal kidney function (eGFR ≥60ml/min/1,73m^2) to abnormal kidney function(eGFR <60ml/min/1,73m^2)
2. Progression from normo-albuminuria (<30mg/g Cr) to micro- or macro-albuminuria (≥30mg/g Cr) for Kyoto Real World Data Company (RWD) database analysis only
3. Composite outcome (transition from eGFR >60 and UACR <30 to 1 and/or 2 above) for RWD database analysis
4. eGFR decline <40% or more from baseline eGFR >60
5. Lab test defined ESRD: eGFR <15

9.3.3 Covariates

- Age
- Sex
- Index eGFR value
- Medical history (hypertension, hypercholesterolemia, stroke, MI, CHF, Alzheimer's disease, depression, chronic obstructive pulmonary disease, asthma, solid tumor, leukemia, lymphoma, see エラー! 参照元が見つかりません。~~Table 1~~)
- presence or absence of type 2 diabetes (defined as E11, E14 by ICD-10)
- Elixhauser's Comorbidity Index (ECI) will be calculated as a numerical value and included as a covariate (4).
- CV related medications by class (anti-hypertensive, anti-diabetic by mode of action, diuretics, erythropoietins, Vitamin D, iron, bisphosphonates, bronchodilator, anti-arrythmia, anti-platelet, anti-coagulation, etc.)

9.4 DATA SOURCES

Data source

Two sources of data will be used for this study. MDV data will be the primary data source, while Kyoto RWD data is exploratory.

- Medical Data Vision (MDV) Database: (Jan 1, 2013 – Sept 31, 2019)

MDV database contains hospital administrative claims data from more than 16 million uniquely identifiable in- and out-patients treated at more than 260 acute care hospitals within secondary medical care blocs around Japan. These hospitals used the DPC case-mix classification system for inpatient reimbursement claims. The database contains pseudonymous information from health insurance claims for outpatients, administrative data for in- and out-patients, prescriptions, operations and medical procedures, hospitalisation and results of laboratory tests from some of the participating hospitals. Laboratory data including eGFR is available in approximately 10% of patients. The provision of lab data is dependent on the MDV contract with the hospital providing the data, and not dependent on the characteristics of the patients. Death data is only obtained for in-hospital cases in which the discharge diagnosis is death.

- Kyoto Real World Data Company (RWD) Database: (Jan 1, 2013 – Dec 31, 2019)

This database is available in-house at Nippon Boehringer Ingelheim and contains only patients with at least one type 2 diabetic diagnosis code and one oral anti-diabetic medication. RWD database is maintained by Health, Clinic, and Education Information Evaluation Institute (HCEI: Kyoto, Japan), a not-for-profit research service foundation, with support from Real World Data Co., Ltd (Kyoto, Japan). This database contains the EMRs of about 20 million patients from approximately 160 medical institutions across Japan since year 2000. The stored information includes demographic data, diagnoses, prescriptions, procedures, and laboratory results from both outpatient and inpatient services. The data are automatically extracted from EMRs at each medical institution. Patient records are kept by allocating unique identifiers for each individual, which are valid within the same institution. Death record is in both discharge diagnosis of claims as well as EMR, mostly reflecting in-hospital deaths. Death outside of the hospital is most likely not captured in the database.

9.5 STUDY SIZE

This is an exploratory study with no hypothesis testing.
In the pre-analysis, there were 36,262 patients in MDV database who had at least four eGFR values in the baseline period (Jan 1, 2013 to Dec 31, 2015) with at least one claim every year. If we require patients to have additional two eGFR in the follow up period (index date = last eGFR value in baseline period), approximately 20% reduction in sample size to 30,434 patients was observed.

9.6 DATA MANAGEMENT

Data are provided as electronic data formatted csv by MDV database and RWD database. *Instant health data (IHD) is used to create cohort. R version 3.6.2 and SAS version 9.4 are used for statistical analysis.*

9.7 DATA ANALYSIS

9.7.1 Descriptive analysis

3. Patients' background: descriptive statistics will be provided on the age, sex, presence of medical history (see エラー! 参照元が見つかりません。~~Table 1~~ in 9.3.3), ECI (see 9.3.3) and prescription of CV related medication by class (see 9.3.3) during the baseline period. Sex, medical history, and CV related medication will be described as percentages to all eligible patients, and others will be as mean value ±standard deviation.
4. Slope of eGFR: descriptive analysis will be provided on the annual decline of eGFR overall (mean, 95% CI) and stratified by patients experiencing cardiovascular/renal and in-hospital mortality. The least square regression method will be used to calculate the slope and its 80%CI. Based on the slope all patients will be categorized into six groups:
   ① eGFR slope = -1.00 ~ 1.00 ml/min/1.73m^2/year (reference)
   ② eGFR slope = < - 5.00 (rapid decliner)
   ③ eGFR slope = - 3.00 ~ -5.00

④ eGFR slope = -1.00 ~ -3.00
⑤ eGFR slope = 1.00 ~ 3.00
⑥ eGFR slope = >3.00 (rapid improver)

5. A sensitivity analysis will be performed to the patients limited to those whose 80%CI of the slope is fully included in the each group.
6. Set a maximum value of eGFR at 150 to eGFR values above 150.

9.7.2 Main analysis

1. Cox proportional hazards model will be applied to ②－⑥category of patients with ① as the reference group with time to event analysis conducted for each outcome (see 9.3.2).The model will be adjusted for age, gender, medical history (see 9.3.3), presence or absence of type 2 diabetes (see 9.3.3), baseline Elixhauser Comorobidity Index score and baseline kidney function defined as the index eGFR and the last UACR value during baseline period .

9.7.3 Further analysis

Stratified analysis
An additional stratified analysis for primary and secondary outcomes will be conducted in patients grouped as below:
1. By index eGFR value (>90, 60-89.9, 30-59.9, 15-29.9 ml/min/1.73m^2)
2. For A) T2DM cohort (ICD 10 diagnosis code E11 and E14) and B) others (see 9.2)
3. For C) pediatric patients (see 9.2)

Sensitivity analysis
1. Without setting the maximum eGFR value of150 ml/min/1.73m^2
2. Setting the maximum eGFR value at 120 ml/min/1.73m^2 to values above 120.

9.8 QUALITY CONTROL

Milliman will conduct a quality check as below:
- Calculation check: Both program codes for calculation and the data codes used for the calculation, will be checked by different person from who calculated it.
- Pre-release peer review: Comprehensive check on methodology, calculation process, and consistency of results will be performed by a qualified peer-reviewer.
- Post-release peer review: Comprehensive check on the project will be conducted by qualified peer-reviewer belonging to a different office.

9.9 LIMITATIONS OF THE RESEARCH METHODS

- Selection bias: since we are using hospital administrative claims database and EMR data from hospitals, and further selecting patients based on the availability of laboratory values in each database, generalizability of the findings will be limited.
- Mis-classification bias: since mortality outcomes are not validated against death registry, there is a certain risk of mis-classification.
- Lack of UACR value in MDV data makes proteinuria analysis using MDV not feasible

9.10 OTHER ASPECTS

None

9.11 SUBJECTS

See 9.2 and 9.4

9.11.1 Cases

None

9.11.2 Controls

None

9.12 BIAS

Internal validity has been checked in the Japanese sub-study of Emprise Extension Study using MDV database (CTMS 1245.195). Internal validity of RWD database will be assessed in this study using the diabetic population database. External validity will be checked against some registry study data involving Japanese CKD patients.

10. PROTECTION OF HUMAN SUBJECTS

Not applicable. This is a study based on databases using pseudonymized and personally unidentifiable data.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Not applicable. This is an observational cohort study using existing database.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results of the study will be written as a manuscript to be submitted to a peer-reviewed journal and will be presented at the international kidney disease conference.

13. REFERENCES

13.1 PUBLISHED REFERENCES

1. GBD 2017 Disease and Injury Incidence and Prevalenc Collaborators. Global, regional and national incidence, prevalence, and years lived with disability for 354 disease nad injuries for 195 countries and territories, 1990-2017: A systematic analysis of the Global Burden of Disease Study 2017. Lancet. 2018. 392(10159): 1789-1958
2. Matsushita et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality: a collaborative meta-analysis of general population cohorts. Lancet. 2010 June 12; 375 (9731): 2073-2081
3. Van Pottelbergh et al. Is there a correction between an eGFR slope measured over a 5-year period and incident cardiovascular events in the following 5 years among a Flemish general practice population; a retrospective cohort study. BMJ Open 2018: 8:e023594. doi:10.1136/bmjopen-2018-023594
4. Quan et al. Coding Algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Medical Care 2005, Nov 2005

13.2 UNPUBLISHED REFERENCES

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Table 1 Definition of medical history

	ICD-10 code by Ministry of Health, Labour and Welfare
Hypertension	I10.x, I11.x–I13.x, I15.x
Hypercholesterolemia (hyperlipidemia)	E780.x, E782x E784, E785
myocardial infarction	I21.x, I22.x
congestive heart failure	I50.x
stroke	I60.x, I61.x, I62.x, I63.x, I64.x
Alzheimer's disease (Dementia)	F00.x–F03.x, F05.1, G30.x, G31.1
depression	F20.4, F31.3–F31.5, F32.x, F33.x, F34.1, F41.2, F43.2
chronic obstructive pulmonary disease	J44.x
asthma	J45.x
solid tumor	C00 – D49
solid tumor without metastasis	C00.x–C26.x, C30.x–C34.x,C37.x–C41.x, C43.x,C45.x–C58.x,C60.x–C76.x, C97.x
metastatic solid tumor	C77.x–C80.x
leukemia	C90.x-C95.x (excluding C90.0, 90.2)
lymphoma	C81.x–C85.x, C88.x, C96.x, C90.0, C90.2
Cardiovascular Diseases	Diseases of heart (ICD–10 codes I00–I09, I11, I13, I20–I51); Essential hypertension and hypertensive renal disease (I10, I12, I15) and Cerebrovascular diseases (I60–169)

Table 2. Medication Codes List for Baseline Variables

Medication Class	ATC	Description
Anti-diabetic	A10xxxx	anti-diabetic
Bronchodilator		Reference
Anti-arrythmia	C01Bxxx	anti-arrythmia
Anti-platelet	B01AC06	acetylsalicylic acid (asprin)
	B01AC04	clopidogrel
	B01AC22	prasugrel

	B01AC05	ticlopidine
	B01AC07	dipyridamole
	B01AC23	cilostazol
	B01AC24	ticagrelor
Anti-coagulation	B01AA03	warfarin
	B01AE07	dabigatran etexilate
	B01AF01	rivaroxaban
	B01AF02	apixaban
Anti-hypertensive	C02xxxx	Anti–hypertensive
	C03xxxx	diuretics
	C07xxxx	beta blocking agents
	C08xxxx	calcium channel blockers
	C09xxxx	agents acting on the renin-angiotensin
	C01DA02	glyceryl trinitrate
	C01DA08	isosorbide dinitrate
	C01DA14	isosorbide mononitrate
	C01EB18	ranolazine Including doxazosin, eplerenone, prazosin, terazosin, clonidine, guanabenz (no ATC code), guanadrel (no ATC code), guanethidine, guanfacine, hydralazine,methyldopa, metirosine (also known as metyrosine), reserpine, minoxidil, aliskiren
	C02CA04	doxazosin
	C02CA01	prazosin
	C02AC01	clonidine
	C02AC02	guanfacine
	C02DB02	hydralazine
	C03DA04	eplerenone
	G04CA03	terazosin
	C09XA02	aliskiren
	C09XA52	aliskiren and hydrochlorothiazide
Bisphosphonates	M05BA	etidronate, alendronate, zoledronic acid, risedronate, ibandronate, pamidronate, tiludronate,
bisphosphonates, combination	M05BB	andronate and cholecalciferol, calcium carbonate and risedronate
Erythropoietin	B03XA01	darbepoietin,alpha, epoetin alpha, petinesatide,
Iron preparation	B03A	iron preparations
	B03AA	iron bivalent oral preparations

	B03AB	iron trivalent, oral preparations
	B03AC	iron parenteral preparations
	B03AD	iron in combination with folic acid
	B03AE	iron in other combiantions
	B03AE03	iron and multivitamins
	B03CB03	iron oxide, nanoparticles
	B03AE02	iron, multivitamins and folic acid
	B03AE04	iron, multivitamins and minerals
	B03AE01	iron, vitamin B12 and folic acid
	A11AA01	multi-vitmins and iron
High ceiling diurtics	C03CA	Sulfonamides, plain
	C03CB	Sulfonamides and potassium in combination
	C03CC	Aryloxyacetic acid derivatives
	C03CD	Pyrazolone derivatives
	C03CX	Other high-ceiling diuretics
High-ceiling diuretics and potassium-sparing agents	C03EB01	furosemide and potassium-sparing agents
	C03EB02	bumetanide and potassium-sparing agents

Table 3 Medication Codes List for bronchodilators

Medication class	**Therapeutic chemicals**	**ATC codes**	**Marketing year in Taiwan**
Oral bronchodilators Oral beta-2 agonists	salbutamol	r03CC02	1974
Oral beta-2 agonists	Terbutaline	r03CC03	1979
Oral beta-2 agonists	Fenoterol	r03CC04	1979
Oral beta-2 agonists	hexoprenaline	r03CC05	1982
Oral beta-2 agonists	Procaterol	r03CC08	1985
Oral beta-2 agonists	Trimetoquinol	r03CC09	1975
Oral beta-2 agonists	Bambuterol	r03CC12	1993
Oral beta-2 agonists	Clenbuterol	r03CC13	1988
Oral beta-2 agonists	Formoterol	r03CC91	1993
Oral xanthines	Theophylline	r03Da04	1972
Oral xanthines	aminophylline	r03Da05	1970
Inhaled short-acting bronchodilators saBas	salbutamol	r03aC02	1989
saBas	Terbutaline	r03aC03	1989

saBas	Fenoterol	r03aC04	1992
saBas	hexoprenaline	r03aC06	1995
saMas	Ipratropium	r03BB01	1981
saBa/saMa FDCs[a]	Fenoterol/Ipratropium	r03aK03	1986
saBa/saMa FDCs[a]	salbutamol/Ipratropium	r03aK04	2000
Inhaled long-acting bronchodilators laBas	salmeterol	r03aC12	1996
laBas	Formoterol	r03aC13	2000
laBas	Procaterol	r03aC16	1989
laBas	Indacaterol	r03aC18	2010
laMas	Tiotropium	r03BB04	2003
laBa/ICs FDCs	salmeterol/Fluticasone	r03aK06	2001
laBa/ICs FDCs	Formoterol/Budesonide	r03aK07	2001

ANNEX 2. ENCEPP CECKLIST FOR STUDY PROTOCOLS

None

ANNEX 3. ADDITIONAL INFORMATION

None