APPENDIX 1. ANTIDIABETIC MEDICATIONS

Class	Drug	Formulations	ATC	CPRD GOLD & GOLD-HES
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	Pioglitazone.txt
other TZDs	troglitazone	troglitazone	A10BG01	GOLD Entity 26 (current
insulin	insulin (fast)	insulin (human)	A10AB01	diabetes status) = 2
insulin	insulin (fast)	insulin (beef)	A10AB02	"using insulin". GOLD
insulin	insulin (fast)	insulin (pork)	A10AB03	Entity 97 (insulin
insulin	insulin (fast)	insulin lispro	A10AB04	dosage) AND Insulin.txt
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.txt
Biguanides	phenformin	phenformin	A10BA01	
Biguanides	phenformin	phenformin and sulfonamides	A10BD01	
Biguanides	buformin	buformin	A10BA03	Not in GOLD
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	Sulfonylureas.txt
sulphonylureas	Sulfonamides, urea derivatives	carbutamide	A10BB06	Not in GOLD
sulphonylureas	Sulfonamides, urea derivatives	glipizide	A10BB07	
sulphonylureas	Sulfonamides, urea derivatives	gliquidone	A10BB08	
sulphonylureas	Sulfonamides, urea derivatives	gliclazide	A10BB09	Sulfonylureas.txt
sulphonylureas	Sulfonamides, urea derivatives	metahexamide	A10BB10	Not in GOLD
sulphonylureas	Sulfonamides, urea derivatives	glisoxepide	A10BB11	Not in GOLD
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	Sulfonylureas.txt
sulphonylureas	Sulfonamides, urea derivatives	phenformin and sulfonamides	A10BD01	Not in GOLD
sulphonylureas	Sulfonamides, urea derivatives	metformin and sulfonamides	A10BD02	

sulphonylureas	Sulfonamides, heterocyclic	glymidine	A10BC01	Sulfonylureas.txt
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	DDP4.txt
DDP-4 inhibitors	alogliptin	alogliptin	A10BH04	
DDP-4 inhibitors	alogliptin	metformin and alogliptin	A10BD13	Not in GOLD
DDP-4 inhibitors	alogliptin	pioglitazone and alogliptin	A10BD09	
DDP-4 inhibitors	linagliptin	linagliptin	A10BH05	
DDP-4 inhibitors	linagliptin	metformin and linagliptin	A10BD11	DDP4.txt
Alpha glucosidase inhibitors	acarbose	acarbose	A10BF01	AlphaglucosidaseI.txt
Alpha glucosidase inhibitors	miglitol	miglitol	A10BF02	
Alpha glucosidase inhibitors	voglibose	voglibose	A10BF03	Not in GOLD
GLP-1 agonists	exenatide	exenatide	A10BX04	
GLP-1 agonists	liraglutide	liraglutide	A10BX07	GLP1.txt
meglitinides	repaglinide	repaglinide	A10BX02	
meglitinides	nateglinide	nateglinide	A10BX03	Meglitanides.txt
meglitinides	mitiglinide	mitiglinide	A10BX08	Not in GOLD
amylin	pramlintide	pramlintide	A10BX05	Not in GOLD
others	benfluorex	benfluorex	A10BX06	Not in GOLD
others	guar gum	guar gum	A10BX01	OtherGuarGum.txt
others	dapagliflozin	dapagliflozin	A10BX09	Others.txt

NOTE: Further details of the definitions available on request.

Appendix 2: Calculation of exposure

Pooled Analysis Protocol & SAP, Version 1.0, 12 February 2014

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 non-insulin antidiabetic
Alpha glucosidase inhibitors	6	4 other non-insulin antidiabetic
GLP-1 agonists	7	4 other non-insulin antidiabetic
Meglitinides	8	4 other non-insulin antidiabetic
Amylin analogues	9	4 other non-insulin antidiabetic
Other oral antidiabetic	10	4 other non-insulin antidiabetic
Insulin	11	5

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

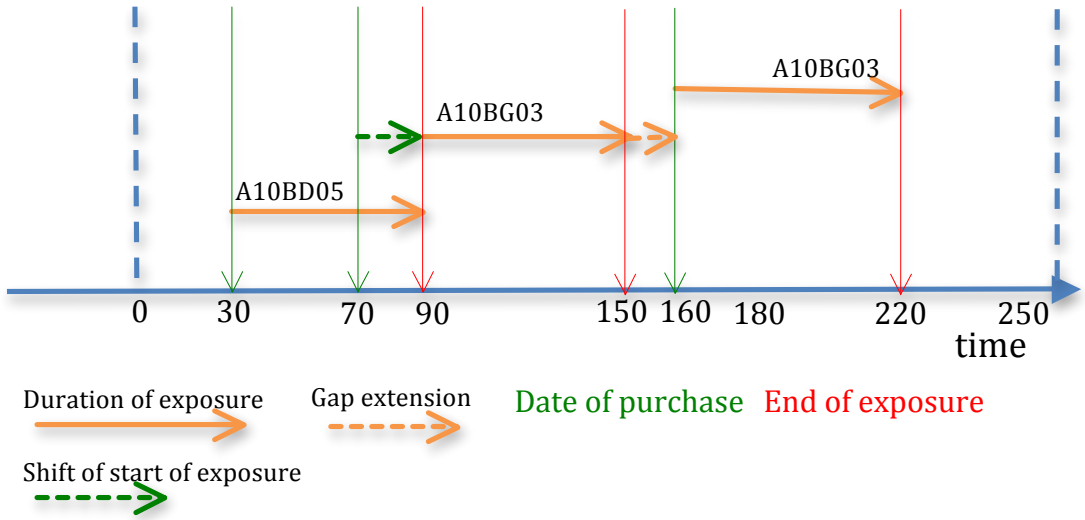
Drug exposure periods for diabetes drug groups

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.

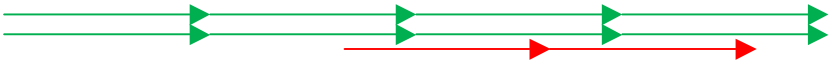
Combination therapy and switch/add-on definitions

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.

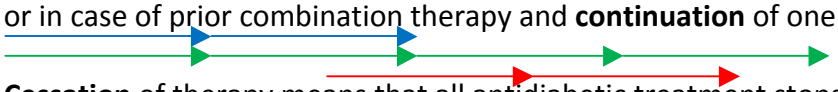
- **Add-on** to existing treatment. This is defined as a **continuation** of all previous antidiabetic treatment, with the addition of a **new drug** to this treatment.

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**	**CPRD GOLD** **READ codes**	**CPRD HES linkage** **ICD-10 Hospital codes** **OPCS4 Hospital codes**
end of follow-up		default 30 June 2011	default 30 June 2011	default 30 June 2011	default 30 June 2011	default 30 June 2011	default 30 June 2011	CPRD Gold to 30 June 2011 HES to 30 June 2011 Deaths 30 June 201 Ca reg 31 Dec 2010
secondary malignancy of bladder			C79.1 Secondary malignant neoplasm of bladder or other urinary site (excluding kidney & renal pelvis)	C79.1 Secondary malignant neoplasm of bladder or other urinary site (excluding kidney & renal pelvis)	U76 bladder cancer, mention of secondary tumor in free text	198.1 Secondary malignant neoplasm of other urinary organs (excluding kidney & renal pelvis)		C79.1 Secondary malignant neoplasm of bladder or other urinary site (excluding kidney & renal pelvis)
death		bladder cancer death is an endpoint, all other deaths are a censor	All deaths	All deaths	All deaths	all deaths	all deaths except bladder endpoints	all deaths except bladder endpoints
pt transfer-our			migration	migration	transfer-out	transfer out	transfer out (pt) in GOLD	transfer out (pt) in GOLD
end of GP practice coverage			n/a	n/a	Last GP collection date or exit date for patient	n/a	Last GP collection date in GOLD	Last GP collection date in GOLD
Rosiglitazone or Troglitazone			Start of other TZD on or after CED	Start of other TZD on or after CED	Start of other TZD on or after CED	Start of other TZD on or after CED	Start of other TZD on or after CED	Start of other TZD on or after CED

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	CPRD GOLD READ codes	CPRD HES linkage ICD-10 Hospital codes OPCS4 Hospital codes
Diabetic retinopathy or diabetic maculopathy (T)	Classified as never (0) or ever (1)	specific mention of diabetes required	hospital care register: H36.0 Diabetic retinopathy E11.3 T2DM with ophthalmic complications (code not used in Finland) E14.3 DM unspecified with ophthalmic complications (code not used in Finland)	PAR: H360 Diabetic retinopathy E113 Type 2 DM with ophthalmic complications E143 DM unspecified type with ophthalmic complicatons	F83.01 diabetic retinopathy (if decimals available) F83 retinopathy (if no decimals available, majority), but excluding any mention of hypertensive retinopathy examination codes: DMRPFALI 1652 (diabetic retinopathy left) = 1 DMRPFARE 1653 (diabetic retinopathy right) = 1 search episodes for - 'retinop' and 'diabet' - 'maculop' and 'diabet' -'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'	362.0 diabetic retinopathy 362.83 retinal oedema 250.5 Diabetes with ophthalmic manifestations	03_Diabetic_maculopathyANDretinopathy.txt	E11.3 Type2 MD with ophthalic complications E14.3 DM unspecified with ophthalmic complications H36.0 Diabetic retinopathy
Ketoacidosis (T)	Classified as never (0) or ever (1)	Excludes ketoacidotic with coma Note no specific ICD code for ketoacidosis without mention of diabetes. Acidosis is too broad.	hospital care register: E11.1 T2DM with ketoacidosis E14.1 DM unspecified with ketoacidosis	PAS: E111 T2DM with ketoacidosis E141 DM unspecified with ketoacidosis	"text mining episodes: 'ketoacid' exclude: 'coma' "	250.1 Diabetes with ketoacidosis	09_Ketoacidosis.txt. GOLD or Entity 432 (Urine dipstick for ketones) with positive values.	09_Ketoacidosis_ICD.txt
Diabetic coma (T)	Classified as never (0) or ever (1)	Includes diabetic and ketoacidotic coma, and hyperosmolarity	hospital care register: E11.0 T2DM with coma E14.0 DM unspecified with coma E87.0 Hyperosmolality and hypernatraemia	PAR: E110 T2DM with coma E140 DM unspecified with coma E87.0 Hyperosmolality and hypernatraemia	text mining episodes: 'coma' AND ('diab' or 'keto' or 'acidos' or 'hypoglyc' or 'hyperosmo')	250.3 Diabetes with other coma 250.2 Diabetes with hyperosmolarity	10_Diabetic_coma.txt.	10_coma_ICD.txt
Diabetic lower limb severe complications (T)	Classified as never (0) or ever (1)	limited to lower limb (toe, foot, ankle, lower leg, knee, upper leg). Includes: diabetic foot ulcer of lower limb, cellulitis and abscus of lower limb osteomyelitis of lower limb gangrene of lower limb, amputation of lower plus gengrene, site not specified, in 24 months prior to amputation	hospital care register: E11.5 type 2 DM with peripheral circulatory complications E14.5 DM unspecified with peripheral circulatory complications L97 Ulcer of lower limb R02 Gangrene, not elsewhere classified A48.0 Gas gangrene with: Z89.4 Acquired absence of foot and ankle Z89.5 Acquired absence of leg at or below knee Z89.6 Acquired absence of leg above knee Z89.7 Acquired absence of both lower limbs Z89.8 Acquired absence of upper and lower limbs	E11.5 type 2 DM with peripheral circulatory complications E14.5 DM unspecified with peripheral circulatory complications L97 Ulcer of lower limb R02 Gangrene, not elsewhere classified A48.0 Gas gangrene with: Z89.4 Acquired absence of foot and ankle Z89.5 Acquired absence of leg at or below knee Z89.6 Acquired absence of leg above knee Z89.7 Acquired absence of both lower limbs Z89.8 Acquired absence of upper and lower limbs	Free text search on: - foot necrosis - SIMMS classification >2 (1: neuropathy (NP) or peripheral vascular disease (PAD) 2 : NP + PAD or foot deformity, 3: Ulcus, or amputation) - gangrene - charcot foot - foot ulcer - peripheral artery disease (PAD) Examination codes: - 2203 doorgemaakt voetulcus ULCULV - 2196 risico voetulcera (SIMM's) RIVUSQ >2 - 1757 ulcera linkervoet ULCELVLI - 1758 ulcera rechtervoet ULCELVRE - 1593 amputatie linkervoet AMPULVLI - 1594 amputatie rechtervoet AMPULVRE	250.7 Diabetes with peripheral circulatory disorders 707.1 Ulcer of lower limbs 785.4 Gangrene (associated with extremities only) 040.0 Gas gangrene (associated with extremities only) 440.24 Atherosclerosis of the extremities with gangrene V49.7x Lower limb amputation status E878.5 Amputation of limb(s) Procedure codes (Dutch CvV classification) 5-845.x amputatie en exarticulatie teen 5-846.x amputatie en exarticulatie voet 5-897.16 debridement huidtranspl. benen in combination with above diagnostic ICD-9 codes or codes such as osteomyelitis, cellulitis of the lower extremities	04_footUlcer.txt 04_gangrene.txt with 04_footAmputation.txt	L97 Ulcer of lower limb R02 Gangrene, not elsewhere classified A48.0 Gas gangrene with: Z89.4 Acquired absence of foot and ankle Z89.5 Acquired absence of leg at or below knee Z89.6 Acquired absence of leg above knee Z89.7 Acquired absence of both lower limbs Z89.8 Acquired absence of upper and lower limb E11.5 type 2 DM with peripheral circulatory complications E14.5 DM unspecified with peripheral circulatory complications
Diabetic renal complications (T)	Classified as never (0) or ever (1)	Includes: diabetic nephropathy nephrotic syndrome glomerulosclerosis glomerulonephritis persistent proteinuria/macroalbuminuria CKD grade 3+ renal transplant renal dialyssis excludes: isolated proteinuria microalbuminuria	hospital care register: E11.2 type 2 DM with renal complications (not used in Finland) E14.2 DM unspecified with renal complications (not used in Finland) N02 Recurrent and persistent haematuria N04 Nephrotic syndrome N06.1 - N06.9 glumerulonephritis N08.3 Glomerular disorders in diabetes mellitus N18 chronic renal failure N19 Unspecified renal failure N39.1 Persistent proteinuria, unspecified N39.2 Orthostatic proteinuria, unspecified T82.4 Mechanical complication of vascular dialysis catheter T86.1 Kidney transplant failure and rejection Y60.2 During kidney dialysis or other perfusion Y61.2 During kidney dialysis or other perfusion Y62.2 During kidney dialysis or other perfusion Y84.1 Kidney dialysis Z49 Care involving dialysis Z99.2 Dependence on renal dialysis NOMESCO procedure codes DR015, DR016, DR023, DR055, DR056	E11.2 type 2 DM with renal complications E14.2 DM unspecified with renal complications N02 Recurrent and persistent haematuria N04 Nephrotic syndrome N06.1 - N06.9 glumerulonephritis N08.3 Glomerular disorders in diabetes mellitus N18 chronic renal failure N19 Unspecified renal failure N39.1 Persistent proteinuria, unspecified N39.2 Orthostatic proteinuria, unspecified T82.4 Mechanical complication of vascular dialysis catheter T86.1 Kidney transplant failure and rejection Y60.2 During kidney dialysis or other perfusion Y61.2 During kidney dialysis or other perfusion Y62.2 During kidney dialysis or other perfusion Y84.1 Kidney dialysis Z49 Care involving dialysis Z99.2 Dependence on renal dialysis NOMESCO procedure codes DR015, DR016, DR023, DR055, DR056	U88 glomerulonephritis / nephrosis U90 orthostatic albuminuria/proteinuria U98.01 proteinuria search episodes for: (('nier' OR 'renal') AND 'chron' AND (('insuf' OR 'falen') OR ('dialyse' OR 'transplant')) OR'nefropathie' OR 'nephropathie' OR 'nefrotisch syndroom' OR 'nephrotisch syndroom' OR 'glomerulone' OR 'nephrosis' OR 'nephrose' OR 'proteinurie' OR 'albuminurie')) 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 Diabetes with renal manifestations, 403 Hypertensive chronic kidney disease, 404 Hypertensive heart and chronic kidney disease, 581 Nephrotic syndrome 585 Chronic kidney disease (CKD) 588 Disorders resulting from impaired renal function, 593.6 Postural proteinuria 791.0 Proteinuria 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	06_renalcomlications_incl_persproteinuria	E11.2 type 2 DM with renal complications E14.2 DM unspecified with renal complications N02 Recurrent and persistent haematuria N04 Nephrotic syndrome N06.1 - N06.9 glumerulonephritis N08.3 Glomerular disorders in diabetes mellitus N18 chronic renal failure N19 Unspecified renal failure N39.1 Persistent proteinuria, unspecified N39.2 Orthostatic proteinuria, unspecified T82.4 Mechanical complication of vascular dialysis catheter T86.1 Kidney transplant failure and rejection Y60.2 During kidney dialysis or other perfusion Y61.2 During kidney dialysis or other perfusion Y62.2 During kidney dialysis or other perfusion Y84.1 Kidney dialysis Z49 Care involving dialysis Z99.2 Dependence on renal dialysis
Proteinuria/albuminuria test conducted within 12 months of failure/censoring (F)	part of labs algorithm		not applicable	not applicable	see below?	not applicable	06_proteinuriaTest	not applicable

Proteinuria/ macroalbuminuria test result within 12 months of failure/censoring (F)	0= Negative, trace or microalbuminuria 1=Positive. Macroalbuminuria, proteinuria 2= Not known or not tested see Proteinuria labs data (below)		not applicable	not applicable	see below?	not applicable	06_proteinuriaTestPos	not applicable
Proteinuria -Lab data within 12 months of failure/censoring (F)	part of labs algorithm	* 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 ** At least 1+ on protein dipstick	not applicable	not applicable	search episodes for 'albuminurie' 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	not applicable	not applicable	
MI or Stroke (T)	Classified as never (0) or ever (1)	exclude: 435 Transient cerebral ischaemia 436 Acute, ill defined cerebrovascular disease 437 Other ill defined cerebrovascular disease	hospital care register: I21-I22 for myocardial infarction I63,I64,I69.3-I69.4 for stroke	PAR: 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 'infarct' OR 'myocard' OR 'hartaanval' OR 'hersenbloeding'	410 myocardial infarction 412 Old myocardial infarction 430 Subarachnoid haemorrhage 431 Intracerebral haemorrhage 432 Other unspecified intracranial haemorrhage 433 Occlusion of pre-cerebral arteries 434 occlusion of cerebral arteries	16a_MIorStroke.txt	include 433 Occlusion of pre-cerebral arteries
CHF (T)	Classified as never (0) or ever (1)		hospital care register: I50 for chronic cardiac insufficiency I11.0 Hypertensive heart disease with CHF I13.0 Hypertensive heart and renal disease with CHF I13.2 Hypertensive heart and renal disease, with both CHF and renal fauilure or entitled for special reimbursement for chronic insufficiency (refund category 201)	PAR: I50 for chronic cardiac insufficiency I11.0 Hypertensive heart disease with CHF I13.0 Hypertensive heart and renal disease with CHF I13.2 Hypertensive heart and renal disease, with both CHF and renal fauilure	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 404.0 Hypertensive heart and CKD, malignant, with HF 404.1 Hypertensive heart and CKD, benign, with HF 404.9 Hypertensive heart and CKD, unspecified, with HF	17_CHF.txt	I11.0 Hypertensive heart disease with CHF I13.0 Hypertensive heart and renal disease with CHF I13.2 Hypertensive heart and renal disease, with both CHF and renal fauilure I50 Heart failure
Baseline Cigarette smoking (F)	Never vs. Ever vs. Unknown	Never vs Ever Never vs. Ex vs. Current	Not available	Smoker Y/N/missing from the diabets register	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	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
Baseline 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	Weight and height from the diabets register	examination code: QUETAO quetelet-index OR search lab for 'BMI' OR 'quetelet'	n.a.	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

Baseline HbA1C (F)	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 will be coded as 'missing'. HbA1C will also be measured as a time varingvarying variablecovariate, using the most recent HbA1C record at a point in time.	Not available	HbA1c from the diabets register	Examination codes: 2645 glycohemoglobine (HbA1c) confirmatietest GLHCB 368 glycohemoglobine (HbA1c) DCCT GLHBB (unit %) 2816 HbA1c (glycohemoglobine) IFCC HBACB (unit mmol/mol) 3266 HbA1c (glycohemoglobine) POC-meting HBAPB (Point of care) Examination text search for 'HbA1c'	n.a.	Apply criteria to results related to Read codes specified in 13_hba1c.txt. Apply criteria to values in GOLD Entity 275.	not applicable
PSA elevated within 12 months prior to CED (F)	0= Normal 1=Elevated 2= not evaluated or result not recorded NOTE: Closest PSA measurement within 12 months prior to CED used.	PSA 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	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')	Not available	Diagnostic code or PSA lab value	not applicable
Other urinary tract cancer		Kidney, renal pelvis, ureter, urethra.			U75 - Malignant neoplasm of kidney U77 - Malignant neoplasm urinary other free text search for 'nierkanker' OR ('kanker' AND 'urineweg') OR ('malig' AND 'urineweg') OR ('malig' AND 'nier') U75 Malignant neoplasm of kidney U76 Malignant neoplasm of bladder U77 Malignant neoplasm urinary other U78 Benign neoplasm urinary tract U79 Neoplasm urinary tract NOS Records in the GP journal text will be evaluated to complement the ICPC codes where they are filled in, to exclude ICPC coded neoplasms not pertaining to the bladder. Furthermore the GP journal text will be text mined for uncoded cases of bladder cancer, carcinoma in situ of the bladder and neoplasms of the bladder with uncertain or unspecified behaviour	189 Malignant neoplasm of kidney and other and unspecified urinary organs		
Other cancers, excluding urinary tract (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.	All malignant neoplasms except: Kidney, renal pelvis, ureter, urethra.	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 '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	Read codes specified in 15_AllOtherCancers.txt.	As GOLD plus ICD10 codes specified in 15_AllOtherCA_ICD.txt
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	443.9 Peripheral vascular disease, unspecified	Read codes specified in 16b_PVD.txt	As GOLD plus ICD10 codes specified in 16b_PVD_ICD.txt

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 Emphysema / 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')	Read codes specified in 19_COPD.txt	As GOLD plus ICD10 codes specified in 19_COPD_ICD.txt
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	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.
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	599.0 Urinary tract infection, site not specified 595.0 Acute cystitis	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
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	Read codes specified in 22_Urinary_pyelonephritis.txt	As GOLD plus ICD10 codes specified in 22_Urinary_pyelonephritis_ICD.txt
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.	kidney, renal pelvis, ureter, bladder or urethra stones	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	Read codes specified in 23_Urolithiasis.txt	As GOLD plus ICD10 codes specified in 23_Urolithiasis_ICD.txt.
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(.9) 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)	599.7 Hematuria	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
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(.9) 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	Read codes specified in25_UrinaryRetention.txt.	As GOLD plus ICD10 codes specified in 25_UrineRetention_ICD.txt
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)	Read codes specified in 26_Neurogenic_Bladder.txt	As GOLD plus ICD10 codes specified in 26_Neurogenic_Bladder_ICD.txt
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	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
Age at start of follow-up (T)	classified as 40-49; 50-59; 60-69; >=70	Age in completed years at start of follow-up						
Gender	0 - male / 1 - female							

Variable (F = fixed at CED, T = time dependent)	Classification	Comment	Finland	Sweden	PHARMO GP database	PHARMO hospital database	CPRD GOLD	CPRD HES linkage
Diabetic drug use after cohort entry (T)	Drug exposure as defined in Appendix 2 (Calculation of exposure). A separate variable for each of the following classes:metformin, sulphonylureas, other thiazolidinediones, alpha-glucosidase inhibitors, DPP-4 inhibitors, GLP-1 agonists, meglitinides, amylin analogues, insulins and other oral antidiabetic medications. Classified as never (0) or ever (1) use evaluated at any given time during the follow-up; Starting at 1 if prior use at cohort entry, 0 otherwise.	For other antidiabetic drug groups (than pioglitazone and insulin) we use only ever vs never definition						
Use of Statins after cohort entry (T)	Drug exposure defined as never vs ever	based on date of first prescription/purchase						
Use of ARB after cohort entry (T)	Drug exposure defined as never vs ever	based on date of first prescription/purchase						
Use of ACE after cohort entry (T)	Drug exposure defined as never vs ever	based on date of first prescription/purchase						
Use of BPH after cohort entry (T)	Drug exposure defined as never vs ever	based on date of first prescription/purchase						
Antidiabetic treatment at cohort entry date (F)	Categories: pioglitazone only pioglitazone +metformin pioglitazone + SU pioglitazone +metformin + SU pioglitazone + insulin pioglitazone +insulin + metformin pioglitazone +insulin + SU pioglitazone +insulin + other pioglitazone +other metformin only SU only metformin + SU insulin only insulin + metformin insulin + SU insulin + other other							
Type of treatment change at CED (F)	(1) add-on to prior treatment (2) add-on to no previous treatment (3) switch to monotherapy (4) switch to combination therapy	Used in summary tables						
Pioglitazone use after cohort entry	(T) Current use : 0 - No / 1 - Yes (T) Ever used : 0 - No / 1 - Yes (T) Duration of exposure : 0 - Never / 1 - <12 months / 2 - 12-24 months / 3 - >24 months (T) Cumulative dose : 0 - 1-10,500 mg / 1 - 10,501-28,000 mg / 3 - >28,000 mg (from KNPC tertiles) (T) Time since last dose : 0 - current / 1 - <1 yr / 2 - 1-2 yrs / 3 - 2-3 yrs / 4 - 3-4yrs / 5 - >4 yrs / 6 - never							
Insulin use after cohort entry	(T) Ever used : 0 - No / 1 - Yes (T) Cumulative duration of insulin: 0 - never / 1 - <yr / 2 - 1-<2 yrs / 3 - 2-<4 yrs / 4 - >=4 yrs							
Number of different antidiabetic drug classes prior to cohort entry (F)	Score from 0 to 10 with one point from each of the following classes used prior to cohort entry: metformin, sulphonylureas, other TDZs, alphaglucosidase inhibitors, DPP-4 inhibitors, GLP-1 agonists, meglitinides, amylin analogues, insulin, other oral antidiabetic drugs. Combination products contribute separately to each drug class based on the active substances included in the product.							

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	CPRD GOLD READ codes	CPRD HES linkage ICD-10 Hospital codes OPCS4 Hospital codes
Type 1 or other form of DM at cohort entry		Includes: T1DM gestational diabetes nutritional diabetes secondary diabetes neonatal diabtes	E08 DM due to underlying disease, E09 Drug or chemical induced DM E10 Type 1 DM E12 Malnutrition-related DM E13 Other specified DM O24.0 Pre-existing T1DM in pregnancy O24.2 Pre-existing malnutrition DM in pregnancy O24.4 Gestational diabetes P70.2 Neonatal DM	E08 DM due to underlying disease (code not used in Sweden) E09 Drug or chemical induced DM (code not used in Sweden) E10 Type 1 DM E12 Malnutrition-related DM, E13 Other specified DM, O24.0 Pre-existin T1DM in pregnancy O24.2 Pre-existing malnutrition DM in pregnancy O24.4 Gestational diabetes P70.2 Neonatal DM	T90.01, mention of: insulin dependent DM, drug induced DM, gestational DM, secondary diabetes mellitus malnutrition diabetes neonatal diabetes	250.x1 (x=0-9) Type 1 DM, juvenile onset DM 249 Secondary DM 648.8 Abnormal glucose tolerance of mother complicating pregnancy	01_Type1DM.txt	E08 DM due to underlying disease (code not used in UK) E09 Drug or chemical induced DM (code not used in UK) E10 Type 1 DM E12 Malnutrition-related DM, E13 Other specified DM, O24.0 Pre-existing T1DM in pregnancy O24.2 Pre-existing malnutrition DM in pregnancy O24.4 Gestational diabetes P70.2 Neonatal DM
History of bladder neoplasm		Includes : malignant neoplasm of bladder, carcinoma in situ of bladder, benign neoplasm of bladder, neoplasm of undertain or unknown behaviour of bladder,	C67 Malignant neoplasm of bladder C79.1 Secondary malignant neoplasm of bladder D09.0 Carcinoma in situ of the bladder D30.3 Benign neoplasm of bladder D41.4 Neoplasm of uncertain or unknown behaviour of bladder Z85.5 Personal history of malignany neoplasm of urinary tract	C67 Malignant neoplasm of bladder C79.1 Secondary malignant neoplasm of bladder D09.0 Carcinoma in situ of the bladder D30.3 Benign neoplasm of bladder D41.4 Neoplasm of uncertain or unknown behaviour of bladder Z85.5 Personal history of malignany neoplasm of urinary tract	U76 bladder cancer free text search for ('kanker' OR 'carcinoma' OR ('neopl' AND 'malign') OR ('neopl' AND 'in situ' AND 'malign')) AND 'blaas'	188 Malignant neoplasm of bladder 233.7 Carcinoma in situ of bladder 223.3 benign neoplasm of bladder 236.7 Neoplasm of uncertain behaviour of bladder 239.4 Neoplasm of unspecified nature of bladder V10.51 Personal hisory of malignant neoplasm of bladder Cvv codes: 32202 radiumimplantatie via cystostomie voor maligne blaastumor		C67 Malignant neoplasm of bladder C79.1 Secondary malignant neoplasm of bladder D09.0 Carcinoma in situ of the bladder D30.3 Benign neoplasm of bladder D41.4 Neoplasm of uncertain or unknown behavious of bladder Z85.5 Personal history of malignany neoplasm of urinary tract
History of cystectomy	surgical procedure	Partial or complete cystectomy	Not available		free text search 'cystectomie' OR 'resectie blaas'	Cvv codes 5575 partiële blaasresectie 5576 totale en radicale blaasresectie 5577 reconstructie blaas		
History of resection or removal of bladder tumour (benign or malignant)		includes resection, diathermy & laser removal	Not available		free text search 'resectie' AND 'blaas' AND ('kanker' OR 'tumor' OR 'neopl' or 'ca')	Cvv codes : 5573 transurethrale excisie of destructie aandoening blaas 5574 open excisie of destructie aandoening blaas		
History of biopsy of bladder tumour or lesion			Not available		free text search for 'blaas' AND 'biop'	Cvv codes : 1462x biopsie zonder incisie blaas		
History of secondary malignant neoplasm of bladder			C79.1 Secondary malignant neoplasm of bladder and other urinary organs (excluding kidney & renal pelvis)	C79.1 Secondary malignant neoplasm of bladder and other urinary organs (excluding kidney & renal pelvis)	U76 bladder cancer free text search for ('kanker' OR 'carcinoma' OR ('neopl' AND 'malign') OR ('neopl' AND 'in situ' AND 'malign')) AND 'blaas' AND 'secundair'	198.1 Secondary malignant neoplasm of other urinary organs (excluding kidney & renal pelvis)		C79.1 Secondary malignant neoplasm of bladder and other urinary organs (excluding kidney & renal pelvis)

Variable **F=Fixed at CED**	**Classification**	**Comment**	**Finland** **ICD-10**	**Sweden** **ICD-10**	**PHARMO GP database** **ICPC**	**PHARMO hospital database** **ICD-9**	**CPRD GOLD** **READ codes**	**CPRD HES linkage** **ICD-10 Hospital codes** **OPCS4 Hospital procedure codes**
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 from first purchase of DM medication in medication registry to cohort entry date	Time from first purchase of DM medication in medication registry to cohort entry	Time from first prescription of DM medication in GP record to cohort entry date. 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 dispensing of DM medication to cohort entry date	Time since first prescription of DM medication in CPRD GOLD to cohort entry	Time since first prescription of DM medication in CPRD GOLD to cohort entry
Diabetic retinopathy or diabetic maculopathy (F)	Classified as never (0) or ever (1) at cohort entry	specific mention of diabetes required	hospital care register: H36.0 Diabetic retinopathy E11.3 T2DM with ophthalmic complications (code not used in Finland) E14.3 DM unspecified with ophthalmic complications (code not used in Finland)	PAR: H360 Diabetic retinopathy E113 Type 2 DM with ophthalmic complications E143 DM unspecified type with ophthalmic complicatons	F83.01 diabetic retinopathy (if decimals available) F83 retinopathy (if no decimals available, majority), but excluding any mention of hypertensive retinopathy examination codes: DMRPFALI 1652 (diabetic retinopathy left) = 1 DMRPFARE 1653 (diabetic retinopathy right) = 1 search episodes for - 'retinop' and 'diabet' - 'maculop' and 'diabet' -'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'	362.0 diabetic retinopathy 362.83 retinal oedema 250.5 Diabetes with ophthalmic manifestations	03_Diabetic_maculopathyANDretinopathy.txt	E11.3 Type2 MD with ophthalic complications E14.3 DM unspecified with ophthalmic complications H36.0 Diabetic retinopathy
Ketoacidosis (F, T)	Classified as never (0) or ever (1) at cohort entry	Excludes ketoacidotic with coma Note no specific ICD code for ketoacidosis without mention of diabetes. Acidosis is too broad.	hospital care register: E11.1 T2DM with ketoacidosis E14.1 DM unspecified with ketoacidosis	PAR: E111 T2DM with ketoacidosis E141 DM unspecified with ketoacidosis	"text mining episodes: 'ketoacid' exclude: 'coma' "	250.1 Diabetes with ketoacidosis	09_Ketoacidosis.txt. GOLD or Entity 432 (Urine dipstick for ketones) with positive values.	09_Ketoacidosis_ICD.txt
Diabetic coma (F, T)	Classified as never (0) or ever (1) at cohort entry	Includes diabetic and ketoacidotic coma, and hyperosmolarity	hospital care register: E11.0 T2DM with coma E14.0 DM unspecified with coma E87.0 Hyperosmolality and hypernatraemia	PAR: E110 T2DM with coma E140 DM unspecified with coma E87.0 Hyperosmolality and hypernatraemia	text mining episodes: 'coma' AND ('diab' or 'keto' or 'acidos' or 'hypoglyc' or 'hyperosmo')	250.3 Diabetes with other coma 250.2 Diabetes with hyperosmolarity	10_Diabetic_coma.txt.	10_coma_ICD.txt
Diabetic lower limb severe complications (F)	Classified as never (0) or ever (1) at cohort entry	limited to lower limb (toe, foot, ankle, lower leg, knee, upper leg). Includes: diabetic foot ulcer of lower limb, cellulitis and abscus of lower limb osteomyelitis of lower limb gangrene of lower limb, amputation of lower plus gengrene, site not specified, in 24 months prior to amputation	hospital care register: E11.5 type 2 DM with peripheral circulatory complications E14.5 DM unspecified with peripheral circulatory complications L97 Ulcer of lower limb R02 Gangrene, not elsewhere classified A48.0 Gas gangrene with: Z89.4 Acquired absence of foot and ankle Z89.5 Acquired absence of leg at or below knee Z89.6 Acquired absence of leg above knee Z89.7 Acquired absence of both lower limbs Z89.8 Acquired absence of upper and lower limbs	E11.5 type 2 DM with peripheral circulatory complications E14.5 DM unspecified with peripheral circulatory complications L97 Ulcer of lower limb R02 Gangrene, not elsewhere classified A48.0 Gas gangrene with: Z89.4 Acquired absence of foot and ankle Z89.5 Acquired absence of leg at or below knee Z89.6 Acquired absence of leg above knee Z89.7 Acquired absence of both lower limbs Z89.8 Acquired absence of upper and lower limbs	Free text search on: - foot necrosis - SIMMS classification >2 (1: neuropathy (NP) or peripheral vascular disease (PAD) 2 : NP + PAD or foot deformity, 3: Ulcus, or amputation) - gangrene - charcot foot - foot ulcer - peripheral artery disease (PAD) Examination codes: - 2203 doorgemaakt voetulcus ULCULV - 2196 risico voetulcera (SIMM's) RIVUSQ >2 - 1757 ulcera linkervoet ULCELVLI - 1758 ulcera rechtervoet ULCELVRE - 1593 amputatie linkervoet AMPULVLI - 1594 amputatie rechtervoet AMPULVRE	250.7 Diabetes with peripheral circulatory disorders 707.1 Ulcer of lower limbs 785.4 Gangrene (associated with extremities only) 040.0 Gas gangrene (associated with extremities only) 440.24 Atherosclerosis of the extremities with gangrene V49.7x Lower limb amputation status E878.5 Amputation of limb(s) Procedure codes (Dutch CvV classification) 5-845.x amputatie en exarticulatie teen 5-846.x amputatie en exarticulatie voet 5-897.16 debridement huidtranspl. benen in combination with above diagnostic ICD-9 codes or codes such as osteomyelitis, cellulitis of the lower extremities	04_footUlcer.txt 04_gangrene.txt with 04_footAmputation.txt	L97 Ulcer of lower limb R02 Gangrene, not elsewhere classified A48.0 Gas gangrene with: Z89.4 Acquired absence of foot and ankle Z89.5 Acquired absence of leg at or below knee Z89.6 Acquired absence of leg above knee Z89.7 Acquired absence of both lower limbs Z89.8 Acquired absence of upper and lower limb E11.5 type 2 DM with peripheral circulatory complications E14.5 DM unspecified with peripheral circulatory complications
Diabetic renal complications (F)	Classified as never (0) or ever (1) at cohort entry	Includes: diabetic nephropathy nephrotic syndrome glomerulosclerosis glomerulonephritis persistent proteinuria/macroalbuminuria CKD grade 3+ renal transplant renal dialyssis excludes: isolated proteinuria microalbuminuria	hospital care register: E11.2 type 2 DM with renal complications (not used in Finland) E14.2 DM unspecified with renal complications (not used in Finland) N02 Recurrent and persistent haematuria N04 Nephrotic syndrome N06.1 - N06.9 glumerulonephritis N08.3 Glomerular disorders in diabetes mellitus N18 chronic renal failure N19 Unspecified renal failure N39.1 Persistent proteinuria, unspecified N39.2 Orthostatic proteinuria, unspecified T82.4 Mechanical complication of vascular dialysis catheter T86.1 Kidney transplant failure and rejection Y60.2 During kidney dialysis or other perfusion Y61.2 During kidney dialysis or other perfusion Y62.2 During kidney dialysis or other perfusion Y84.1 Kidney dialysis Z49 Care involving dialysis Z99.2 Dependence on renal dialysis NOMESCO procedure codes DR015, DR016, DR023, DR055, DR056	E11.2 type 2 DM with renal complications E14.2 DM unspecified with renal complications N02 Recurrent and persistent haematuria N04 Nephrotic syndrome N06.1 - N06.9 glumerulonephritis N08.3 Glomerular disorders in diabetes mellitus N18 chronic renal failure N19 Unspecified renal failure N39.1 Persistent proteinuria, unspecified N39.2 Orthostatic proteinuria, unspecified T82.4 Mechanical complication of vascular dialysis catheter T86.1 Kidney transplant failure and rejection Y60.2 During kidney dialysis or other perfusion Y61.2 During kidney dialysis or other perfusion Y62.2 During kidney dialysis or other perfusion Y84.1 Kidney dialysis Z49 Care involving dialysis Z99.2 Dependence on renal dialysis NOMESCO procedure codes DR015, DR016, DR023, DR055, DR056	U88 glomerulonephritis / nephrosis U90 orthostatic albuminuria/proteinuria U98.01 proteinuria search episodes for: (('nier' OR 'renal') AND 'chron' AND (('insuf' OR 'falen') OR ('dialyse' OR 'transplant')) OR'nefropathie' OR 'nephropathie' OR 'nefrotisch syndroom' OR 'nephrotisch syndroom' OR 'glomerulone' OR 'nephrosis' OR 'nephrose' OR 'proteinurie' OR 'albuminurie')) 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 Diabetes with renal manifestations, 403 Hypertensive chronic kidney disease, 404 Hypertensive heart and chronic kidney disease, 581 Nephrotic syndrome 585 Chronic kidney disease (CKD) 588 Disorders resulting from impaired renal function, 593.6 Postural proteinuria 791.0 Proteinuria 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	06_renalcomlications_incl_persproteinuria	E11.2 type 2 DM with renal complications E14.2 DM unspecified with renal complications N02 Recurrent and persistent haematuria N04 Nephrotic syndrome N06.1 - N06.9 glumerulonephritis N08.3 Glomerular disorders in diabetes mellitus N18 chronic renal failure N19 Unspecified renal failure N39.1 Persistent proteinuria, unspecified N39.2 Orthostatic proteinuria, unspecified T82.4 Mechanical complication of vascular dialysis catheter T86.1 Kidney transplant failure and rejection Y60.2 During kidney dialysis or other perfusion Y61.2 During kidney dialysis or other perfusion Y62.2 During kidney dialysis or other perfusion Y84.1 Kidney dialysis Z49 Care involving dialysis Z99.2 Dependence on renal dialysis

Proteinuria/albuminuria test conducted	part of labs algorithm		not applicable	not applicable	test codes as in proteinuria	not applicable	06_proteinuriaTest	not applicable
Proteinuria/macroalbuminuria positive	part of labs algorithm	excludes: test result = unknown test result = trace excludes: isolated microalbuminuria persistent microalbuminuria	not applicable	Som information on micro- and macroalbuminuria from the diabetesregister: Y/N/missing	test codes as in proteinuria, test results as in comment column	not applicable	06_proteinuriaTestPos	not applicable
Proteinuria/macroalbuminuria test negative	part of labs algorithm	excludes: test result unknown Includes: test result = trace includes: isolated microalbuminuria isolated proteinuria persistent microalbuminuria	not applicable	Som information on micro- and macroalbuminuria from the diabetesregister: Y/N/missing	test codes as in proteinuria, test result < comment column	not applicable	06_proteinuriaTestNeg	not applicable
Proteinuria -Lab data	part of labs algorithm	* 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 ** At least 1+ on protein dipstick	not applicable	not applicable	search episodes for 'albuminurie' 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	not applicable	not applicable	
MI or Stroke (F,T)	Classified as never (0) or ever (1) at cohort entry	exclude: 435 Transient cerebral ischaemia 436 Acute, ill defined cerebrovascular disease 437 Other ill defined cerebrovascular disease	hospital care register: I21 - I22 for MI I63, I64, I69.3, I69.4 for stroke	PAR: 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 'infarct' OR 'myocard' OR 'hartaanval' OR 'hersenbloeding'	410 myocardial infarction 412 Old myocardial infarction 430 Subarachnoid haemorrhage 431 Intracerebral haemorrhage 432 Other unspecified intracranial haemorrhage 433 Occlusion of pre-cerebral arteries 434 occlusion of cerebral arteries	16a_MIorStroke.txt	include 433 Occlusion of pre-cerebral arteries
CHF (F,T)	Classified as never (0) or ever (1) at cohort entry		hospital care register: I50 for chronic cardiac insufficiency I11.0 Hypertensive heart disease with CHF I13.0 Hypertensive heart and renal disease with CHF I13.2 Hypertensive heart and renal disease, with both CHF and renal fauilure or entitled for special reimbursement for chronic insufficiency (refund category 201)	PAR: I50 for chronic cardiac insufficiency I11.0 Hypertensive heart disease with CHF I13.0 Hypertensive heart and renal disease with CHF I13.2 Hypertensive heart and renal disease, with both CHF and renal fauilure	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 404.0 Hypertensive heart and CKD, malignant, with HF 404.1 Hypertensive heart and CKD, benign, with HF 404.9 Hypertensive heart and CKD, unspecified, with HF	17_CHF.txt	I11.0 Hypertensive heart disease with CHF I13.0 Hypertensive heart and renal disease with CHF I13.2 Hypertensive heart and renal disease, with both CHF and renal fauilure I50 Heart failure
Year of cohort entry (F)	Calendar year of cohort entry	Calendar years						

Duration of database membership before cohort entry (F)	Duration (years) of membership in medication database prior to cohort entry.	Categories: 0-<2 / 2-<4 / 4-<6 / 6-<8 / 8-<10 / >=10						
Number of different antidiabetic drug classes prior to cohort entry (F)	Score from 0 to 10 with one point from each of the following classes used prior to cohort entry: metformin, sulphonylureas, other TDZs, alphaglucosidase inhibitors, DPP-4 inhibitors, GLP-1 agonists, meglitinides, amylin analogues, insulin, other non-insulin antidiabetic. Combination products contribute separately to each drug class based on the active substances included in the product.	As numeric variable						
Use of other TDZs prior to cohort entry (F)	Use of other thiazolidinediones (other than pioglitazone) prior to cohort entry (N/Y)							
Type of antidiabetic treatment prior to cohort entry (F)	Type of antidiabetic medication immediately prior to cohort entry classified as: • No pharmacotherapy • Metformin only • Sulphonylurea only • Metformin + sulphonylureas only • Insulin with or without other antidiabetic medications • Any other antidiabetic medications or combinations							
Type of modification in baseline therapy (F)	Type of modification in baseline antidiabetic therapy at cohort entry classified into two classes: treatment switch (1) or addition of new treatment (2) to all prior treatment (if any existed). See Appendix 2.							
Geographical area (F)	Living in geographical area for which cancer data are available (Y/N, used in the Netherlands only)							

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	CPRD GOLD READ codes	CPRD HES linkage ICD-10 Hospital codes OPCS4 Hospital codes
Primary endpoint		Data soures for cancer ascertainment Fin: Cancer registry only Swe: Cancer registry only PHARMO GP: GP record or (cancer registry or hospital record, where available) PHARMO Hosp: hospital data or (cancer registry, where available) CPRD GOLD: GP record only CPRD GOLD + HES: GP record or cancer registry or hospital record or cause of death	C67 Malignant neoplasm of bladder D09.0 Carcinoma in situ of the bladder	C67 Malignant neoplasm of bladder D09.0 Carcinoma in situ of the bladder	U76 bladder cancer free text search for ('kanker' OR 'carcinoma' OR ('neopl' AND 'malign') OR ('neopl' AND 'in situ' AND 'malign')) AND 'blaas'	188 Malignany neoplasm of bladder 233.7 Carcinoma in situ of bladder		C67 Malignant neoplasm of bladder D09.0 Carcinoma in situ of the bladder
sensivity endpoints			C67 Malignant neoplasm of bladder D09.0 Carcinoma in situ of the bladder D41.4 Neoplasm of uncertain or unknown behavious of bladder	C67 Malignant neoplasm of bladder D09.0 Carcinoma in situ of the bladder D41.4 Neoplasm of uncertain or unknown behavious of bladder	U76 bladder cancer free text search for ('kanker' OR 'carcinoma' OR ('neopl' AND 'malign') OR ('tumor' AND 'malign') OR ('neopl' AND 'in situ' AND 'malign')) AND 'blaas' OR ('neopl' OR 'tumor' OR 'in situ') AND 'blaas' AND (('?' and 'malign') OR ('?' AND 'kanker') OR ('?' AND 'invasief'))	188 Malignany neoplasm of bladder 233.7 Carcinoma in situ of bladder 236.7 Neoplasm of uncertain behaviour of bladder 239.4 Neoplasm of unspecified nature of bladder		C67 Malignant neoplasm of bladder D09.0 Carcinoma in situ of the bladder D41.4 Neoplasm of uncertain or unknown behavious of bladder

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.

1 PAN EUROPEAN MULTI-DATABASE BLADDER CANCER RISK CHARACTERISATION STUDY: LIST OF PLANNED ANALYSES

1.1 Population summary

The following summary tables will be constructed based on available study variables. For the matched population the tables will be stratified according to pioglitazone never/ever exposure.

Summary	Description	* Non-matched population	Matched population	Include in pooled analysis
1	Flowchart of patient selection		X	
1	Patient general characteristics at cohort entry	X	X	X
2	Patient clinical characteristics at cohort entry (Smoking, BMI, HBA1c)	X	X	X
3	Antidiabetic and other treatment characteristics before and at cohort entry	X	X	X
4	Treatment changes at cohort entry	X	X	
5	History of diabetic complications, other comorbidities and bladder comorbidities before cohort entry	X	X	X
6	Patient characteristics before censoring		X	X
7	Pioglitazone exposure before censoring (all definitions)		X	X
8	History of diabetic complications, other comorbidities and bladder comorbidities before censoring		X	X

* Based on all potential cohort entry points

1.2 Descriptive analysis

Crude bladder cancer incidence, bladder cancer mortality, and all-cause mortality rates with 95% confidence intervals (CI) will be estimated for each pioglitazone exposure definition separately within the following strata

Analysis	Strata	Notes	Country if specific	Include in pooled analysis
1	Gender			X
2	Age			X
3	Year of cohort entry			X
4	Smoking		UK & NL & (SWE)	Only pool 3
5	BMI at CED		UK & NL & (SWE)	Only pool 3
6	HBA1c		UK & NL & (SWE)	Only pool 3
7	Duration of treated diabetes mellitus			X
8	Previous antidiabetic treatment			X
9	History of diabetic complications	7 separate strata. Protocol Table		X
10	History of bladder comorbidities	8 separate strata		X
11	History of other relevant comorbidities	6 separate strata		X
12	History of other relevant medications	5 separate strata		X

1.3 Formal Analysis

The hazard ratio (HR) estimates with 95% CIs for pioglitazone exposure will be estimated using the Cox's proportional hazards model for the following analyses.

Analysis	Bladder cancer inc.	Bladder cancer mort.	All-cause mort.	Pio-exposure	Crude/base/ adjusted	Notes	Country if specific	Include in Meta
PRIMARY ANALYSIS								
1	X	X	X	Never/ever	Crude			X
2	X	X	X	Never/ever	Base			X
3	X	X	X	Never/ever	Adjusted	This model is used to choose covariates		X
4	X	X	X	Duration of	Crude	cut points as		X

				exposure		KNPC 10 year		
5	X	X	X	Duration of exposure	Base	cut points as KNPC 10 year		X
6	X	X	X	Duration of exposure	Adjusted	cut points as KNPC 10 year		X
7	X	X	X	Cumulative dose	Crude	cut points as KNPC 10 year		X
8	X	X	X	Cumulative dose	Base	cut points as KNPC 10 year		X
9	X	X	X	Cumulative dose	Adjusted	cut points as KNPC 10 year		X
10	X	X	X	Time since last dose	Crude			X
11	X	X	X	Time since last dose	Base			X
12	X	X	X	Time since last dose	Adjusted			X
SECONDARY ANALYSIS								
13	X	X	X	Duration of exposure	Adjusted	cut points as KNPC 5 year		X
14	X	X	X	Cumulative dose	Adjusted	cut points as KNPC 5 year		X

1.4 Stratified analysis

The hazard ratio (HR) estimates with 95% CIs for pioglitazone exposure will be estimated using the Cox's proportional hazards model for the following analyses.

1	X	X	X	Never/ever	Adjusted	Stratified by duration of treated diabetes at CED		X
2	X	X	X	Never/ever	Adjusted	Use of other TZDs prior to CED		X
3	X	X	X	Never/ever	Adjusted	History of diabetic renal complications at CED		X

1.5 Sensitivity analysis

The hazard ratio (HR) estimates with 95% CIs for pioglitazone exposure will be estimated using the Cox's proportional hazards model for the following analyses.

1	X			Never/ever	Adjusted	Incidence density sampling only if >2.5% have no match		
2	X			Never/ever	Adjusted	Exclusion of bladder cancers occurring within 12 after CED		
3	X			Never/ever	Adjusted	Exclude adenocarcinomas and squamous cell carcinomas		
4	X			Never/ever	Adjusted	Censor follow-up if prescription gap >4 months	FIN & SWE	
5	X			Never/ever	Adjusted	Impact of adjusting for smoking	NL & UK	
6	X			Never/ever	Adjusted	Impact of adjusting for BMI	NL & UK	
7	X			Never/ever	Adjusted	Impact of adjusting for HBA1c	NL & UK	
8	X			Never/ever	Adjusted	Use of first smoking entry after CED	NL & UK	
9	X			Never/ever	Adjusted	Use of first BMI entry after CED	NL & UK	
10	X			Never/ever	Adjusted	Incident vs. prevalent	NL & UK	
11	X			Never/ever	Adjusted	Insulin as cumulative duration		
12	X			Never/ever	Adjusted	Pioglitazone group at least two prescriptions within 6 months		
13	X			Never/ever	Adjusted	Inclusion of neoplasm of uncertain or unknown behavior. Only if		

						5% increase in bladder cancer event count.		

1.6 Model assumption checks

The hazard ratio (HR) estimates with 95% CIs for pioglitazone exposure will be estimated using the Cox's proportional hazards model for the following analyses.

Analysis	Bladder cancer inc.	Bladder cancer mort.	All-cause mort.	Pio-exposure	Crude/base/ adjusted	Notes	Country if specific	Include in pooled
1	X	X	X	Never/ ever	Adjusted	Include time dependent variables: Age x log(time), Gender x log(time), Never/ever x log(time)		

1.7 Bladder cancer description

The following bladder cancer summaries (number of cases) will be presented at time of diagnose

Summary	Description	Strata	Notes	Country if specific	Include in pooled analysis
1	Age and gender	Ever vs never pioglitazone exposure			
3	Tumor staging	Ever vs never pioglitazone exposure	Based on available information (e.g. morphology code 5th digit, TNM coding)		
4	Tumor grade and differation	Ever vs never pioglitazone exposure	Based on available information (e.g. morphology code 6th digit, TNM coding)		
5	Bladder cancer cases	Duration of pioglitazone exposure			
6	Bladder cancer cases	Cumulative dose of pioglitazone			

7	Bladder cancer cases	Time since last pioglitazone exposure			
8	Bladder cancer cases	Ever vs never insulin exposure			
9	Bladder cancer cases	Duration of insulin exposure			
10-13	Bladder cancer distribution	Ever vs. never exposure of other diabetic treatments	Separately for groups metformin, sulphonylureas and "other oral diabetic" treatments		

1.8 Figures: Kaplan-Meier Curves

	Outcome	**Groups**	**Notes**	
1	All-cause mortality	Ever vs. never exposed to pioglitazone	With or without bladder cancer. T_0 = cohort entry	X
2.	All-cause mortality within patients diagnosed with bladder cancer	Ever vs. never exposed to pioglitazone	T_0 = diagnosis of bladder cancer	X
3	Bladder cancer morality	Ever vs. never exposed to pioglitazone	With or without bladder cancer. T_0 = cohort entry	X
4	Bladder cancer mortality within patients diagnosed with bladder cancer	Ever vs. never exposed to pioglitazone	T_0 = diagnosis of bladder cancer	X