APPENDIX 1. ANTIDIABETIC MEDICATIONS

Class	Drug	Formulations	ATC
Pioglitazone	pioglitazone	glimepiride and pioglitazone	A10BD06
Pioglitazone	pioglitazone	metformin and pioglitazone	A10BD05
Pioglitazone	pioglitazone	pioglitazone	A10BG03
Pioglitazone	pioglitazone	pioglitazone and alogliptin	A10BD09
Pioglitazone	pioglitazone	pioglitazone and sitagliptin	A10BD12
other TZDs	rosiglitazone	glimepiride and rosiglitazone	A10BD04
other TZDs	rosiglitazone	metformin and rosiglitazone	A10BD03
other TZDs	rosiglitazone	rosiglitazone	A10BG02
other TZDs	troglitazone	troglitazone	A10BG01
insulin	insulin (fast)	insulin (human)	A10AB01
insulin	insulin (fast)	insulin (beef)	A10AB02
insulin	insulin (fast)	insulin (pork)	A10AB03
insulin	insulin (fast)	insulin lispro	A10AB04
insulin	insulin (fast)	insulin aspart	A10AB05
insulin	insulin (fast)	insulin glulisine	A10AB06
insulin	insulin (fast)	combinations	A10AB30
insulin	insulin (Intermediate)	insulin (human)	A10AC01
insulin	insulin (Intermediate)	insulin (beef)	A10AC02
insulin	insulin (Intermediate)	insulin (pork)	A10AC03
insulin	insulin (Intermediate)	insulin lispro	A10AC04
insulin	insulin (Intermediate)	combinations	A10AC30
insulin	insulin (intermediate + fast)	insulin (human)	A10AD01
insulin	insulin (intermediate + fast)	insulin (beef)	A10AD02
insulin	insulin (intermediate + fast)	insulin (pork)	A10AD03
insulin	insulin (intermediate + fast)	Insulin lispro	A10AD04
insulin	insulin (intermediate + fast)	insulin aspart	A10AD05
insulin	insulin (intermediate + fast)	combinations	A10AD30
insulin	insulin (long acting)	insulin (human)	A10AE01
insulin	insulin (long acting)	insulin (beef)	A10AE02
insulin	insulin (long acting)	insulin (pork)	A10AE03
insulin	insulin (long acting)	insulin glargine	A10AE04

insulin	insulin (long acting)	insulin detemir	A10AE05
insulin	insulin (long acting)	combinations	A10AE30
insulin	insulin (inhaled)	insulin (human aerosol, powder)	A10AF01
Biguanides	metformin	metformin	A10BA02
Biguanides	metformin	metformin and alogliptin	A10BD13
Biguanides	metformin	metformin and linagliptin	A10BD11
Biguanides	metformin	metformin and pioglitazone	A10BD05
Biguanides	metformin	metformin and rosiglitazone	A10BD03
Biguanides	metformin	metformin and saxagliptin	A10BD10
Biguanides	metformin	metformin and sitagliptin	A10BD07
Biguanides	metformin	metformin and sulfonamides	A10BD02
Biguanides	metformin	metformin and vildagliptin	A10BD08
Biguanides	phenformin	phenformin	A10BA01
Biguanides	phenformin	phenformin and sulfonamides	A10BD01
Biguanides	buformin	buformin	A10BA03
sulphonylureas	Sulfonamides, urea derivatives	glibenclamide	A10BB01
sulphonylureas	Sulfonamides, urea derivatives	chlorpropamide	A10BB02
sulphonylureas	Sulfonamides, urea derivatives	tolbutamide	A10BB03
sulphonylureas	Sulfonamides, urea derivatives	glibornuride	A10BB04
sulphonylureas	Sulfonamides, urea derivatives	tolazamide	A10BB05
sulphonylureas	Sulfonamides, urea derivatives	carbutamide	A10BB06
sulphonylureas	Sulfonamides, urea derivatives	glipizide	A10BB07
sulphonylureas	Sulfonamides, urea derivatives	gliquidone	A10BB08
sulphonylureas	Sulfonamides, urea derivatives	gliclazide	A10BB09
sulphonylureas	Sulfonamides, urea derivatives	metahexamide	A10BB10
sulphonylureas	Sulfonamides, urea derivatives	glisoxepide	A10BB11
sulphonylureas	Sulfonamides, urea derivatives	glimepiride	A10BB12
sulphonylureas	Sulfonamides, urea derivatives	glimepiride and rosiglitazone	A10BD04
sulphonylureas	Sulfonamides, urea derivatives	glimepiride and pioglitazone	A10BD06
sulphonylureas	Sulfonamides, urea derivatives	acetohexamide	A10BB31
sulphonylureas	Sulfonamides, urea derivatives	phenformin and sulfonamides	A10BD01
sulphonylureas	Sulfonamides, urea derivatives	metformin and sulfonamides	A10BD02

sulphonylureas	Sulfonamides, heterocyclic	glymidine	A10BC01
DDP-4 inhibitors	sitagliptin	sitagliptin	A10BH01
DDP-4 inhibitors	sitagliptin	sitagliptin and simvastatin	A10BH51
DDP-4 inhibitors	sitagliptin	metformin and sitagliptin	A10BD07
DDP-4 inhibitors	sitagliptin	pioglitazone and sitagliptin	A10BD12
DDP-4 inhibitors	vildagliptin	vildagliptin	A10BH02
DDP-4 inhibitors	vildagliptin	metformin and vildagliptin	A10BD08
DDP-4 inhibitors	saxagliptin	saxagliptin	A10BH03
DDP-4 inhibitors	saxagliptin	metformin and saxagliptin	A10BD10
DDP-4 inhibitors	alogliptin	alogliptin	A10BH04
DDP-4 inhibitors	alogliptin	metformin and alogliptin	A10BD13
DDP-4 inhibitors	alogliptin	pioglitazone and alogliptin	A10BD09
DDP-4 inhibitors	linagliptin	linagliptin	A10BH05
DDP-4 inhibitors	linagliptin	metformin and linagliptin	A10BD11
Alpha glucosidase inhibitors	acarbose	acarbose	A10BF01
Alpha glucosidase inhibitors	miglitol	miglitol	A10BF02
Alpha glucosidase inhibitors	voglibose	voglibose	A10BF03
GLP-1 agonists	exenatide	exenatide	A10BX04
GLP-1 agonists	liraglutide	liraglutide	A10BX07
meglitinides	repaglinide	repaglinide	A10BX02
meglitinides	nateglinide	nateglinide	A10BX03
meglitinides	mitiglinide	mitiglinide	A10BX08
amylin	pramlintide	pramlintide	A10BX05
others	benfluorex	benfluorex	A10BX06
others	guar gum	guar gum	A10BX01
others	dapagliflozin	dapagliflozin	A10BX09

NOTE: Further details of the definitions available on request.

CPRD GOLD & GOLD-HES

Pioglitazone.txt
GOLD Entity 26 (current diabetes status) = 2 "using insulin". GOLD Entity 97 (insulin dosage) AND Insulin.txt

Biguanides.txt

Not in GOLD

Sulfonylureas.txt
Not in GOLD

Sulfonylureas.txt
Not in GOLD
Not in GOLD

Sulfonylureas.txt
Not in GOLD

Sulfonylureas.txt

DDP4.txt

Not in GOLD

DDP4.txt
AlphaglucosidaseI.txt

Not in GOLD

GLP1.txt

Meglitanides.txt
Not in GOLD
Not in GOLD
Not in GOLD
OtherGuarGum.txt
Others.txt

Appendix 2: Calculation of exposure

Version 2.0, 20 June 2013

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Version 2.0, 20 June 2013

This appendix states how drug exposure is defined in the Pan EU bladder cancer study for diabetes drug groups listed in Table 1. The following time dependent exposure variables will be constructed:

I. All diabetes drug groups
   - Ever vs. never use

II. Pioglitazone group and insulin group
   - Duration of exposure (cumulative time),

III. Pioglitazone group only
   - Cumulative dose, and
   - Time since last dose

Table 1: Diabetes drug groups

Group name*	Groups used to define i) number of treatments prior to CED** ii) add-on/switch at CED	Groups used in Follow-up
Pioglitazone	1	1
Other thiazolidinediones (including rosiglitazone)	2	Censoring of follow-up time
Metformin	3	2
Sulphonylureas	4	3
DDP-4 inhibitors	5	4 other oral
Alpha glucosidase inhibitors	6	4 other oral
GLP-1 agonists	7	4 other oral
Meglitinides	8	4 other oral
Amylin analogues	9	4 other oral
Other oral diabetic	10	4 other oral
Insulin	11	5

* ATC codes given in separate document. Combination products are included into multiple groups. **CED = cohort entry date.

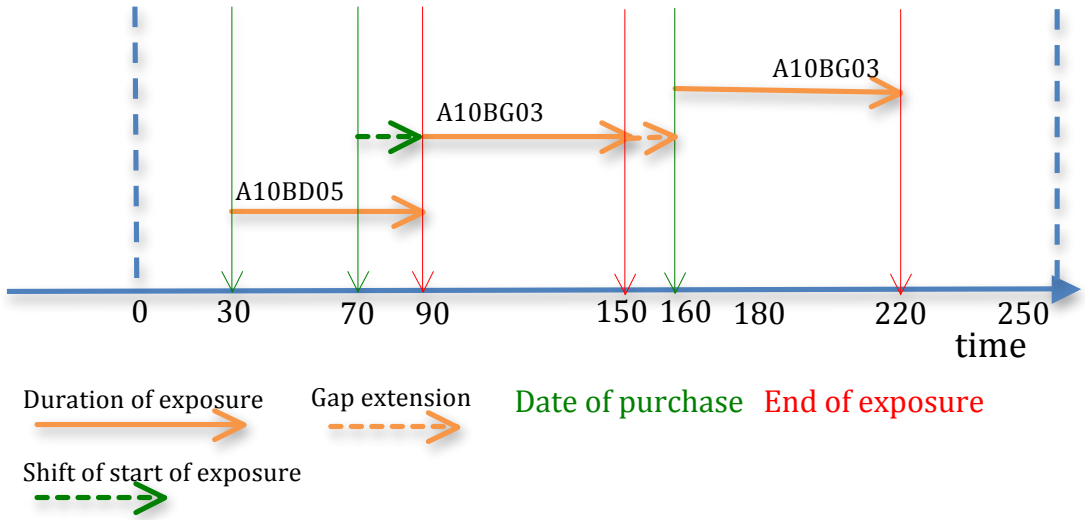
Drug exposure periods for diabetes drug groups

The follow-up time of each individual is divided into drug exposure periods, i.e., non-overlapping time intervals, such that drug exposure within each period is constant. The periods are defined as half closed sets $(t_1,t_2]$ where the left boundary t_1 is not included and the right boundary t_2 is included in the set.

Depending on the database the information used in defining drug exposure originates from drug purchase, drug prescription, or drug dispensing records. Hereon, for simplicity and clarity of notation, the term "purchase" refers equally to all three cases.

The following steps are used to define drug exposure periods for study drug groups. An exception is insulin, for which the procedure is described in a separate section. Note also, that for combination products the individual components are handled as separate purchases.

Figure 1: Drug exposure periods for use of pioglitazone as single and combination product



Step 1: Start of exposure

For each purchase define the start of exposure as (see Figure 1 and Table 3).

- **Case 1, no ongoing exposure within drug group:** Use the date of purchase as start date
- **Case 2, ongoing exposure within drug group:** The start date is moved to the end of the ongoing exposure period. The maximum shift of the start date is limited to 30 days.

Step 2: Duration of exposure of a purchase

The duration of exposure for each purchase is calculated by dividing the total amount (TA) purchased by the daily dosage (dpt).(see Figure 1, Table 2 and Table 3)

The exposure period is cut short at the start of a new purchase of the same drug group

Step 3: Gap extension

A gap extension of maximum 50% of the duration of the exposure of a purchase is added only when a "permissible" gap is identified, .i.e., a gap that can be completely covered by the 50% extension.

Table 2: Database specific definitions for *total amount* and *daily dosage*

Data set	FIN	SWE	PHARMO	CPRD
Total amount (TA)	Given in number of DDDs[1]	Given in number of DDDs	Total quantity as dispensed	Total quantity given in prescription
Daily dosage (dpt)	Estimate daily dosage from previous purchases[3]. If not available apply best available information as detailed in data specific SAP	Text mining when possible. Otherwise as in FIN	Daily dosage as given in prescription. If not available apply best available information as detailed in data specific SAP	As in PHARMO

[1]*The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults as defined by WHO.* [2]*This is both individual and ATC-code specific.*[3]*Daily dosage is calculated by dividing the total amount previously purchased by the time between the present and the previous purchase (for pills round to nearest ½ pill).*

Table 3: Example of defining start of exposure and duration of exposure based on drug purchases for the case in Figure 1.

Study ID	ATC-code	Total amount (TA)	Date of purchase	Start of exposure	Dosage (dpt)	Duration (TA/dpt)	Gap extension (max 50%)	End of exposure
100001	A10BD05	1800mg*	30	30	30mg	60	0	90
100001	A10BG03	1800mg	70	90	30mg	60	10	160
100001	A10BG03	1800mg	160	160	30mg	60	0	220

**1800mg = 60DDD*

Step 4: Produce exposure periods on group level: For each individual produce drug (group) level period data based on drug purchases (see Figure 1 and Table 4).

Table 4: Time dependent current exposure

Study ID	Date start	Date end	Total amount (TA)	Pioglitazone current
100001	0	30	0mg	0
100001	30	90	1800mg	1
100001	90	150	1800mg	1
100001	150	160	0mg	1*
100001	160	220	1800mg	1
100001	220	260	0mg	0

* Gap extension: no extra dosage

Step 5: Define ever vs. never use on drug group level based on previous current treatment. An individual is in category "never use" up to the "start of exposure" of the first purchase and is in the "ever use" category there on (see Table 5).

Exposure definitions for pioglitazone group

Step 6: Define duration of exposure (cumulative time) on pioglitazone group level as the cumulative sum of the durations of the previous pioglitazone exposure periods. Overlapping periods are only calculated once.
Step 7: **Define cumulative dose** by estimating the amount of pioglitazone used at the end of each period based on the daily dosage information. The cumulative dose does not increase during a gap extension, since the whole purchase is estimated to be used out before a possible gap extension. If after shifting the start of a new purchase the allowed 30 days, the exposure period still starts before the older exposure ends, the remaining dose of the old purchase is included into the cumulative dose summation. Thus, during overlapping of the periods the daily dosage is the sum of the separate daily dosages.
Step 8: Define time since last dose as current time - time when last current exposure to pioglitazone containing prescriptions since entry into the study cohort.

Table 5: Time dependent exposure

Study ID	Date start	Date end	Total amount (TA)	Pioglitazone current	Pioglitazone ever vs never	Pioglitazone cum time	Pioglitazone cum dose	Time since last dose
100001	0	30	0mg	0	0	0	0	0
100001	30	90	1800mg	1	1	60	1800mg	0
100001	90	150	1800mg	1	1	120	3600mg	0
100001	150	160	1800mg	1	1	130	3600mg	0
100001	160	220	1800mg	1	1	190	5400mg	0
100001	220	260	0mg	0	1	190	5400mg	40

Exposure definitions for insulin group

Step 9: Insulin drug exposure periods are defined in two steps. First the exposure periods are constructed separately for the group "long acting insulin" (ATC A10AC / A10AE), the group "fast acting insulin" (ATC A10AB / A10AF inhaled insulin) and the group "premixed insulin" (ATC A10AD) using steps 1-4 above. The duration of each insulin purchase is assumed fixed. For example 120 days (4 months) plus a possible 50% gap extension. The database specific value will be defined in the database specific SAP. In a second step insulin drug exposure periods are constructed by combining "long acting insulin", "fast acting insulin" and "premixed insulin" drug exposure periods that are allowed to overlap.
Step 10: Define ever vs. never use on insulin group level based on previous current insulin treatment. An individual is in category "never use" up to the "start of exposure" of the first insulin

purchase (either long acting, fast acting or premixed insulin) and is in the "ever use" category from there on.
Step 11: Define duration of exposure (cumulative time) on insulin group level as the cumulative sum of the durations of the previous insulin exposure periods.

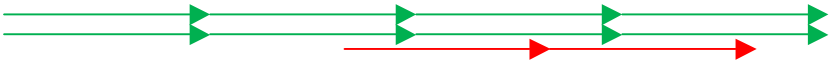
Combination therapy and switch/add-on definitions

Determine what is a switch and what an add-on by looking whether there is a dispensing of the prior drug after the start of the new drug (see definitions below).

- **Initiation** of antidiabetic treatment. The patient has not received any medication directly prior to the start of a new treatment.

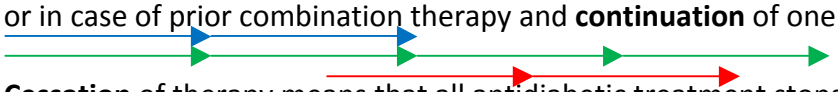
- **Add-on** to existing treatment. This is defined as a **continuation** of all previous antidiabetic treatment, with the addition of a **new drug** to this treatment.

or in case of prior combination therapy:



- **Switches** are defined as changes in existing antidiabetic treatment (group level), this always includes **discontinuation** of part or all of the previous treatment. This means that a switch occurs when the start of the **new drug** occurs between the last prescription of the episode of the prior drug group, and the end of that episode.

or in case of prior combination therapy and **continuation** of one of the combination drugs:



- **Cessation** of therapy means that all antidiabetic treatment stops. This may be temporary.

Variable (F = fixed at CED, T = time dependent)	Classification	Comment	Finland ICD-10	Sweden ICD-10	PHARMO GP database ICPC	PHARMO hospital database ICD-9
Type 1 diabetes mellitus at cohort entry (F)	N/Y		ICD-10: E10 and O24.0 for type 1 DM O24.4 for gestational diabetes E08, E09, E12, E13, P70.2 for secondary and other types of diabetes mellitus	ICD-10: E10 and O24.0 for type 1 DM O24.4 for gestational diabetes E08, E09, E12, E13, P70.2 for secondary and other types of diabetes mellitus If a subject has only E14 (unspecified diabetes) the record should be exclude. Use the whole chapter O24 (except O24.1 which is type 2). E08 and E09 do not exist in Sweden.	T90.01 or mention of insulin dependent diabetes mellitus, drug induced diabetes mellitus, gestational diabetes mellitus, secondary diabetes mellitus	250.x1 (diabetes mellitus with juvenile onset), 249 (Secondary diabetes mellitus), 648.8 (gestational diabetes)
Duration of treated diabetes mellitus at cohort entry (F)	Years of prior DM Tx at cohort entry Classes <1 year, 1-<2 years, 2-<4 years, 4-<6 years, >=6 years		Time since first recorded purchase of DM medication (ATC code A10) prior to cohort entry in prescription register	Time since first recorded purchase of DM medication (ATC code A10) prior to cohort entry in prescription register	Time since first recorded prescription of DM medication (ATC code A10) prior to cohort entry in GP records. If there is less than 6 months of recorded history before this date, and a date of onset of diabetes is provided, the date of onset will be used to estimate the date of start of treatment.	Time since first recorded dispensing of DM medication (ATC code A10) prior to cohort entry
Diabetic retinopathy (F, T)	Classified as never (0) or ever (1) with the condition evaluated at any given time during the follow-up; Starting at 1 if condition exists at cohort entry, 0 otherwise.		ICD-10: H36.0 excluding H36.01 All codes that begin with H36.0 are related to diabetes. (These are H36.00*, H36.01*, H36.02*, H36.03*, H36.04*, H36.05*, H36.09*, H36.09*E10.3, H36.09*E11.3.) E11.0 is not then ment to be used alone here. E11.31-E11.35, E14.31-E14.35 not used in Finland.	ICD-10 diagnostic codes H36.0, E113 in PAR Theguide line seems to be for the coding for cause of death. The ICD code for retinopathy In Sweden are E113A and E113B. E113C is proliphrative retinopathy.	F83 Retinopathy F83.01 diabetic retinopaty F83.02 hypertensive retinopaty (exclude, even if only minority with decimals) examination codes DMRPFALI 1652 (diabetic retinopathy left) = 1 DMRPFARE 1653 (diabetic retinopathy right) = 1 search episodes for 'retinop' EXCLUDE combinations with: 'spoed' OR 'preventie' OR 'acuut' OR 'acute' OR 'dd' OR 'd.d.' OR '?' OR 'familie' OR 'broer' OR 'zus' OR 'vader' OR 'moeder' OR 'dochter' OR 'zoon' OR 'kind'	362.0 diabetic retinopathy 362.10 Background Retinopathy, unspecified
Diabetic maculopathy (F,T)	Classified as never (0) or ever (1) with the condition evaluated at any given time during the follow-up; Starting at 1 if condition exists at cohort entry, 0 otherwise.	New variable: this condition is due to leaking of fluid from the macular capillaries. Associated with advanced diabetes	ICD-10: H36.01* Finland does not have codes mentioned above. Diabetic maculopathy is H36.01* (n.b. This code is listed in the previous cell.) H35 group refers to other retinal diseases.	ICD-10 E11.311, E11.321, E11.331, E11.341, E11.351, H35.81 in Sweden H36.01=H36.0A	F84 macular degeneration search episodes for 'maculop' OR ('macula' AND 'oedeem') EXCLUDE combinations with: 'spoed' OR 'preventie' OR 'acuut' OR 'acute' OR 'dd' OR 'd.d.' OR '?' OR 'familie' OR 'broer' OR 'zus' OR 'vader' OR 'moeder' OR 'dochter' OR 'zoon' OR 'kind'	ICD-9 362.83 retinal oedema 362.07 (diabetic macular oedema) does not exist in Dutch ICD-9-CM version
Diabetic retinopathy or maculopathy (F, T)	Classified as never (0) or ever (1) with the condition evaluated at any given time during the follow-up; Starting at 1 if condition exists at cohort entry, 0 otherwise.		SEE DEFINITIONS FOR Diabetic retinopathy and Diabetic maculopathy	SEE DEFINITIONS FOR Diabetic retinopathy and Diabetic maculopathy	SEE DEFINITIONS FOR Diabetic retinopathy and Diabetic maculopathy	SEE DEFINITIONS FOR Diabetic retinopathy and Diabetic maculopathy

Diabetic peripheral neuropathy (F, T)	Classified as never (0) or ever (1) with the condition evaluated at any given time during the follow-up; Starting at 1 if condition exists at cohort entry, 0 otherwise.	Acute sensory neuropathy & Chronic sensorimotor neuropathy	ICD-10 diagnostic code G63.2 in hospital care register (with E11.4)	ICD-10 diagnostic codes G63.2, E114 in PAR Add G59.0 = "Diabetic mononeuropathy Add E144	N94 peripheral neuritis/neuropathy N94.02 diabetic neuropathy episode text mining for 'neuropathie' examinations: 1750 SNSVNSLI sensibility left foot 1751 SNSVNSRE sensibility right foot	250.6 Diabetes with neurological manifestations Use additional code to identify manifestation, as: mononeuropathy (354.0-355.9) peripheral autonomic neuropathy (337.1) polyneuropathy (357.2)
CKD (F,T) including dialysis or translant	Classified as never (0) or ever (1) with the condition evaluated at any given time during the follow-up; Starting at 1 if condition exists at cohort entry, 0 otherwise.	diagnosis of CKD grade ≥ 3 (moderate) or dialysis or transplant or ≥2 recorded eGFR measurements (glomerular filtration rate) ≤60 mls/min/1.73m2, which had to be recorded at least 90 days, but not more than 365 days apart.	ICD-10: N18, Z49, Z99.2, Z94.0, T86.1 NCSP procedure codes KA_4, TK800, TK820 for dialysis, haemodialysis, or peritoneal dialysis, KAS00, KAS10, KAS20 for transplantation, auto transplantation, or allogenic of kidney N18 as a group refers to CHRONIC renal insufficiency. Under that Finland has only N18.0, N18.8 and N18.9.	ICD-10 diagnostic codes N18, Z49, Z992 and/or NOMESCO procedure codes DR015, DR016, DR023, DR055, DR056 in PAR	search episodes for: ((('nier' OR 'renal') AND 'chron' AND (('insuf' OR 'falen') OR ('dialyse' OR 'transplant')))) EXCLUDE combinations with: 'spoed' OR 'preventie' OR 'acuut' OR 'acute' OR 'dd' OR 'd.d.' OR '?' OR 'familie' OR 'broer' OR 'zus' OR 'vader' OR 'moeder' OR 'dochter' OR 'zoon' OR 'kind' examination codes: 523 KREAB creatinine 357 GEWAO weight patient 2408 GEWAOMH weight patient (home) 1918 KREAOFB eGFR Cockcroft 1919 KREMOFB eGFR MDRD formula ≥2 recorded eGFR ≤90mls/min/1.73m2, which had to be recorded at least 90 days, but not more than 365 days apart."	250.4 diabetic nephropathy, 403 Hypertensive chronic kidney disease, 404 Hypertensive heart and chronic kidney disease, 585 Chronic kidney disease (CKD) 588 Disorders resulting from impaired renal function, V42.0 kidney transplant, V45.1 renal dialysis status, V56 Encounter for dialysis and dialysis catheter care CvV codes: '8-853' haemodialysis, '8-860' peritoneal dialysis '5-555' renal transplantation
Proteinuria (micro or macro) or diabetic nephropathy (F, T)	Classified as never (0) or ever (1) with the condition evaluated at any given time during the follow-up; Starting at 1 if condition exists at cohort entry, 0 otherwise.	* Diagnostic record or medical history of proteinuria, microalbuminuria, macroalbuminuria or diabetic nephropathy, or * At last 2 positive urine tests at least 7 days apart within a 6 month period using any of the following thresholds: ** ≥30 mg albumin/24 hours (24 hour urine sample) or ** ≥30 mg albumin/g creatinine (spot urine test) or ** ≥2.5 mg albumin /mmol creatinine for men, and ≥3.5mg albumin / mmol creatinine for women (spot urine test) or ** ≥30mg albumin / litre of urine	SEE DEFINITIONS FOR Proteinuria, microalbuminuria and diabetic nephropathy	SEE DEFINITIONS FOR Proteinuria, microalbuminuria and diabetic nephropathy	SEE DEFINITIONS FOR Proteinuria, microalbuminuria and diabetic nephropathy	SEE DEFINITIONS FOR Proteinuria, microalbuminuria and diabetic nephropathy

Proteinuria (F, T)	Classified as never (0) or ever (1) with the condition evaluated at any given time during the follow-up; Starting at 1 if condition exists at cohort entry, 0 otherwise.	Disgnostic code for proteinuria or ≥30mg/g of creatinine or protein dipstick + to ++++	ICD-10: N06 Isolated proteinuria N39.1 Persistent proteinuria N39.2 Orthostatic proteinuria, unspecified R80 Proteinuria N04 Nephrotic syndrome	ICD-10 diagnostic codes N06, R809, N391, N392 in PAR	U88 glomerulonephritis / nephrosis U90 orthostatic albuminuria/proteinuria U98.01 proteinuria search episodes for 'nefropathie' OR 'nephropathie' OR 'nefrotisch syndroom' OR 'nephrotisch syndroom' OR 'glomerulone' OR 'nephrosis' OR 'nephrose' OR 'proteinurie' OR 'albuminurie' OR ('crea' OR 'krea') AND 'u' AND result: ≥30mg/24 hrs OR (('dipstick' OR 'ustick') AND '+' AND ('prot' OR 'eiwit')) examination codes: 2194 ALBUUQ (micro)albuminuria (comorbidity) = 1 525 KREAU kreatinine urine 527 KREAUEMT creatinine urine 24u 38 ALBU albumine urine portion 39 ALBUEMT albumine urine 24u 40 ALBKUMI albumine/creatinine urine 42 ALBKUEMI albumine/creatinine urine 24u 278 EIWUSK protein urine (stick) apply criteria as in comments column	791.0 Proteinuria 593.6 Postural proteinuria 581 Nephrotic syndrome
Microalbuminuria (F, T)	Classified as never (0) or ever (1) with the condition evaluated at any given time during the follow-up; Starting at 1 if condition exists at cohort entry, 0 otherwise.	≥30mg albumin in 24 hrs urine sample >30mg/L (urine spot test) albumin:creatinine ratio (ACR) >2.5 mg/mmol (males) >3.5 mg/mmol (females) OR protein dipstick = 'trace'	ICD-10: N08.30 Microalbuminuria related to diabetes	Not available, can not find ICD-10 code for Microalbuminuria	search episodes for 'microalbuminurie' OR ('crea' OR 'krea') AND 'u' AND result: ≥30mg/24 hrs OR (('dipstick' OR 'ustick') AND 'spoor' (=trace) AND ('prot' OR 'eiwit')) examination codes: 525 KREAU kreatinine urine 527 KREAUEMT creatinine urine 24u 38 ALBU albumine urine portion 39 ALBUEMT albumine urine 24u 40 ALBKUMI albumine/creatinine urine 42 ALBKUEMI albumine/creatinine urine 24u 278 EIWUSK protein urine (stick) apply criteria as in comments column	No specific ICD code
Proteinuria (micro or macro)(F, T)	Classified as never (0) or ever (1) with the condition evaluated at any given time during the follow-up; Starting at 1 if condition exists at cohort entry, 0 otherwise.		SEE DEFINITIONS FOR Proteinuria and microalbuminuria	SEE DEFINITIONS FOR Proteinuria and microalbuminuria	SEE DEFINITIONS FOR Proteinuria and microalbuminuria	SEE DEFINITIONS FOR Proteinuria and microalbuminuria

Diabetic nephropathy (F, T)	Classified as never (0) or ever (1) with the condition evaluated at any given time during the follow-up; Starting at 1 if condition exists at cohort entry, 0 otherwise.		ICD-10: N08.3 Finland does not have codes E11.21, E14.21. Codes beginning with N08.3 refer all to DIABETIC nephropathy.	ICD-10 diagnostic codes N08.3, E112 in PAR In Sweden the codes N08.3, E11.2A and E142 exist.	U88 glomerulonephritis / nephrosis search episodes for 'nefropathie' OR 'nephropathie' OR 'nefrotisch syndroom' OR 'nephrotisch syndroom' OR 'glomerulone' OR 'nephrosis' OR 'nephrose' Reply on text mining only, specific to nephropathy	250.4 Diabetes with renal manifestations Use additional code to identify manifestation, as: . diabetic: nephropathy NOS (583.81) nephrosis (581.81)
Serum creatinine (F)	Serum creatinine will be used to calculate eGFR. The normal value for eGFR is ≥90 ml/min/1.73m^2, eGFR is calculated from serum creatinine level, with adjustment for age, sex and race. The MDRD conversion equation for adults (Levey el al, 2006) is tused: eGFR (mL/min/1.73 m^2) = 175 × (Serum creatinine)$^{-1.154}$ × (Age)$^{-0.203}$ × (0.742 if female) × (1.212 if African American). Note: Serum creatinine in mg/dL. 1 mg/dL = 88.4 µmol/L	elevated ≥1.4 mg/dL for females . Elevated ≥1.5mg/dL for males	Not available	Not available	examination code: 523 KREAB, or search labtests for: ('krea' OR 'crea') and B(lood) AND result ≥ 1.4 mg/dL for females and ≥ 1.5 mg/dL for male	not available
Ketoacidosis (F, T)	Classified as never (0) or ever (1) with the condition evaluated at any given time during the follow-up; Starting at 1 if condition exists at cohort entry, 0 otherwise.	Excludes ketoacidotic coma	ICD-10 diagnostic code E11.1 or E14.1 in hospital care register	ICD-10 diagnostic codes E111, E141 In PAR	"text mining episodes: 'ketoacid' exclude: 'coma' "	250.1 Diabetes with ketoacidosis
Diabetic coma (F, T)	Classified as never (0) or ever (1) with the condition evaluated at any given time during the follow-up; Starting at 1 if condition exists at cohort entry, 0 otherwise.	Includes diabetic and ketoacidotic coma	ICD-10 diagnostic code E11.0 or E14.0 for type 2 DM with unconsciousness in hospital care register	ICD-10 diagnostic codes E110, E140 in PAR	text mining episodes: 'coma' AND ('diab' or 'keto' or 'acidos' or 'hypoglyc')	250.3 Diabetes with other coma Diabetic coma (with ketoacidosis) 250.2 Diabetes with hyperosmolarity Hyperosmolar (nonketotic) coma
Cigarette smoking (F)	Never vs. Ever vs. Unknown	Never vs Ever Never vs. Ex vs. Current	Not available	Not available	search examination codes for: ROOKAQ (Coded as no/yes/previously/never). PAKJAQ (number of packs per day * number of years) ICPC code: P17 (tabaksmisbruik) - It provides information only when it is a problem for the patient.	305.1 Tobacco use disorder (Tobacco dependence) V15.82 History of tobacco use 649.0 Tobacco use disorder complicating pregnancy, childbirth, or the puerperium (Smoking complicating pregnancy, etc) will be very incomplete
BMI (F)	Classified as missing, <30, 30-34.9 and ≥ 35.	If not available at baseline, the first record within 12 months of cohort entry is adopted. If no BMI data, coded as 'missing'.	Not available	Not available	examination code: QUETAO quetelet-index OR search lab for 'BMI' OR 'quetelet' ICPC T82 Adipositas (Quetelet-index >30)	n.a.

HbA1C (F, T)	Classified as missing, <7.5%, 7.5-8.9%, ≥9.0%.	Baseline HbA1C measurement will be most recent record within 6 months prior to cohort entry. Persons with no baseline HbA1C	Not available	Not available	examination codes: 'GLHBB'=glycohemoglobine dcct % OR 'HBACB' Hba1c - glycohemoglobine - ifcc -mmol/mol	n.a.
PSA elevated (T)	PSA elevated at any given time during the follow-up. Classified as Never vs. ever elevated; and Never elevated vs. Elevated vs. Not elevated.	Never vs. Ever Never vs. Elevated vs. Not elevated	Not available	Not available	examination code: 1921 PSACB PSA complex 896 PSAB PSA 2157 PSAVB free PSA 2124 PSARB free PSA / total PSA ratio OR text mining episodes for: (('Prostaat' AND 'spec') OR 'PSA') AND NOT ('ratio' OR '/' OR 'velocity' OR 'opm') PSAB Elevated when: age 40-49 < 2,5 µg/l age 50-59 < 3,5 µg/l age 60-69 < 4,5 µg/l age 70-79 < 6,5 µg/l	n.a.
Other cancers (T)	Classified as never (0) or ever (1) with the condition evaluated at any given time during the follow-up; Starting at 1 if condition exists at cohort entry, 0 otherwise.	Any other cancer	ICD-O-3 codes C00-C97 in the Finnish Cancer Registry	ICD-O-3, ICD-10 and ICD-7 diagnostic codes are availabe in cancer register since 1958	'A79' Malignancy NOS 'B72' Hodgkin's disease/lymphoma 'B73' Leukaemia 'B74' Mal. neopl. blood other 'D74' Mal. neopl. stomach 'D75' Mal. neopl. colon/rectum 'D76' Mal. neopl. pancreas 'D77' Malig. neoplasm digestive tract Other/NOS 'L71' Mal. neopl. musculoskeletal 'N74' Mal. neopl. nervous system 'R84' Mal. neopl. bronchus/lung 'R85' Mal. neopl. respiratory, other 'S77' Mal. neopl. of skin 'U75' Mal. neopl. of kidney 'U76' Mal. neopl. of bladder 'U77' Mal. neopl. urinary other 'W72' Mal. neopl. relate to pregnancy 'X75' Mal. neopl. cervix 'X76' Mal. neopl. breast female 'X77' Mal. neopl. genital other 'Y77' Mal. neopl. prostate 'Y78' Mal. neopl. male genital other OR 'carcino' OR 'metasta' OR 'kanker' OR 'lymfoom' OR 'lymfoma' OR 'neopl' OR 'lympho' OR 'leukemie' OR 'sarcoom' OR 'hodgkin' OR 'adenoma' OR 'adenoom' OR 'tumor' OR 'malign' OR 'mesothelioom' OR 'melanoom' EXCLUDE 'benign', OR 'goedaard'	140.xx-209.xx, E8792 Compl. radiol. verr./radiother. E9331 Ongew. gevolg ther.gebr. cytostaticum/immunosuppr. M8-M9 V07.2 Profylact. immunotherapie V07.3 Profylact. chemotherapie nec V15.3 Pers. anamn. bestraling V66.1 Reconvalescentie na radiotherapie V66.2 Reconvalescentie na chemotherapie V67.1 Follow-up onderzoek na radiotherapie V67.2 Follow-up onderzoek na chemotherapie V58.0 RADIOTHERAPY ENCOUNTER V58.1 Encounter for chemotherapy and immunotherapy for neoplastic conditions
Cardiovascular disease (T) (MI and STROKE Separated out from other cardiovascular disease)	Classified as never (0) or ever (1) with the condition evaluated at any given time during the follow-up; Starting at 1 if condition exists at cohort entry, 0 otherwise.		ICD-10 diagnostic codes: I10-I15 for hypertension, I20-I25 for coronary heart disease (I20-I21 for myocardial infarction) I60-I69 for cerebrovascular diseases in hospital care register (I63,I64,I69.3-I69.4 for stroke), or entitled for special reimbursement for chronic hypertension (refund category 205) chronic coronary disease (refund category 206) Divided into the next cells.	ICD-10 diagnotic codes: I00-I99 Excluding I21-I22, I241, I252, I63, I64, I693-I694, I73.9, I60-I89, I50, I110, I130, I132 (the codes for MI, stroke, vascular disaes and CHF)	K85 for Elevated blood pressure K74 for Ischaemic heart disease w. Angina K75 for Acute myocardial infarction K76 for Ischaemic heart disease w/o angina K89 for Transient cerebral ischaemia K90 for Stroke/cerebrovascular accident K91 for Cerebrovascular disease + text mining episodes for relevant terms K92 for Atherosclerosis/PVD K78 for Atrial fibrillation/flutter K79 for Paroxysmal tachycardia K80 for Cardiac arrhythmia NOS K81 for Heart/arterial murmur NOS K82 for Pulmonary heart disease K83 for Heart valve disease NOS K84 for Heart disease other K86 for Hypertension uncomplicated K87 for Hypertension complicated K88 for Postural hypotension K93 for Pulmonary embolism K94 for Phlebitis/thrombophlebitis K95 for Varicose veins of leg K96 for Haemorrhoids K99 for Cardiovascular disease other	401-405 HYPERTENSIVE DISEASE 410-414 ISCHEMIC HEART DISEASE 430-438 CEREBROVASCULAR DISEASE

MI or Stroke (F,T)	Classified as never (0) or ever (1) with the condition evaluated at any given time during the follow-up; Starting at 1 if condition exists at cohort entry, 0 otherwise.	ICD-10: I21-I22, I63-I64, I69.3-I69.4	ICD-10 diagnostic codes: I21-I22 for myocardial infarction I63,I64,I693-I694 for stroke	K75 for Acute myocardial infarction K90 for Stroke/cerebrovascular accident examination codes: 1693 HRINKQ episode of myocardial infarction 1636 CVAKQ stroke search episodes for: 'beroerte' OR 'CVA' OR 'herseninfarct' OR 'myocard' or 'hartaanval'	410 myocardial infarction, 412 Old myocardial infarction, 433 Occlusion and stenosis of precerebral arteries, 434 occlusion of cerebral arteries
Peripheral vascular disease (T)	Classified as never (0) or ever (1) with the condition evaluated at any given time during the follow-up; Starting at 1 if condition exists at cohort entry, 0 otherwise.	I73.9	I73.9	K92 for atherosclerosis/PVD	440, 443-445?
Other vascular disease (T)	Classified as never (0) or ever (1) with the condition evaluated at any given time during the follow-up; Starting at 1 if condition exists at cohort entry, 0 otherwise.	ICD-10: I10-I15, I20, I23-I25, I60-I62, I65-I68, I69.0-I69.2, I69.8 refund categories 205 and 206	I60-I69 (Excluding I63,I64,I693, I694) I70-I79 (Excluding I73.9) I80-I89	K85 for Elevated blood pressure K86 for Hypertension uncomplicated K87 for Hypertension complicated K74 for Ischaemic heart disease w. Angina K76 for Ischaemic heart disease w/o angina K89 for Transient cerebral ischaemia K91 for Cerebrovascular disease + text mining episodes for relevant terms	401-405 HYPERTENSIVE DISEASE 411, 413-414 ISCHEMIC HEART DISEASE (excluding MI) 430-432, 435-437 CEREBROVASCULAR DISEASE (excluding ischemic stroke)
CHF (F,T)	Classified as never (0) or ever (1) with the condition evaluated at any given time during the follow-up; Starting at 1 if condition exists at cohort entry, 0 otherwise.	ICD-10 diagnostic code I50 for chronic cardiac insufficiency or entitled for special reimbursement for chronic insufficiency (refund category 201)	ICD-10 diagnostic codes I50 in PAR	K77 Heart failure OR 1643 hartfalen (comorbiditeit) DECCKQ 1644 tekenen van hartfalen (anamnese) DETKKQ 2722 ernst klachten hartfalen ernstDecC DCERKQ 3016 hoofdbehandelaar hartfalen hfdbehdec DCHBAZ 3188 therapietrouw medicatie (hartfalen) DCTTKQ 3189 bijwerkingen medicatie (hartfalen) DCBMKQ 3190 aard bijwerking(en) medicatie(hartfalen) DCABKQ 3243 klachten en vragen patiënt (hartfalen) KLHFKQ 3244 aanvullende geg. anamn/onderz(hartfalen) HFOKQ 3245 evaluatie (hartfalen) HFEKZ 3246 medicatie (hartfalen) wijzigen HFMWKQ 3247 inschakelen zorg/verwijzing (hartfalen) HFVWKZ 3248 reden verwijzing (hartfalen) HFRVKZ 3249 termijn vervolgconsult (hartfalen) HFTVKZ 3250 vervolgconsult hartfalen bij HFVCKZ 3251 aanvullende gegevens plan (hartfalen) HFPEKZ 3256 vermoeidheid (anamnese hartfalen) VMHFKQ 3286 controlebeleid hartfalen HFCBKZ	428 Heart failure
COPD (T)	Classified as never (0) or ever (1) with the condition evaluated at any given time during the follow-up; Starting at 1 if condition exists at cohort entry, 0 otherwise.	ICD-10 diagnostic code J44 for chronic asthma and other chronic obstructive pulmonary diseases in hospital care register or Entitled for special reimbursement for chronic asthma and other chronic obstructive pulmonary disease (refund category 203) or Purchase record of anticholinergics medication (ATC code R03BB) in prescription register	ICD-10 diagnostic codes J44 in PAR and/or ATC code R03BB in PDR	R95 Enfyseem / COPD OR text mining lab/episodes 'gold' AND '1' or '2' or '3' or '4' or 'I' or 'II' or 'III' or 'IV' OR 'COPD' OR 'enfyseem' EXCLUDE: 'golden' 'gold' Use of anticholinergics medication(ATC code 'R03BB')	496 Chronic airway obstruction, not elsewhere classified Use of anticholinergics medication(ATC code 'R03BB')
Urinary incontinence (T)	Classified as never (0) or ever (1) with the condition evaluated at any given time during the follow-up; Starting at 1 if condition exists at cohort entry, 0 otherwise.	ICD-10 diagnostic code N39.3 for incontinence, N39.4 for other urinary incontinence, or R32 for unspesified urinary incontinence in hospital care register, or recorded purchase of urinary antispasmodics ATC code G04BD in presciption register	ICD-10 diagnostic codes N393, N394, R329 in PAR and/or ATC-code G04BD in PDR	"U04 incontinence urine + text mining episodes for 'incontinent' AND 'urine'" OR labcodes 3279 amount INCHUQB 3280 frequency frqincont INCFUQB 3281 Sandvik Severity Scale ScandvSS SNDVUQ	788.3 Urinary incontinence + pharmacy dispensings for incontinence material
Urinary tract infection (T)	Classified as never (0) or ever (1) with the condition evaluated at any given time during the follow-up; Starting at 1 if condition exists at cohort entry, 0 otherwise.	ICD-10 diagnostic code N39.0 in hospital care register	ICD-10 diagnostic codes N390 in PAR	"U71 Cystitis/urinary infection other, U72 Urethritis + use of antibiotics specific to UTI + text mining episodes for 'uti' OR 'uwi' OR 'urineweginfectie' OR labtests: Bacteria in urine: BACTU OR BATCUD OR BACTUSMM OR BACTUDMU OR URICUM OR BATCUD OR GRAMU Leukocytes in urine: LEUKUSMT OR LEUKU OR LEUKUSK OR LEUKUSMG OR LEUKUKW Nitrate in urine: NITRU OR NITRUSK"	599.0 Urinary tract infection, site not specified 595.0 Acute cystitis

Pyelonephritis (T)	Classified as never (0) or ever (1) with the condition evaluated at any given time during the follow-up; Starting at 1 if condition exists at cohort entry, 0 otherwise.	ICD-10 diagnostic code N10-N12 in hospital care register	ICD-10 diagnostic codes N10 - N12 in PAR	U70 Pyelonephritis/pyelitis text mining episodes for 'pyelone'	590.0 Chronic pyelonephritis 590.1 Acute pyelonephritis 590.3 Pyeloureteritis cystica 590.8 Other pyelonephritis or pyonephrosis, not specified as acute or chronic
Urolithiasis (T)	Classified as never (0) or ever (1) with the condition evaluated at any given time during the follow-up; Starting at 1 if condition exists at cohort entry, 0 otherwise.	ICD-10 diagnostic code N20-N23 in hospital care register	ICD-10 diagnostic codes N20 - N23 in PAR	U95 Urinary calculus text mining episodes for: (('blaas' OR 'nier' OR 'ureter') AND ('steen' OR 'stenen')) OR 'urolithiasis' OR 'nephrolithiasis' OR 'nefrolithiasis'	594 Calculus of lower urinary tract 594.0 Calculus in diverticulum of bladder 594.1 Other calculus in bladder 594.2 Calculus in urethra 594.8 Other lower urinary tract calculus 594.9 Calculus of lower urinary tract, unspecified 592 Calculus of kidney and ureter 592.0 Calculus of kidney 592.1 Calculus of ureter 592.9 Urinary calculus, unspecified
Hematuria (T)	Classified as never (0) or ever (1) with the condition evaluated at any given time during the follow-up; Starting at 1 if condition exists at cohort entry, 0 otherwise.	ICD-10 diagnostic code N02 or R31 in hospital care register	ICD-10 diagnostic codes N02, R319	U06 Haematuria examination codes: 2182 BLOEUSK bloed urine (stick) 294 ERYUSMT erytrocyten in urine sediment 292 ERYUSK erytrocyten urine 293 ERYUSMG erytrocyten urine pgv 413 HBU hemoglobine urine 414 HBUSK hemoglobine urine (stick) 751 OCCBU occult blood urine OR text mining episodes or 'hematuri' OR 'haematuri'	599.7 Hematuria
Urinary retention (T)	Classified as never (0) or ever (1) with the condition evaluated at any given time during the follow-up; Starting at 1 if condition exists at cohort entry, 0 otherwise.	ICD-10 diagnostic code R33 in hospital care register	ICD-10 diagnostic codes R339 in PAR	U05.02 urinary retention text mining episodes for 'LUTS' OR ('urine' AND 'retentie')	788.2 Retention of urine
Neurogenic bladder (T)	Classified as never (0) or ever (1) with the condition evaluated at any given time during the follow-up; Starting at 1 if condition exists at cohort entry, 0 otherwise.	ICD-10 diagnostic code N31.9 for neuromuscular dysfunction of bladder, unspecified, in hospital care register	ICD-10 diagnostic codes N31 in PAR	text mining episodes: 'neurogene blaas'	344.61 cauda equina syndrome with neurogenic bladder (596.54 not used in NL)
Catheterisation (T)	Classified as never (0) or ever (1) with the condition evaluated at any given time during the follow-up; Starting at 1 if condition exists at cohort entry, 0 otherwise.	NCSP code TKC20 for catheterization of bladder in hospital care register	NOMESCO procedure codes TKC20 in PAR	text mining episodes: 'catheter' AND 'blaas'	V53.6 Urinary devices - urinary catheter CvV code 8-13 catheterisation of bladder

CPRD GOLD **READ codes**	**CPRD Gold- HES linkage** **READ Codes** **ICD-10 Hospital codes** **OPCS4 Hospital codes**	**Include in meta analysis?**
Read codes specified in 01_Type1DM.txt	As CPRD GOLD plus ICD codes specified in 01_Type1Diabetes_ICD.txt	Y
Time since first recorded prescription of DM medication prior to cohort entry	As CPRD GOLD	Y
Read codes specified in 03_Diabetic_retinopathy.txt	As CPRD GOLD plus ICD10 codes specified in 03_DiabeticRetinopathy_ICD.txt	N
Read codes specified in 03_Diabetic_maculopathy.txt	As CPRD GOLD	N
SEE DEFINITIONS FOR Diabetic retinopathy and Diabetic maculopathy	SEE DEFINITIONS FOR Diabetic retinopathy and Diabetic maculopathy	Y

Read codes specified in 04_DiabeticNeuropathy.txt	As GOLD plus ICD10 codes specified in 04_DiabeticNeuropathy_ICD.txt	Y
Read codes specified in 18_CKD3_to_5.txt and ≥2 recorded eGFR ≤90mls/min/1.73m2, which had to be recorded at least 90 days, but not more than 365 days apart (calculated using serum creatinine values)	As GOLD plus ICD 10 codes specified in 18_CKD_ICD.txt and OPCS codes specified in 18_CKD_OPCS	Y
SEE DEFINITIONS FOR Proteinuria, microalbuminuria and diabetic nephropathy	SEE DEFINITIONS FOR Proteinuria, microalbuminuria and diabetic nephropathy	N

Read codes specified in 06_Proteinuria. Apply criteria to results related to Read codes specified in 06_Proteinuria_labs.txt. Apply criteria to values in GOLD Entity 287 (Urinalysis - Protein) and GOLD Entity 431 (Urine dipstick for protein)	As GOLD plus ICD10 codes specified in 06_Proteinuria_ICD.txt	N
Read codes specified in 07_Microalbuminuria.txt. Apply criteria to results related to Read codes specified in 07_Microalbuminuria_ACR_labs.txt. Apply criteria to values in GOLD Entity 166 (Creatinine clearance) and GOLD Entity 435 (Urine microalbumin).	As GOLD	N
SEE DEFINITIONS FOR Proteinuria and microalbuminuria	SEE DEFINITIONS FOR Proteinuria and microalbuminuria	Y

Read codes specified in 05_Diabetic_nephropathy.txt	As GOLD plus ICD10 codes specified in 05_Diabetic_nephropathy_ICD.txt	Y
Apply criteria to results related to Read codes specified in 08_SerumCreatinine.txt. Apply criteria to values in GOLD Entity 165 (Serum creatinine).	As GOLD	Y
Read codes specified in 09_Ketoacidosis.txt. GOLD Entity 432 (Urine dipstick for ketones) with positive values.	As GOLD plus ICD10 codes specified in 09_Ketoacidosis_ICD.txt	Y
Read codes specified in 10_Diabetic_coma.txt.	As GOLD plus ICD10 codes specified in 10_coma_ICD.txt	Y
Read codes specified in 11_Smoking_Jun2010_RBAG.txt. Product codes specified in 11_Smoking_Products.txt. GOLD Entity type 4 (smoking) - status (Y/N/X), cigarettes / cigars / ounces of tobacco per day, start and stop dates.	As GOLD	Y
Read codes specified in 12_BMI_Diagnosis.txt. Apply criteria to results related to Read codes specified in 12_BMI.txt. GOLD Entity type 13 (weight) - weight, BMI. GOLD Entity type 14 (height).	As GOLD	Y

Apply criteria to results related to Read codes specified in 13_hba1c.txt. Apply criteria to values in GOLD Entity 275.	As GOLD	Y
Apply criteria to results related to Read codes specified in 14_PSA.txt	As GOLD	Y
Read codes specified in 15_AllOtherCancers.txt.	As GOLD plus ICD10 codes specified in 15_AllOtherCA_ICD.txt	Y
Read codes specified in 16_AllCHDexceptHF.txt (or subset in 16_IHD_and_Stroke.txt). GOLD Entity type 16 (coronary heart disease register). GOLD Entity type 17 (stroke / TIA register). GOLD Entity type 57 (angina state) = yes.	As GOLD plus ICD10 codes specified in 16_AllCHDexceptHF_ICD.txt (or subset in 16_IHD_n_Stroke_ICD.txt). OPCS codes specified in 16_CHD_OPCS.txt	N

Read codes specified in 16a_MIorStroke.txt	As GOLD plus ICD10 codes specified in 16a_MIorStroke_ICD.txt	Y
Read codes specified in 16b_PVD.txt	As GOLD plus ICD10 codes specified in 16b_PVD_ICD.txt	Y
Read codes specified in 16c_othervasc.txt	As GOLD plus ICD10 codes specified in 16c_othervasc_ICD.txt	Y
Read codes specified in 17_CHF.txt	As GOLD plus ICD10 codes specified in 17_CHF_ICD.txt	Y
Read codes specified in 19_COPD.txt	As GOLD plus ICD10 codes specified in 19_COPD_ICD.txt	Y
Read codes specified in 20_UrinaryIncontinence.txt. GOLD Entity type 142 (continence - urinary) = no. Antispasmodics specified in UrinaryIncontinanceDrugs.txt	As GOLD plus ICD10 codes specified in 20_UrinaryIncontinence_ICD.txt.	Y
Read codes specified in 21_UrinaryTractInfection.txt. Apply criteria to results related to Read codes specified in 21_UrinaryTractInfection_labs.txt. Apply criteria to values in GOLD Entity 240 (Urine test) and GOLD Entity 357 (Urethral swab).	As GOLD plus ICD10 codes specified in 21_UrinaryTractInfection_ICD.txt	Y

Read codes specified in 22_Urinary_pyelonephritis.txt	As GOLD plus ICD10 codes specified in 22_Urinary_pyelonephritis_ICD.txt	Y
Read codes specified in 23_Urolithiasis.txt	As GOLD plus ICD10 codes specified in 23_Urolithiasis_ICD.txt.	Y
Read codes specified in 24_Urine_Haematuria.txt. Apply criteria to results related to Read codes specified in 25_Haematuria_labs.txt. Apply criteria to values in GOLD Entity 433 (Urine dipstick for blood)	As GOLD plus ICD10 codes specified in 24_Urine_Haematuria_ICD.txt	Y
Read codes specified in25_UrinaryRetention.txt.	As GOLD plus ICD10 codes specified in 25_UrineRetention_ICD.txt	Y
Read codes specified in 26_Neurogenic_Bladder.txt	As GOLD plus ICD10 codes specified in 26_Neurogenic_Bladder_ICD.txt	Y
Read codes specified in 27_Urine_catheter.txt	As GOLD plus ICD10 codes specified in 27_Urine_catheter_ICD. OPCS codes in 27_Urine_catheter_OPCS.txt	Y

Class	Active	Formulation	ATC code	CPRD comment
Ace inhibitors	ACE inhibitor	benazepril	C09AA07	Not in GOLD
Ace inhibitors	ACE inhibitor	captopril	C09AA01	ACEI.txt
Ace inhibitors	ACE inhibitor	cilazapril	C09AA08	ACEI.txt
Ace inhibitors	ACE inhibitor	delapril	C09AA12	Not in GOLD
Ace inhibitors	ACE inhibitor	enalapril	C09AA02	ACEI.txt
Ace inhibitors	ACE inhibitor	fosinopril	C09AA09	ACEI.txt
Ace inhibitors	ACE inhibitor	imidapril	C09AA16	ACEI.txt
Ace inhibitors	ACE inhibitor	lisinopril	C09AA03	ACEI.txt
Ace inhibitors	ACE inhibitor	moexipril	C09AA13	Not in GOLD
Ace inhibitors	ACE inhibitor	perindopril	C09AA04	ACEI.txt
Ace inhibitors	ACE inhibitor	quinapril	C09AA06	ACEI.txt
Ace inhibitors	ACE inhibitor	ramipril	C09AA05	ACEI.txt
Ace inhibitors	ACE inhibitor	spirapril	C09AA11	Not in GOLD
Ace inhibitors	ACE inhibitor	temocapril	C09AA14	Not in GOLD
Ace inhibitors	ACE inhibitor	trandolapril	C09AA10	ACEI.txt
Ace inhibitors	ACE inhibitor	zofenopril	C09AA15	Not in GOLD
Ace inhibitors	ACE inhibitor + calcium cl	delapril and manidipine	C09BB12	Not in GOLD
Ace inhibitors	ACE inhibitor + calcium cl	enalapril and lercanidipine	C09BB02	Not in GOLD
Ace inhibitors	ACE inhibitor + calcium cl	enalapril and nitrendipine	C09BB06	Not in GOLD
Ace inhibitors	ACE inhibitor + calcium cl	lisinopril and amlodipine	C09BB03	Not in GOLD
Ace inhibitors	ACE inhibitor + calcium cl	perindopril and amlodipine	C09BB04	Not in GOLD
Ace inhibitors	ACE inhibitor + calcium cl	ramipril and amlodipine	C09BB07	Not in GOLD
Ace inhibitors	ACE inhibitor + calcium cl	ramipril and felodipine	C09BB05	ACEI.txt
Ace inhibitors	ACE inhibitor + calcium cl	trandolapril and verapamil	C09BB10	ACEI.txt
Ace inhibitors	ACE inhibitor + diuretic	benazepril and diuretics	C09BA07	Not in GOLD
Ace inhibitors	ACE inhibitor + diuretic	captopril and diuretics	C09BA01	ACEI.txt
Ace inhibitors	ACE inhibitor + diuretic	cilazapril and diuretics	C09BA08	Not in GOLD
Ace inhibitors	ACE inhibitor + diuretic	delapril and diuretics	C09BA12	Not in GOLD
Ace inhibitors	ACE inhibitor + diuretic	enalapril and diuretics	C09BA02	ACEI.txt
Ace inhibitors	ACE inhibitor + diuretic	fosinopril and diuretics	C09BA09	Not in GOLD
Ace inhibitors	ACE inhibitor + diuretic	lisinopril and diuretics	C09BA03	ACEI.txt
Ace inhibitors	ACE inhibitor + diuretic	moexipril and diuretics	C09BA13	Not in GOLD
Ace inhibitors	ACE inhibitor + diuretic	perindopril and diuretics	C09BA04	ACEI.txt
Ace inhibitors	ACE inhibitor + diuretic	quinapril and diuretics	C09BA06	Not in GOLD
Ace inhibitors	ACE inhibitor + diuretic	ramipril and diuretics	C09BA05	Not in GOLD
Ace inhibitors	ACE inhibitor + diuretic	zofenopril and diuretics	C09BA15	Not in GOLD

Ace inhibitors	ACE inhibitor + statin	simvastatin, acetylsalicylic acid and ramipril	C10BX04	Not in GOLD
Angiotension receptor blocker	ARB	azilsartan medoxomil	C09CA09	ARB.txt
Angiotension receptor blocker	ARB	eprosartan	C09CA02	ARB.txt
Angiotension receptor blocker	ARB	irbesartan	C09CA04	ARB.txt
Angiotension receptor blocker	ARB	losartan	C09CA01	ARB.txt
Angiotension receptor blocker	ARB	olmesartan medoxomil	C09CA08	ARB.txt
Angiotension receptor blocker	ARB	tasosartan	C09CA05	Not in GOLD
Angiotension receptor blocker	ARB	telmisartan	C09CA07	ARB.txt
Angiotension receptor blocker	ARB	valsartan	C09CA03	ARB.txt
Angiotension receptor blocker	ARB	candesartan	C09CA06	ARB.txt
Angiotension receptor blocker	ARB + calcium channel bl	irbesartan and amlodipine	C09DB05	Not in GOLD
Angiotension receptor blocker	ARB + calcium channel bl	losartan and amlodipine	C09DB06	Not in GOLD
Angiotension receptor blocker	ARB + calcium channel bl	olmesartan medoxomil and amlodipine	C09DB02	ARB.txt
Angiotension receptor blocker	ARB + calcium channel bl	telmisartan and amlodipine	C09DB04	Not in GOLD
Angiotension receptor blocker	ARB + calcium channel bl	valsartan and amlodipine	C09DB01	ARB.txt
Angiotension receptor blocker	ARB + calcium channel bl	valsartan, amlodipine and hydrochlorothiazide	C09DX01	Not in GOLD
Angiotension receptor blocker	ARB + calcium channel bl	olmesartan medoxomil, amlodipine and hydrochlorothiazide	C09DX03	ARB.txt
Angiotension receptor blocker	ARB + diuretic	candesartan and diuretics	C09DA06	Not in GOLD
Angiotension receptor blocker	ARB + diuretic	eprosartan and diuretics	C09DA02	Not in GOLD
Angiotension receptor blocker	ARB + diuretic	irbesartan and diuretics	C09DA04	ARB.txt
Angiotension receptor blocker	ARB + diuretic	losartan and diuretics	C09DA01	ARB.txt
Angiotension receptor blocker	ARB + diuretic	olmesartan medoxomil and diuretics	C09DA08	ARB.txt
Angiotension receptor blocker	ARB + diuretic	telmisartan and diuretics	C09DA07	ARB.txt
Angiotension receptor blocker	ARB + diuretic	valsartan and diuretics	C09DA03	ARB.txt
Angiotension receptor blocker	ARB + renin inhibitor	valsartan and aliskiren	C09DX02	Not in GOLD
Angiotension receptor blocker	Renin Inhibitor	aliskiren	C09XA02	found in protocol
Angiotension receptor blocker	Renin Inhibitor	remiken	C09XA01	found in protocol
Angiotension receptor blocker	Renin Inhibitor + calcium	aliskiren and amlodipine	C09XA53	found in protocol
Angiotension receptor blocker	Renin Inhibitor+ calcium	aliskiren , amlopidine amd diuretic	C09XA54	found in protocol
Angiotension receptor blocker	Renin Inhibitors + diureti	aliskiren and diuretic	C09XA52	found in protocol
Anticolinergics	other obstructive airways drugs	aclidinium bromide	R03BB05	found in protocol
Anticolinergics	other obstructive airways drugs	glycopyrronium bromide	R03BB06	found in protocol
Anticolinergics	other obstructive airways drugs	ipratropium bromide	R03BB01	found in protocol

Anticolinergics	other obstructive airways drugs	oxitropium bromide	R03BB02	found in protocol
Anticolinergics	other obstructive airways drugs	stramoni preparations	R03BB03	found in protocol
Anticolinergics	other obstructive airways drugs	tiotropium bromide	R03BB04	found in protocol
BPH	5-DHT	dutasteride	G04CB02	BPH.txt
BPH	5-DHT	finasteride	G04CB01	BPH.txt
BPH	alpha blocker	alfuzosin	G04CA01	BPH.txt
BPH	alpha blocker	doxazosin	C02CA04	coded to HTN
BPH	alpha blocker	indoramin	C02CA02	coded to HTN
BPH	alpha blocker	prazosin	C02CA01	coded to HTN
BPH	alpha blocker	silodosin	G04CA04	Not in GOLD
BPH	alpha blocker	tamsulosin	G04CA02	BPH.txt
BPH	alpha blocker	terazosin	G04CA03	BPH.txt
BPH	alpha blocker	trimazosin	C02CA03	coded to HTN
BPH	alpha blocker	urapidil	C02CA06	coded to HTN
BPH	alpha blocker + 5-DHT	alfuzosin and finasteride	G04CA51	Not in GOLD
BPH	alpha blocker + 5-DHT	tamsulosin and dutasteride	G04CA52	BPH.txt
BPH	alpha blocker + LUTS	tamsulosin and solifenacin	G04CA53	Not in GOLD
BPH	other BPH drugs	meparrtricin	G04CX03	found in protocol
BPH	other BPH drugs	prunus africanae cortex	G04CX01	found in protocol
BPH	other BPH drugs	sabalis serrulatae fructus	G04CX02	found in protocol
HMG CoA reductase inhibitors	atorvastatin	atorvastatin	C10AA05	Statins.txt
HMG CoA reductase inhibitors	atorvastatin	atorvastatin and amlodipine	C10BX03	Not in GOLD
HMG CoA reductase inhibitors	atorvastatin	atorvastatin and ezetimibe	C10BA05	Not in GOLD
HMG CoA reductase inhibitors	cerivastatin	cerivastatin	C10AA06	Statins.txt
HMG CoA reductase inhibitors	fluvastatin	fluvastatin	C10AA04	Statins.txt
HMG CoA reductase inhibitors	lovastatin	lovastatin	C10AA02	Not in GOLD
HMG CoA reductase inhibitors	lovastatin	lovastatin and nicotinic acid	C10BA01	Not in GOLD
HMG CoA reductase inhibitors	pitavastatin	pitavastatin	C10AA08	Not in GOLD
HMG CoA reductase inhibitors	pravastatin	pravastatin	C10AA03	Statins.txt
HMG CoA reductase inhibitors	pravastatin	pravastatin and acetylsalicylic acid	C10BX02	Not in GOLD
HMG CoA reductase inhibitors	pravastatin	pravastatin and fenofibrate	C10BA03	Not in GOLD
HMG CoA reductase inhibitors	rosuvastatin	rosuvastatin	C10AA07	Statins.txt
HMG CoA reductase inhibitors	simvastatin	simvastatin	C10AA01	Statins.txt
HMG CoA reductase inhibitors	simvastatin	simvastatin and acetylsalicylic acid	C10BX01	Not in GOLD
HMG CoA reductase inhibitors	simvastatin	simvastatin and ezetimibe	C10BA02	Statins.txt

HMG CoA reductase inhibitors	simvastatin	simvastatin and fenofibrate	C10BA04	Not in GOLD
HMG CoA reductase inhibitors	simvastatin	simvastatin, acetylsalicylic acid and ramipril	C10BX04	Not in GOLD
HMG CoA reductase inhibitors	simvastatin	sitagliptin and simvastatin	A10BH51	Not in GOLD
urinary incontinance / frequency	LUTS	darifenacin	G04BD10	Urinary Incontinance Drugs.txt
urinary incontinance / frequency	LUTS	emepronium	G04BD01	Urinary Incontinance Drugs.txt
urinary incontinance / frequency	LUTS	fesoterodine	G04BD11	Urinary Incontinance Drugs.txt
urinary incontinance / frequency	LUTS	flavoxate	G04BD02	Urinary Incontinance Drugs.txt
urinary incontinance / frequency	LUTS	meladrazine	G04BD03	Not in GOLD
urinary incontinance / frequency	LUTS	mirabegron	G04BD12	Not in GOLD
urinary incontinance / frequency	LUTS	oxybutynin	G04BD04	Urinary Incontinance Drugs.txt
urinary incontinance / frequency	LUTS	propiverine	G04BD06	Not in GOLD
urinary incontinance / frequency	LUTS	solifenacin	G04BD08	Urinary Incontinance Drugs.txt
urinary incontinance / frequency	LUTS	terodiline	G04BD05	Urinary Incontinance Drugs.txt
urinary incontinance / frequency	LUTS	tolterodine	G04BD07	Urinary Incontinance Drugs.txt
urinary incontinance / frequency	LUTS	trospium	G04BD09	Urinary Incontinance Drugs.txt

NOTE: Further details of the definitions available on request.

Appendix 5: Criteria and process for sharing the analytical country specific datasets and meta-analysis dataset for third parties

The purpose of this document is to define clear criteria and process for any requests of sharing of the study data by third parties and has been written according to the Implementation Guidance for Sharing of ENCePP Study Data (http://encepp.eu/code_of_conduct/documents/Annex4_SharingData.pdf). The procedure describes various options which are needed to respect national requirements for data privacy and access and to avoid potential misuse of data.

Analytical dataset

The analytical dataset is defined as the dataset used in the statistical analyses leading to the results reported for the study. The analytical dataset is processed from the individual level raw data. A detailed description documenting the steps undertaken to transform the raw data into the analytical dataset is accompanied with the analytical dataset. Each participating centre fully controls the country specific analytical dataset(s).

Time restrictions

Sharing of the analytical dataset(s) may only be requested after the final study report is available. Participating centres will provide the possibility to request data sharing for five (5) years after the study ends.

Applicant

The applicant requesting data sharing must be clearly identifiable (name of individual, affiliation and contact details) and must agree to follow the transparency requirements of the ENCePP Code of Conduct, including provision of declarations of interest. The applicant must be qualified and competent to understand the data processing and underlying data structures with their possible limitations. The applicant should have a degree in epidemiology, biostatistics, statistics, medical sciences or similar, and relevant experience in the analysis of observational research.

Purpose for sharing study data

Requests for sharing study data must be made on specific grounds either

1. with the aim to corroborate the study results in the interest of Public Health,
2. to confirm compliance with the ENCePP Code of Conduct, e.g. to demonstrate that the audit trail established in line with the Code's requirements does allow corroboration of results, or
3. in the context of an audit by a competent authority.

Sufficient information needs to be provided to confirm that the request is made for one of the above-mentioned purposes, including a sound justification and, in case of a request with a view to corroborate study results, a protocol on the research for which the data will be used or a plan for quality control checks, as applicable .

The requests must be sent to the original researcher or to a relevant representative from the participating centres. In case the request concerns the meta-analysis dataset then the request must be sent to all original researchers at the same time.

The original researcher(s) from the participating centres may require the conclusion of a data sharing agreement with the applicant restricting the use of the shared data to one of the above-mentioned purposes and/or the protocol.

Possible options for sharing study data

On a case-by-case basis, original researchers from the participating centres may choose to reply to access requests in different ways which suffice to address the issue raised by the applicant and ensure full transparency. Some of the options do not involve sharing of data. The possible options to reply and fulfil the data sharing request include the following:

1. **Written response:** The original researcher provides a response in writing to the applicant addressing the issue based on which access is requested.
2. **Re-analysis by original researcher:** The original researcher provides the applicant with the outcome of additional data analyses to address the issue raised.
3. **Collaboration:** Both the applicant and the original researcher jointly investigate the issue raised.

4. **On-site access:** Analytical data are shared at the premises of the original researcher only, with or without having concluded a data sharing agreement.
5. **Analysis by an independent third person:** Post-hoc analyses are performed by an independent third person, e.g. statistician or other.
6. **Applicant to apply for access to relevant databases**: As the study datasets are arising from the use secondary data, it may be necessary for the applicant to directly apply for access to the relevant database in line with applicable license and governance rules.

Whenever there is disagreement between the applicant for access to data and the original researcher the matter should be referred to the ENCePP Steering Group who will act as an arbiter.

Compliance of research with shared data with ENCePP Code of Conduct transparency requirements

There is no guarantee that re-analysing the study data will produce results of a better quality than the original study. The outcome of the re-analysis should always be read in the context of the original results taking into account that it has been done post-hoc. In order for the applicant to meet the claimed purpose of improving Public Health, the research conducted with the shared data needs to be equally transparent as the original study. Therefore, any research or review conducted with the shared data should be compliant with the transparency requirements of the ENCePP Code of Conduct:

- Making available the study protocol for the re-analysis of the data including the statistical analysis plan. It is acceptable to include reference to the protocol of the relevant ENCePP study.
- Compliance with the Code's requirements of declarations of interests.
- Compliance with the Code's requirements as regards the recording and access to data and relevant steps throughout the research process and to take all possible steps to provide for audits by competent authorities.
- Making publicly available the results in line with ENCePP requirements. In particular, the origin of the data should be acknowledged in line with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals by the International Committee of Medical Journal Editors. In addition to the requirements of the Code the original researcher should be consulted before the publication of the results in order to enable him/her to provide comments.
- Registration in a publicly available register: Notwithstanding the general need to comply with the Code, the requirement for registration of the study in a publicly available register shall only apply if the additional research qualifies as a stand-alone study. In any event, information on post-hoc research with shared ENCePP study data including the study report and publications of the results should be linked to the original study in the ENCePP register of studies. To this end, it is the responsibility of the applicant for access to data to provide all relevant material to the original researchers or the ENCePP Secretariat who should add this information to the ENCePP study register.

Financial considerations

Original researchers from the participating centres may ask the applicant for compensation of the costs incurred for processing data sharing requests. The amount of the compensation has to be reasonable and will be communicated to the applicant prior to sharing the data.