

Supplementary appendix

Indholdsfortegnelse

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S1 Text: Prisma-Checklist

'The effects of adding angiotensin receptor neprilysin inhibitors to usual care in patients with heart failure – a protocol for a systematic review of randomised clinical trials with meta-analysis and Trial Sequential Analysis'

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	<input type="checkbox"/>	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Support					
Sources	5a	Indicate sources of financial or other support for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Sponsor	5b	Provide name for the review funder and/or sponsor	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e.,	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
		screening, eligibility, and inclusion in meta-analysis)			
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2 , Kendall's tau)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

S2 Text: Search strategies

Search strategy for MEDLINE and EMBASE

1. (ARNI or angiotensin receptor neprilysin inhibitor or angiotensin receptor neprilysin blocker).af.
2. (entrest* or LCZ696 or LCZ-696).af
3. (sacubitril* or AHU377 or neprilysin).af.
4. 1 or 2 or 3
5. (random* or placebo* or randomised clinical trial* or trial* or meta-analys* or meta analys* or blind*).af.
6. 4 and 5

Search strategy for CNKI

(SU=('沙卡布曲'+ '沙库巴曲'+ '沙库比曲'+ '沙库必曲'+ '塞克比曲'+ '萨库比尔')* '缬沙坦' OR
SU='ARNI'+ 'entresto'+ 'LCZ-696'+ 'LCZ696'+ 'AHU377'+ ('sacubitril'* 'valsartan')+'诺欣妥') and SU='心衰'+ '心力衰竭'+
心脏衰竭'+ '心功能不全'+ '心脏功能不全'+ '心脏失代偿'+ '心脏代偿失调' and SU='RCT'+ '随机'+ '对照'+ '安慰剂'+ '盲
'+'盲法'

Search strategy for VIP,

R=((沙卡布曲 OR 沙库巴曲 OR 沙库比曲 OR 沙库必曲 OR 塞克比曲 OR 萨库比尔) AND 缬沙坦) OR (ARNI OR
entresto OR LCZ-696 OR LCZ696 OR AHU377 OR (sacubitril AND valsartan) OR 诺欣妥) AND R=(心衰 OR 心力衰竭 OR
心脏衰竭 OR 心功能不全 OR 心脏功能不全 OR 心脏失代偿 OR 心脏代偿失调) AND R=(RCT OR 随机 OR 对照 OR 安
慰剂 OR 盲 OR 盲法)

S1 Table: Serious Adverse events

	Serious adverse events	Event: Sacubitril/valsartan	Total: Sacubitril/valsartan	Event: Control	Total: Control
Blood and lymphatic disorders	Anaemia	34	4662	48	4691
	Anemia Macrocytic	1	4203	0	4229
	Anaemia of malignant disease	1	4203	0	4229
	Autoimmune haemolytic anaemia	1	4203	0	4229
	Coagulopathy	3	4203	2	4229
	Disseminated intravascular coagulation	0	4203	1	4229
	Haemorrhagic anaemia	2	4203	3	4229
	Harmorrhagic disorder	0	4203	1	4229
	Hypochromic anaemia	1	4203	0	4229
	Immune thrombocytopenic purpura	0	4203	1	4229
	Iron deficiency anaemia	0	4203	1	4229
	Leukocytosis	1	4203	1	4229
	Leukopenia	1	4203	1	4229
	Lymphadenopathy	1	4203	0	4229
	Microcytic anaemia	1	4203	0	4229
	Nephrogenic anaemia	1	4203	0	4229
	Neutropenia	0	4203	1	4229
	Normochromic normocytic anaemia	2	4203	2	4229
	Pancytopenia	1	4203	1	4229
	Pernicious anaemia	0	4203	1	4229
Spontaneous haematoma	0	4203	1	4229	
Thrombocytopenia	4	4203	4	4229	
Cardiac disorders	Acute coronary syndrome	18	4513	19	4539
	Acute left ventricular failure	4	4203	5	4229
	Acute myocardial infarction	70	4662	69	4691
	Adams-stokes syndrome	1	4203	0	4229
	Angina pectoris	58	4732	65	4761
	Angina unstable	56	4352	52	4381
	Aortic valve incompetence	3	4203	4	4229
	Aortic valve stenosis	0	4203	4	4229
	Arrhythmia	23	4203	21	4229
	Arrhythmia supraventricular	0	4203	1	4229

Arteriosclerosis coronary artery	4	4203	4	4229
Arteriospasm coronary	0	4203	1	4229
Atrial fibrillation	113	4662	116	4691
Atrial flutter	11	4513	19	4539
Atrial tachycardia	7	4203	1	4229
Atrioventricular block	2	4352	6	4381
Atrioventricular block complete	13	4203	10	4229
Atrioventricular block first degree	1	4203	0	4229
Atrioventricular block second degree	6	4203	5	4229
Atrioventricular dissociation	1	4203	0	4229
Bradycardia	12	4352	13	4381
Bradyarrhythmia	4	4352	4	4381
Bradycardia	12	4352	13	4381
Bundle branch block left	2	4203	3	4229
Bundle branch block left	0	4203	1	4229
Cardiac aneurysm	1	4203	1	4229
Cardiac arrest	30	4513	58	4539
Cardiac asthma	2	4203	3	4229
Cardiac discomfort	1	4203	3	4229
Cardiac disorder	1	4203	1	4229
Cardiac failure	598	4662	662	4691
Cardiac failure acute	68	4352	96	4381
Cardiac failure chronic	112	4203	135	4229
Cardiac failure congestive	113	4732	142	4761
Cardiac fibrillation	0	4203	1	4229
Cardiac hypertrophy	1	4203	0	4229
Cardiac perforatoin	1	4203	0	4229
Cardiac tamponade	0	4203	2	4229
Cardiac valve disease	0	4203	2	4229
Cardiac ventricular thrombosis	3	4203	3	4229
Cardio-respiratory arrest	25	4352	28	4381
Cardiogenic shock	19	4352	39	4381
Cardiomegaly	2	4203	5	4229
Cardiomyopathy	6	4203	10	4229
Cardiopulmonary failure	7	4203	13	4229
Cardiorenal syndrome	2	4203	2	4229
Cardiovascular disorder	1	4203	1	4229
Cardiovascular insufficiency	1	4203	1	4229
Chordae tendinae rupture	0	4203	1	4229
Congestive cardiomyopathy	13	4203	29	4229
Cor pulmonale	0	4203	1	4229
Coronary artery disease	36	4513	38	4539
Coronary artery occlusion	2	4203	1	4229
Coronary artery stenosis	5	4352	8	4381

Coronary artery thrombosis	1	4203	1	4229
Defect conduction intraventricular	1	4203	0	4229
Dilatation atrial	0	4203	1	4229
Dilatation ventricular	1	4203	0	4229
Gastrocardiac syndrome	0	4203	1	4229
Hypertensive cardiomyopathy	1	4203	0	4229
Hypertensive heart disease	1	4203	2	4229
Ischaemic cardiomyopathy	5	4273	15	4299
Left ventricular dysfunction	6	4203	6	4229
Left ventricular failure	9	4203	2	4229
Low cardiac output syndrome	2	4203	2	4229
Mitral valve disease	1	4203	2	4229
Mitral valve disease mixed	0	4203	1	4229
Mitral valve incompetence	10	4203	13	4229
Myocardial infarction	66	4662	73	4691
Myocardial ischaemia	20	4203	29	4229
Myocarditis	0	4203	1	4229
Nodal arrhythmia	1	4203	1	4229
Nodal rhythm	0	4203	1	4229
Palpitations	4	4352	8	4381
Percutaneous coronary intervention	1	0	0	0
Pericardial effusion	1	4203	1	4229
Pulseless electrical activity	1	4203	1	4229
Right ventricular dysfunction	1	4203	0	4229
Right ventricular failure	0	4203	4	4229
Sick sinus syndrome	10	4352	10	4381
Silent myocardial infarction	1	4203	0	4229
Sinus bradycardia	2	4203	3	4229
Sinus tachycardia	2	4203	2	4229
Supraventricular tachycardia	9	4203	9	4229
Systolic dysfunction	0	4203	1	4229
Tachyarrhythmia	0	4352	4	4381
Tachycardia	2	4513	6	4539
Torsade de pointes	0	4203	1	4229
Tricuspid valve incompetence	0	4203	2	4229
Trifascicular block	0	4203	1	4229
Ventricular arrhythmia	5	4513	12	4539
Ventricular dysfunction	0	4203	1	4229
Ventricular dyssynchrony	1	4203	0	4229
Ventricular extrasystoles	6	4203	4	4229
Ventricular fibrillation	23	4513	29	4539
Ventricular flutter	0	4203	1	4229
Ventricular hypokinesia	0	4203	1	4229

	Ventricular tachyarrhythmia	1	4203	0	4229
	Ventricular tachycardia	66	4203	85	4229
Congenital, familial and genetic disorders	Cryptorchism	1	4203	0	4229
	Exomphalos	0	4203	1	4229
	Gastrointestinal arteriovenous malformation	0	4203	1	4229
	Homocystinaemia	0	4203	1	4229
	Hydrocele	2	4203	0	4229
	Hypertrophic cardiomyopathy	2	4203	1	4229
	Sickle cell anaemia with crisis	0	4203	1	4229
Ear and labyrinth disorders	Acute vestibular syndrome	1	4203	0	4229
	Deafness neurosensory	1	4203	0	4229
	Deafness unilateral	0	4203	1	4229
	Ear haemorrhage	1	4203	0	4229
	Mastoid disorder	1	4203	0	4229
	Tinnitus	2	4203	0	4229
	Vertigo	6	4352	9	4381
	Vertigo positional	0	4203	1	4229
Endocrine disorders	Autoimmune thyroiditis	1	4203	0	4229
	Goitre	0	4203	1	4229
	Hyperthyroidism	3	4203	3	4229
	Hypothyroidism	1	4203	4	4229
	Thyroiditis subacute	0	4203	1	4229
Eye disorders	Amaurosis fugax	1	4203	0	4229
	Blindness unilateral	0	4203	1	4229
	Cataract	12	4203	8	4229
	Cataract diabetic	0	4203	1	4229
	Conjunctival haemorrhage	0	4203	1	4229
	Diabetic retinopathy	2	4203	1	4229
	Diplopia	0	4203	1	4229
	Glaucoma	1	4203	0	4229
	Macular oedema	0	4203	1	4229
	Retinal artery embolism	0	4203	1	4229
	Retinal detachment	0	4203	2	4229
	Retinal haemorrhage	1	4203	0	4229
	Trichiasis	0	4203	1	4229
	Vision blurred	2	4203	0	4229
	Vitreous haemorrhage	0	4203	2	4229
Gastrointestinal disorders	Abdominal adhesions	1	4203	0	4229
	Abdominal compartment syndrome	0	4203	1	4229
	Abdominal discomfort	1	4203	0	4229
	Abdominal distension	4	4203	3	4229
	Abdominal hernia	1	4203	1	4229
	Abdominal pain	15	4513	24	4539
	Abdominal pain upper	6	4203	7	4229

Abdominal wall haematoma	0	4203	1	4229
Acute abdomen	1	4203	3	4229
Anal fissure	2	4203	1	4229
Anal fistula	2	4203	0	4229
Anal haemorrhage	0	4203	2	4229
Anorectal discomfort	0	4203	1	4229
Ascites	6	4352	6	4381
Colitis	0	4203	3	4229
Colitis ischaemic	1	4203	4	4229
Colitis ulcerative	1	4203	1	4229
Constipation	3	4203	5	4229
Crohn's disease	1	4203	0	4229
Dental caries	0	4203	1	4229
Diarrhoea	23	4352	15	4381
Diarrhoea haemorrhagic	0	149	1	152
Diverticulum	3	4203	0	4229
Diverticulum intestinal	1	4203	2	4229
Duodenal stenosis	1	4203	0	4229
Duodenal ulcer	3	4352	9	4381
Duodenal ulcer haemorrhage	1	4203	3	4229
Duodenal ulcer perforation	1	4203	0	4229
Duodenitis	1	4203	0	4229
Dyspepsia	3	4203	4	4229
Dysphagia	1	4203	1	4229
Enteritis	3	4203	2	4229
Enterovesical fistula	0	4203	1	4229
Erosive duodenitis	1	4203	0	4229
Erosive oesophagitis	0	4203	3	4229
Faecal incontinence	0	4203	1	4229
Faecaloma	2	4203	0	4229
Femoral hernia	1	4203	0	4229
Gastric haemorrhage	1	4513	3	4539
Gastric hypomobility	0	4203	1	4229
Gastric perforation	1	4203	2	4229
Gastric polyps	0	4203	3	4229
Gastric ulcer	3	4203	3	4229
Gastric ulcer haemorrhage	0	4352	4	4381
Gastritis	7	4352	11	4381
Gastritis erosive	1	4352	3	4381
Gastritis haemorrhagic	0	4203	3	4229
Gastroduodenal haemorrhage	3	4203	3	4229
Gastroduodenitis	0	4203	1	4229
Gastrointestinal disorder	1	4203	1	4229
Gastrointestinal haemorrhage	22	4203	22	4229
Gastrointestinal necrosis	0	4203	1	4229

Gastrointestinal obstruction	0	4203	1	4229
Gastrointestinal ulcer	1	4203	0	4229
Gastroesophageal reflux disease	4	4203	6	4229
Haematemesis	2	4203	3	4229
Haematochezia	1	4203	1	4229
Haemorrhagic erosive gastritis	1	4203	2	4229
Haemorrhoidal haemorrhage	2	4203	1	4229
Haemorrhoids	4	4203	2	4229
Hiatus hernia	2	4203	3	4229
Hyperchlorhydria	1	4203	0	4229
Ileus	5	4352	3	4381
Ileus paralytic	0	4203	1	4229
Impaired gastric emptying	1	4203	0	4229
Inguinal hernia	11	4513	18	4539
Inguinal hernia strangulated	1	4203	2	4229
Inguinal hernia, obstructive	2	4203	3	4229
Intestinal haemorrhage	1	4203	0	4229
Intestinal ischaemic	5	4203	1	4229
Intestinal obstruction	4	4203	5	4229
Intestinal perforation	1	4513	3	4539
Intestinal polyp	0	4203	1	4229
Intra-abdominal haemorrhage	0	4203	1	4229
Large intestinal haemorrhage	0	4203	1	4229
Large intestine perforation	1	4203	0	4229
Large intestine polyp	5	4203	2	4229
Lip oedema	0	4203	1	4229
Lower gastrointestinal haemorrhage	0	4203	1	4229
Mallory-Weiss syndrome	0	4203	2	4229
Melaena	3	4352	6	4381
Mouth haemorrhage	1	4203	2	4229
Nausea	6	4203	6	4229
Obstruction gastric	1	4203	0	4229
Oesophageal achalasia	1	4203	0	4229
Oesophageal ulcer	0	4203	1	4229
Oesophageal ulcer haemorrhage	0	4203	1	4229
Oesophagitis	1	4203	1	4229
Pancreatitis	2	4203	8	4229
Pancreatitis acute	7	4203	4	4229
Pancreatitis chronic	1	4203	0	4229
Parotid duct obstruction	0	4203	2	4229
Parotid gland enlargement	0	4203	1	4229

	Peptic ulcer	2	4203	1	4229
	Peptic ulcer perforation	1	4203	0	4229
	Portal hypertensive gastropathy	0	4203	2	4229
	Proctalgia	1	4203	0	4229
	Rectal haemorrhage	8	4203	3	4229
	Rectal polyp	2	4203	1	4229
	Rectal prolapse	1	4203	0	4229
	Rectal stenosis	0	4203	1	4229
	Retroperitoneal haematoma	1	4203	0	4229
	Retroperitoneal haemorrhage	1	4203	0	4229
	Small intestinal obstruction	3	4203	3	4229
	Stomatitis	0	4203	1	4229
	Subileus	0	4203	1	4229
	Toothache	2	4203	1	4229
	Umbilical hernia	0	4203	6	4229
	Umbilical hernia, obstructive	2	4203	1	4229
	Upper gastrointestinal haemorrhage	9	4203	6	4229
	Urogenital haemorrhage	1	310	0	310
	Varices oesophageal	1	4203	1	4229
	Vomiting	10	4203	14	4229
General disorders	Accidental death	2	4203	0	4229
	Asthenia	11	4352	9	4381
	Cardiac complication associated with device	1	4203	1	4229
	Cardiac death	85	4203	114	4229
	Chest discomfort	4	4352	1	4381
	Chest pain	4	4273	4	4299
	Chills	0	4203	1	4229
	Concomitant disease aggravated	1	4203	0	4229
	Death	56	4203	78	4229
	Device battery issue	11	4203	8	4229
	Device breakage	1	4203	0	4229
	Device dislocation	3	4203	3	4229
	Device failure	6	4203	5	4229
	Device issue	1	4203	2	4229
	Device lead damage	2	4203	1	4229
	Device leakage	0	4203	1	4229
	Device malfunction	15	4352	12	4381
	Device occlusion	1	4203	2	4229
	Device stimulation issue	0	4203	1	4229
	Disease progression	1	4203	0	4229
	Drowning	0	4203	1	4229
	Euthanasia	1	4203	0	4229

	Exercise tolerance decreased	1	4203	1	4229
	Fatigue	1	4203	10	4229
	Gait disturbance	0	4203	1	4229
	General physical health deterioration	2	4203	3	4229
	Generalised oedema	0	4203	1	4229
	Hernia	1	4203	1	4229
	Hernia obstructive	0	4203	1	4229
	Hyperthermia	1	4203	0	4229
	Impaired healing	1	4203	1	4229
	Implant site haematoma	0	4203	1	4229
	Implant site inflammation	1	4203	0	4229
	Implant site reaction	1	4203	0	4229
	Implant site ulcer	1	4203	1	4229
	Inflammation	1	4203	0	4229
	Local swelling	0	4203	3	4229
	Malaise	4	4203	2	4229
	Medical device complication	5	4203	1	4229
	Medical device pain	0	4203	3	4229
	Medical device site reaction	0	4203	1	4229
	Multi-organ disorder	1	4203	0	4229
	Multi-organ failure	14	4203	15	4229
	Necrosis	1	4203	1	4229
	Non-cardiac chest pain	34	4352	37	4381
	Oedema	0	4203	1	4229
	Oedema due to cardiac disease	1	4203	0	4229
	Oedema peripheral	11	4352	15	4381
	Pacemaker generated arrhythmia	0	4203	1	4229
	Perforated ulcer	0	4203	1	4229
	Pyrexia	9	4662	16	4691
	Sudden cardiac death	67	4203	69	4229
	Sudden death	66	4203	78	4229
	Temperature regulation disorder	0	4203	1	4229
Vessel puncture site haematoma	1	4203	0	4229	
Vessel puncture site haemorrhage	0	4203	1	4229	
Hepatobiliary disorders	Acute hepatic failure	1	4203	0	4229
	Bile duct stone	4	4203	3	4229
	Biliary colic	0	4203	2	4229
	Biliary dilatation	2	4203	0	4229
	Cardiac cirrhosis	1	4203	1	4229
	Cholangitis	2	4203	1	4229
	Cholangitis acute	4	4203	0	4229

	Cholecystitis	5	4203	8	4229	
	Cholecystitis acute	12	4203	13	4229	
	Cholecystitis chronic	3	4203	1	4229	
	Cholelithiasis	11	4352	17	4381	
	Cholestasis	0	4203	2	4229	
	Gallbladder perforation	0	4203	1	4229	
	Hepatic cirrhosis	3	4203	5	4229	
	Hepatic congestion	0	4203	3	4229	
	Hepatic failure	5	4203	4	4229	
	Hepatic function abnormal	3	4203	2	4229	
	Hepatic ischaemia	1	4203	0	4229	
	Hepatic steatosis	3	4203	1	4229	
	Hepatitis	2	4203	1	4229	
	Hepatitis acute	1	4203	0	4229	
	Hepatitis toxic	0	4203	1	4229	
	Hepatocellular injury	0	4203	1	4229	
	Hepatomegaly	0	4203	2	4229	
	Hepatorenal syndrome	0	4203	1	4229	
	Hepatotoxicity	1	4203	0	4229	
	Hydrocholecystis	1	4203	1	4229	
	Hyperbilirubinaemia	0	4203	2	4229	
	Ischaemic hepatitis	0	4203	2	4229	
	Jaundice	5	4203	0	4229	
	Jaundice cholestatic	1	4203	1	4229	
	Liver disorder	0	4203	2	4229	
	Liver injury	1	4203	2	4229	
	Portal hypertension	0	4203	1	4229	
	Portal vein thrombosis	1	4203	0	4229	
	Immune system disorders	Allergy to arthropod sting	1	4203	0	4229
		Anaphylactic reaction	2	4203	0	4229
Anaphylactic shock		1	4203	1	4229	
Drug hypersensitivity		1	4203	5	4229	
Hypersensitivity		2	4203	0	4229	
Sarcoidosis		2	4203	0	4229	
Infectious diseases	Abdominal abscess	0	4203	1	4229	
	Abdominal wall abscess	0	4203	1	4229	
	Abdominal wall infection	1	4203	0	4229	
	Abscess limb	1	4203	1	4229	
	Abscess neck	1	4203	2	4229	
	Abscess oral	0	4203	1	4229	
	Acinetobacter bacteraemia	0	4203	1	4229	
	Acinetobacter infection	0	4203	1	4229	
	Acute endocarditis	2	4203	2	4229	
	Acute tonsillitis	0	4203	1	4229	
	American trypanosomiasis	0	4203	1	4229	
	Anal abscess	1	4203	3	4229	
	Appendicitis	5	4352	7	4381	
	Appendicitis perforated	2	4203	1	4229	

Arthritis bacterial	1	4203	0	4229
Arthritis infective	1	4203	2	4229
Atypical pneumonia	2	4203	1	4229
Bacteraemia	2	4203	0	4229
Bacterial diarrhoea	0	4203	1	4229
Bacterial infection	0	4203	1	4229
Bacterial prostatitis	0	4203	1	4229
Bacterial sepsis	0	4352	2	4381
Bacterial tracheitis	0	4203	1	4229
Bacteriuria	0	4203	1	4229
Biliary sepsis	2	4203	1	4229
Breast cellulitis	1	4203	0	4229
Bronchiolitis	1	4203	0	4229
Bronchitis	20	4352	27	4381
Bronchitis bacterial	1	4203	1	4229
Bronchitis fungal	1	4203	0	4229
Bronchitis viral	1	4203	1	4229
Bronchopneumonia	21	4203	14	4229
Campylobacter gastroenteritis	1	4203	1	4229
Carbuncle	0	4203	1	4229
Cellulitis	19	4203	23	4229
Cellulitis staphylococcal	0	4203	1	4229
Cholecystitis infective	2	4203	0	4229
Chronic hepatitis B	0	4203	1	4229
Clostridial infection	0	4203	1	4229
Clostridium difficile colitis	3	4203	2	4229
Clostridium difficile infection	0	4203	3	4229
Cystitis	1	4203	5	4229
Cytomegalovirus infection	0	4203	1	4229
Dacryocanalculitis	0	4203	1	4229
Dermatophytosis	0	4203	1	4229
Device related infection	10	4203	11	4229
Device related sepsis	0	4203	1	4229
Diabetic foot infection	2	4203	1	4229
Diabetic gangrene	2	4203	0	4229
Diarrhoea infectious	1	4203	1	4229
Disseminated tuberculosis	1	4203	0	4229
Diverticulitis	2	4513	4	4539
Empyema	0	4203	1	4229
Encephalitis	0	4203	1	4229
Encephalitis viral	1	4203	0	4229
Endocarditis	5	4352	8	4381
Endocarditis bacterial	1	4203	0	4229
Epididymitis	2	4513	0	4539
Erysipelas	10	4203	11	4229
Escherichia sepsis	1	4203	0	4229

Escherichia urinary tract infection	0	4203	2	4229
Gallbladder abscess	0	4203	1	4229
Gangrene	8	4203	12	4229
Gastroenteritis	23	4352	23	4381
Gastroenteritis clostridial	2	4203	0	4229
Gastroenteritis norovirus	1	4203	0	4229
Gastroenteritis viral	1	4203	1	4229
Gastrointestinal bacterial infection	0	4203	1	4229
Gastrointestinal infection	1	4203	2	4229
Gastrointestinal viral infection	1	4203	0	4229
Groin abscess	2	4203	0	4229
H1N1 influenza	0	4203	2	4229
Haematoma infection	1	4203	0	4229
Haemorrhagic fever	1	4203	0	4229
Hepatitis A	0	4203	2	4229
Hepatitis B	1	4203	1	4229
Herpes simplex meningoencephalitis	0	4203	1	4229
Herpes zoster	1	4203	3	4229
Implant site infection	3	4203	1	4229
Infected cyst	0	4203	1	4229
Infected dermal cyst	1	4203	0	4229
Infected skin ulcer	1	4203	3	4229
Infectious pleural effusion	1	4203	1	4229
Infective exacerbation of bronchiectasis	0	4203	2	4229
Infective exacerbation of chronic obstructive airway disease	5	4203	3	4229
Influenza	5	4203	5	4229
Intervertebral discitis	2	4203	0	4229
Joint abscesses	0	4203	1	4229
Kidney infection	0	4203	1	4229
Labyrinthitis	0	4203	1	4229
Laryngitis	0	4203	1	4229
Liver abscess	1	4203	0	4229
Lobar pneumonia	5	4203	6	4229
Localised infection	4	4203	2	4229
Lower respiratory tract infection	13	4203	21	4229
Lower respiratory tract infective bacterial	0	4203	1	4229
Lower respiratory tract infection viral	0	4203	1	4229
Lung infection	6	4203	12	4229

Meningitis	0	4203	1	4229
Morganella infection	0	4203	1	4229
Myocarditis infectious	0	4203	1	4229
Nasopharyngitis	0	4203	2	4229
Necrotising fasciitis	3	4203	0	4229
Orchitis	1	4203	0	4229
Osteomyelitis	7	4203	2	4229
Otitis Media	0	4203	1	4229
Parotitis	0	4203	1	4229
Perineal abscess	1	4203	0	4229
Peritoneal abscess	1	4203	0	4229
Peritonitis	6	4203	2	4229
Pharyngitis	0	4203	1	4229
Pneumococcal sepsis	0	4203	1	4229
Pneumonia	157	4662	185	4691
Pneumonia bacterial	3	4203	1	4229
Pneumonia haemophilus	1	4203	0	4229
Pneumonia influenzal	0	4203	1	4229
Pneumonia klebsiella	0	4203	1	4229
Pneumonia legionella	0	4203	1	4229
Pneumonia pneumococcal	0	4203	1	4229
Pneumonia staphylococcal	1	4203	0	4229
Pneumonia viral	1	4203	0	4229
Post procedural infection	2	4203	0	4229
Post procedural pneumonia	0	4203	1	4229
Postoperative wound infection	2	4352	3	4381
Pseudomembranous colitis	1	4203	0	4229
Pulmonary sepsis	1	4203	0	4229
Pulmonary tuberculosis	5	4203	2	4229
Pyelonephritis	3	4203	2	4229
Pyelonephritis acute	2	4203	3	4229
Pyelonephritis chronic	2	4203	1	4229
Rabies	1	4203	0	4229
Rectal abscess	1	4203	2	4229
Respiratory syncytial virus infection	1	4203	0	4229
Respiratory tract infection	16	4513	8	4539
Respiratory tract infection bacterial	0	4203	1	4229
Salmonellosis	1	4203	0	4229
Scrotal gangrene	0	4203	1	4229
Scrotal infection	1	4203	0	4229
Sepsis	26	4732	38	4761
Septic shock	17	4203	23	4229
Sinusitis	0	4203	1	4229
Skin bacterial infection	1	4203	0	4229
Soft tissue infection	0	4203	2	4229

	Staphylococcal abscess	0	4203	1	4229
	Staphylococcal bacteraemia	1	4203	2	4229
	Staphylococcal infection	0	4203	4	4229
	Staphylococcal sepsis	4	4203	0	4229
	Stoma site infection	0	4203	1	4229
	Sterptococcal bacteraemia	1	4203	0	4229
	Subcutaneous abscess	1	4203	2	4229
	Tooth abscess	1	4203	1	4229
	Tooth infection	0	4203	1	4229
	Tracheobronchitis	2	4203	3	4229
	Tuberculosis	0	4203	1	4229
	Tuberculosis pleurisy	1	4203	0	4229
	Upper respiratory tract infection	7	4513	11	4539
	Urinary tract infection	42	4662	36	4691
	Urinary tract infection bacterial	2	4203	2	4229
	Urosepsis	8	4203	9	4229
	Vestibular neuronitis	1	4203	1	4229
	Viraemia	1	4203	0	4229
	Viral infection	1	4203	4	4229
	Viral myocarditis	0	4203	1	4229
	Viral upper respiratory tract infection	0	4203	2	4229
	Wound abscess	1	4203	1	4229
	Wound sepsis	1	4203	0	4229
Injury, poisoning and procedural complications	Abdominal injury	1	4203	1	4229
	Accident	0	4203	1	4229
	Alcohol poisoning	1	4203	2	4229
	Animal bite	1	4203	1	4229
	Ankle fracture	0	4203	2	4229
	Arterial restenosis	0	4203	1	4229
	Bone contusion	0	4203	1	4229
	Brain contusion	1	4203	2	4229
	Cardiac contusion	0	4203	1	4229
	Cardiac function disturbance postoperative	0	4203	3	4229
	Cardiac valve replacement complication	0	4203	1	4229
	Cardiac valve rupture	1	4203	1	4229
	Chemical peritonitis	1	4203	1	4229
	Chest injury	2	4203	1	4229
	Clavicle fracture	2	4203	1	4229
	Compression fracture	0	4203	1	4229
	Concussion	1	4203	0	4229
	Contusion	2	4203	4	4229
	Coronary artery restenosis	1	4203	0	4229
	Craniocerebral injury	0	4203	1	4229

Cystitis radiation	1	4203	0	4229
Excoriation	1	4203	1	4229
Extradural haematoma	0	4203	1	4229
Eyeball rupture	0	4203	1	4229
Face injury	0	4203	1	4229
Facial bones fracture	2	4203	1	4229
Fall	6	4203	10	4229
Femoral neck fracture	5	4203	7	4229
Femur fracture	6	4203	7	4229
Fibula fracture	2	4203	2	4229
Foot fracture	0	4203	2	4229
Forearm fracture	1	4203	0	4229
Foreign body	1	4203	0	4229
Graft complication	0	4203	1	4229
Hand fracture	1	4203	1	4229
Head injury	6	4203	5	4229
Hip fracture	6	4203	12	4229
Humerus fracture	2	4352	3	4381
Incisional hernia	3	4203	1	4229
Jaw fracture	1	4203	0	4229
Joint dislocation	0	4203	1	4229
Joint injury	4	4203	0	4229
Laceration	5	4203	1	4229
Limb traumatic amputation	0	4203	1	4229
Lower limb fracture	2	4352	3	4381
Lumbar vertebral fracture	2	4203	1	4229
Median nerve injury	1	4203	0	4229
Medication error	0	4203	1	4229
Meniscus injury	1	4203	2	4229
Multiple fractures	1	4203	0	4229
Multiple injuries	1	4203	1	4229
Muscle rupture	0	4203	1	4229
Overdose	3	4203	5	4229
Patella fracture	1	4203	3	4229
Pelvic fracture	1	4203	0	4229
Post concussion syndrome	1	4203	0	4229
Post procedural complication	2	4203	2	4229
Post procedural discharge	0	4203	1	4229
Post procedural fistula	1	4203	0	4229
Post procedural haematoma	0	4203	1	4229
Post procedural haemorrhage	1	4203	2	4229
Post procedural myocardial infarction	1	4203	1	4229
Postoperative renal failure	1	4203	0	4229
Postoperative thoracic procedure complication	1	4203	0	4229

	Postoperative wound complication	1	4203	0	4229
	Procedural complication	0	4203	1	4229
	Procedural haemorrhage	0	4203	1	4229
	Pubic fracture	1	4203	1	4229
	Radiation proctitis	0	4203	1	4229
	Rib fracture	4	4203	1	4229
	Road traffic accident	7	4203	3	4229
	Sacroiliac fracture	1	4203	0	4229
	Scapula fracture	0	4203	1	4229
	Seroma	1	4203	0	4229
	Skull fracture	0	4203	2	4229
	Soft tissue injury	0	4203	1	4229
	Spinal compression fracture	3	4203	4	4229
	Spinal cord injury lumbar	0	4203	1	4229
	Spinal fracture	3	4352	3	4381
	Subcutaneous haematoma	0	4203	1	4229
	Subdural haematoma	11	4203	5	4229
	Subdural haemorrhage	0	4203	2	4229
	Tendon rupture	3	4203	0	4229
	Thermal burn	1	4203	1	4229
	Thoracic vertebral fracture	0	4203	3	4229
	Tibia fracture	2	4203	2	4229
	Toxicity to various agents	8	4203	9	4229
	Traumatic haematoma	0	4203	2	4229
	Ulna fracture	1	4203	0	4229
	Upper limb fracture	1	4203	0	4229
	Vascular graft complication	2	4203	0	4229
	Vascular graft occlusion	2	4203	0	4229
	Vascular graft thrombosis	1	4513	1	4539
	Vascular procedure complication	1	4203	0	4229
	Vascular pseudoaneurysm	1	4203	0	4229
	Wound	1	4203	1	4229
	Wound dehiscence	0	4203	1	4229
Wound necrosis	1	4203	1	4229	
Injury, poisoning and procedural complications	Acid base balance abnormal	0	4203	1	4229
	Alanine aminotransferase increased	1	4203	0	4229
	Aspartate aminotransferase increased	1	4203	0	4229
	Blood albumin decreased	0	4203	1	4229
	Blood creatinine increased	4	4203	2	4229
	Blood glucose increased	2	4203	0	4229
	Blood potassium decreased	0	4203	1	4229
	Blood pressure decreased	1	4203	0	4229
Blood pressure systolic decreased	0	4203	1	4229	

	Blood sodium decreased	1	4203	0	4229	
	C-reactive protein increased	0	4203	1	4229	
	Cardiac function test abnormal	0	4203	1	4229	
	Coagulation factor increased	0	4203	1	4229	
	Coagulation time prolonged	1	4203	0	4229	
	Creatinine renal clearance decreased	0	4203	1	4229	
	Ejection fraction	1	4203	0	4229	
	Ejection fraction decreased	2	4203	2	4229	
	Electrocardiogram QRS complex abnormal	0	4203	1	4229	
	Escherichia test positive	0	4203	1	4229	
	Gastric pH decreased	0	4203	2	4229	
	Glomerular filtration rate decreased	2	4203	1	4229	
	Haemoglobin decreased	1	4203	2	4229	
	Heart rate decreased	1	4203	0	4229	
	Hepatic enzyme increased	2	4203	0	4229	
	International normalised ratio abnormal	0	4203	2	4229	
	International normalised ratio increased	1	4203	8	4229	
	Liver function test abnormal	1	4203	3	4229	
	Oxygen saturation decreased	1	4203	0	4229	
	Prothrombin time abnormal	1	4203	0	4229	
	Prothrombin time prolonged	0	4203	1	4229	
	Respiratory rate increased	1	4203	0	4229	
	Troponin increased	0	4203	1	4229	
	Urine output decreased	1	4203	0	4229	
	Venous pressure jugular increased	0	4203	1	4229	
	Weight decreased	5	4203	5	4229	
	Weight increased	1	4203	2	4229	
	Metabolism and nutrition disorders	Cachexia	3	4203	1	4229
		Decreased appetite	4	4203	5	4229
		Dehydration	22	4273	30	4299
Diabetes mellitus		24	4203	23	4229	
Diabetes mellitus inadequate control		7	4352	9	4381	
Diabetic ketoacidosis		0	4203	4	4229	
Electrolyte imbalance		1	4203	2	4229	
Failure to thrive		2	4203	0	4229	
Fluid overload		2	4203	2	4229	
Gout		7	4203	10	4229	
Hyperglycaemia	7	4352	4	4381		

	Hyperglycaemic hyperosmolar nonketotic syndrome	0	4203	1	4229
	Hyperkalaemia	19	4352	43	4381
	Hyperuricaemia	0	4203	2	4229
	Hypervolaemia	0	4203	1	4229
	Hypocalcaemia	1	4203	1	4229
	Hypochloraemia	0	4203	1	4229
	Hypoglycaemia	15	4203	14	4229
	Hypokalaemia	12	4203	9	4229
	Hypomagnesaemia	0	4203	2	4229
	Hyponatraemia	6	4203	12	4229
	Hypoproteinaemia	0	4203	1	4229
	Hypovolaemia	3	4203	2	4229
	Insulin resistance	1	4203	0	4229
	Iron deficiency	1	4203	1	4229
	Iron overload	0	4203	1	4229
	Malnutrition	2	4203	1	4229
	Metabolic acidosis	1	4203	3	4229
	Metabolic disorder	1	4203	1	4229
	Mineral deficiency	1	4203	0	4229
	Type 2 diabetes mellitus	2	4203	7	4229
Musculoskeletal and connective tissue disorders	Arthralgia	3	4203	2	4229
	Arthritis	0	4203	2	4229
	Back pain	7	4352	2	4381
	Compartment syndrome	1	4203	1	4229
	Costochondritis	3	4203	2	4229
	Dupuytren's contracture	1	4203	0	4229
	Flank pain	1	4203	0	4229
	Foot deformity	0	4203	1	4229
	Gouty arthritis	1	4203	2	4229
	Haemarthrosis	1	4203	1	4229
	Intervetebraal disc degeneration	1	4203	1	4229
	Intervertebral disc disorder	1	4203	0	4229
	Intervertebral disc displacement	1	4203	0	4229
	Interveterbral disc protrusion	2	4203	2	4229
	Joint effusion	0	4203	1	4229
	Joint laxity	1	4203	0	4229
	Joint swelling	3	4203	1	4229
	Lumbar spinal stenosis	3	4203	1	4229
	Mobility decreased	1	4203	0	4229
	Muscle fatigue	1	4203	0	4229
	Muscle necrosis	0	4203	1	4229
	Muscle swelling C	0	4203	1	4229
	Muscular weakness	4	4352	4	4381

	Musculoskeletal chest pain	4	4203	5	4229
	Musculoskeletal pain	2	4203	1	4229
	Myalgia	1	4203	1	4229
	Myalgia intercostal	0	4203	1	4229
	Osteitis	1	4203	0	4229
	Osteoarthritis	17	4352	15	4381
	Osteochondrosis	0	4203	2	4229
	Osteonecrosis	0	4352	3	4381
	Osteoporotic fracture	1	4203	1	4229
	Pain in extremity	2	4203	3	4229
	Pathological fracture	1	4203	0	4229
	Periarthritis	0	4203	1	4229
	Rhabdomyolysis	4	4203	2	4229
	Rheumatoid arthritis	1	4203	0	4229
	Rotator cuff syndrome	0	4203	3	4229
	Spinal column stenosis	0	4203	3	4229
	Spinal osteoarthritis	2	4203	0	4229
	Spinal pain	3	4203	1	4229
	Synovial cyst	0	4203	1	4229
	Synovitis	0	4203	1	4229
	Tendonitis	1	4203	0	4229
	Trigger finger	0	4203	1	4229
	Neoplasms benign, malignant and unspecified	Adenocarcinoma gastric	2	4203	1
Adenocarcinoma of colon		3	4203	8	4229
Adenosquamous cell lung cancer		0	4203	1	4229
Adrenal carcinoma		0	149	1	152
B-cell lymphoma		0	4203	1	4229
Basal cell carcinoma		2	4513	8	4539
Benign lung neoplasm		0	4203	2	4229
Benign neoplasm		1	4203	0	4229
Benign neoplasm of adrenal gland		0	4203	1	4229
Benign neoplasm of bladder		0	4203	2	4229
Benign salivary gland neoplasm		1	4203	1	4229
Biliary neoplasm		1	4203	0	4229
Bladder adenocarcinoma stage unspecified		0	4203	1	4229
Bladder cancer		11	4513	6	4539
Bladder cancer recurrent		1	4203	1	4229
Bladder transitional cell carcinoma		2	4203	1	4229
Bone cancer		0	4203	1	4229
Brain neoplasm		0	4203	1	4229
Brain neoplasm malignant		0	4203	2	4229
Breast cancer		6	4203	3	4229
Breast cancer recurrent	1	4203	0	4229	

Breast neoplasm	1	4203	0	4229
Bronchial carcinoma	2	4513	5	4539
Bronchioloalveolar carcinoma	0	4203	1	4229
Cerebral haemangioma	1	4203	0	4229
Cervix carcinoma	0	4203	1	4229
Cholangiocarcinoma	1	4203	0	4229
Chronic lymphocytic leukaemia	1	4203	1	4229
Chronic myeloid leukaemia	1	4203	0	4229
Chronic myelomonocytic leukaemia	1	4203	0	4229
Clear cell renal cell carcinoma	0	4203	1	4229
Colon adenoma	1	4203	1	4229
Colon cancer	8	4203	11	4229
Colon cancer metastatic	2	4203	0	4229
Colon neoplasm	2	4203	0	4229
Colorectal adenocarcinoma	1	4203	0	4229
Colorectal cancer	2	4203	1	4229
Diffuse large B-cell lymphoma	1	4203	1	4229
Gastric cancer	2	4203	3	4229
Gastrointestinal cancer metastatic	0	4203	1	4229
Gastrointestinal carcinoma	1	4203	0	4229
Glioblastoma	1	4203	1	4229
Glioblastoma multiforme	1	4203	1	4229
Hepatic cancer	2	4203	2	4229
Hepatic cancer metastatic	1	4203	1	4229
Hodgkins disease	1	4203	0	4229
Hypergammaglobulinaemia benign monoclonal	0	4203	1	4229
Hypopharyngeal neoplasm benign	0	4203	1	4229
Inflammatory carcinoma of the breast	1	4203	0	4229
Intestinal adenocarcinoma	1	4203	1	4229
Invasive ductal breast carcinoma	0	4203	2	4229
Large intestine benign neoplasm	1	4203	0	4229
Laryngeal cancer	0	4203	1	4229
Laryngeal cancer metastatic	0	4203	1	4229
Laryngeal neoplasm	0	4203	1	4229
Leukaemia	0	4203	1	4229
Lip and/or oral cavity cancer	0	4203	1	4229
Lipoma	0	4203	1	4229

Liposarcoma	0	4203	1	4229
Liposaecoma recurrent	0	4203	1	4229
Lung adenocarcinoma	5	4203	1	4229
Lung cancer metastatic	2	4203	0	4229
Lung carcinoma cell type unspecified stage IV	0	4203	2	4229
Lung neoplasm	0	4203	2	4229
Lung neoplasm malignant	11	4203	13	4229
Lymphoma	1	4203	0	4229
Malignant mediastinal neoplasm	1	4203	0	4229
Malignant melanoma	2	4203	1	4229
Malignant neoplasm of pleura	1	4203	0	4229
Malignant neoplasm progression	1	4203	0	4229
Meningioma	0	4203	1	4229
Meningioma benign	1	4203	0	4229
Metastases to bone	3	4203	0	4229
Metastases to central nervous system	3	4203	1	4229
Metastases to liver	6	4203	6	4229
Metastases to lung	4	4203	1	4229
Metastases to lymph nodes	3	4203	2	4229
Metastases to spine	1	4203	2	4229
Metastases to spleen	1	4203	0	4229
Metastatic malignant melanoma	1	4203	0	4229
Metastatic neoplasm	1	4203	0	4229
Myelodysplastic syndrome	1	4203	3	4229
Nasal neoplasm benign	1	4203	0	4229
Nasopharyngeal cancer	1	4203	0	4229
Neoplasm malignant	1	4203	0	4229
Neurilemmoma benign	0	4203	1	4229
Neuroendocrine tumour	0	4203	1	4229
Neuroma	1	4203	0	4229
Non-small cell lung cancer	3	4203	0	4229
Oesophageal adenocarcinoma	0	4203	1	4229
Oesophageal carcinoma	0	4203	1	4229
Ovarian cancer	0	4203	1	4229
Pancreatic carcinoma	5	4352	2	4381
Pancreatic neoplasm	1	4203	1	4229
Parathyroid tumour benign	1	4203	0	4229
Plasma cell myeloma	1	4203	1	4229
Prostate cancer	8	4203	14	4229
Prostate cancer metastatic	1	4203	1	4229
Prostatic adenoma	1	4203	2	4229

	Rectal adenocarcinoma	3	4203	0	4229
	Rectal cancer	1	4203	6	4229
	Rectosigmoid cancer	0	4203	1	4229
	Refractory cytopenia with unilineage dysplasia	0	4203	1	4229
	Renal cancer	3	4203	4	4229
	Renal cancer stage III	1	4203	0	4229
	Renal cell carcinoma	3	4203	2	4229
	Renal neoplasm	0	4203	1	4229
	Salivary gland adenoma	0	4203	1	4229
	Seborrhoeic keratosis	0	4203	1	4229
	Skin cancer	0	4203	2	4229
	Small cell lung cancer	1	4203	2	4229
	Small intestine carcinoma	1	4203	0	4229
	Soft tissue cancer	0	4203	1	4229
	Spermatocytic seminoma	0	4203	1	4229
	Squamous cell carcinoma	3	4203	3	4229
	Squamous cell carcinoma of lung	2	4203	0	4229
	Squamous cell carcinoma of the tongue	1	4203	0	4229
	Thyroid cancer	1	4203	1	4229
	Tonsil cancer	0	4203	1	4229
	Transitional cell carcinoma	2	4203	1	4229
	Tumour ulceration	0	4203	1	4229
	Uterine cancer	2	4203	0	4229
	Uterine leiomyoma	0	4203	2	4229
Nervous system disorders	Amnesia	0	4203	1	4229
	Aphasia	2	4203	0	4229
	Ataxia	1	4203	0	4229
	Basilar artery thrombosis	0	4203	1	4229
	Brain hypoxia	1	4203	1	4229
	Brain injury	2	4203	1	4229
	Brain mass	0	4203	1	4229
	Brain oedema	1	4203	4	4229
	Brain stem infarction	1	4203	1	4229
	Carotid artery disease	1	4203	0	4229
	Carotid artery stenosis	4	4352	3	4381
	Carpal tunnel syndrome	1	4203	1	4229
	Cerebellar atrophy	1	4203	0	4229
	Cerebellar infarction	2	4203	1	4229
	Cerebral atrophy	1	4203	0	4229
	Cerebral haematoma	0	4203	3	4229
	Cerebral haemorrhage	5	4203	6	4229
	Cerebral infarction	9	4203	13	4229
	Cerebral ischaemia	1	4203	2	4229
	Cerebral venous thrombosis	1	4203	0	4229
Cerebrovascular accident	71	4273	73	4299	

Cerebrovascular disorder	1	4203	1	4229
Cerebrovascular insufficiency	2	4352	2	4381
Coma	0	4203	1	4229
Convulsion	5	4203	7	4229
Convulsions local	1	4203	0	4229
Dementia	2	4203	2	4229
Dementia Alzheimer type	1	4203	0	4229
Depressed level of consciousness	0	4203	2	4229
Diabetic coma	2	4203	0	4229
Diabetic neuropathy	2	4203	2	4229
Dizziness	10	4203	5	4229
Dysarthria	2	4203	3	4229
Embolic stroke	3	4203	6	4229
Encephalomalacia	0	4203	1	4229
Epilepsy	3	4203	1	4229
Guillain-Barre syndrome	1	4203	0	4229
Haemorrhage intracranial	4	4203	0	4229
Haemorrhagic stroke	5	4203	5	4229
Haemorrhagic transformation stroke	0	4203	1	4229
Headache	3	4203	0	4229
Hemiparesis	3	4203	1	4229
Hemiplegia	1	4203	3	4229
Hemisensory neglect	0	4203	1	4229
Hepatic encephalopathy	0	4203	1	4229
Hydrocephalus	1	4203	0	4229
Hyperaesthesia	0	4203	1	4229
Hypercapnic coma	0	4203	1	4229
Hypoaesthesia	0	4203	2	4229
Hypoglycaemic coma	1	4203	1	4229
Hypoglycaemic seizure	0	4203	1	4229
Hypoxic-ischaemic encephalopathy	1	4203	2	4229
Intercostal neuralgia	0	4203	1	4229
Ischaemic neuropathy	0	4203	1	4229
Ischaemic stroke	40	4203	37	4229
Lacunar infarction	1	4203	0	4229
Lethargy	1	4203	0	4229
Loss of consciousness	2	4203	4	4229
Mental retardation	1	4203	0	4229
Metabolic encephalopathy	0	4203	1	4229
Motor dysfunction	1	4203	0	4229
Movement disorder	0	4203	1	4229
Mutiple system atrophy	1	4203	0	4229
Neuralgia	0	4203	1	4229
Neuropathy peropheral	1	4203	3	4229

	Paraparesis	0	4203	1	4229
	Paraesthesia	0	310	1	310
	Parkinsons disease	1	4203	0	4229
	Partial seizures	0	4203	1	4229
	Peripheral sensory neuropathy	0	4203	1	4229
	Polyneuropathy	1	4203	0	4229
	Presenile dementia	1	4203	0	4229
	Presyncope	5	4203	7	4229
	Radiculopathy	2	4203	0	4229
	Reversible ischaemic neurological deficit	1	4203	0	4229
	Sciatica	1	4203	1	4229
	Stroke in evolution	1	310	0	310
	Subarachnoid haemorrhage	3	4203	5	4229
	Syncope	43	4662	70	4691
	Tension headache	1	4203	0	4229
	Toxic encephalopathy	0	4203	1	4229
	Transient ischaemic attack	18	4352	23	4381
	VIIIth nerve paralysis	0	4203	2	4229
	Vertebral artery stenosis	1	4203	0	4229
	Vertebrobasilar insufficiency	4	4203	1	4229
	Vocal cord paralysis	0	4203	1	4229
Pregnancy	Pregnancy	2	4203	0	4229
	Alcohol abuse	0	4203	1	4229
	Alcohol withdrawal syndrome	1	4203	0	4229
	Alcoholism	1	4203	0	4229
	Anxiety	3	4203	2	4229
	Completed suicide	2	4203	1	4229
	Confusional state	6	4203	8	4229
	Delirium	2	4203	4	4229
	Delirium tremens	0	4203	1	4229
	Depression	5	4203	0	4229
	Disorientation	0	4203	2	4229
	Emotional distress	0	4203	1	4229
	Generalised anxiety disorder	1	4203	0	4229
	Hallucination	0	4203	2	4229
	Hypochondriasis	0	4203	1	4229
	Insomnia	0	4203	2	4229
	Major depression	0	4203	1	4229
	Mental disorder	2	4203	1	4229
	Mental disorder due to a general medical condition	0	4203	1	4229
	Mental status changes	4	4203	0	4229
	Mood disorder due to a general medical condition	0	4203	1	4229
	Panic disorder	1	4203	1	4229

	Psychiatric symptom	0	4203	1	4229
	Psychiatric disorder	0	4203	2	4229
	Psychotic disorder due to a general medical condition	0	4203	1	4229
	Schizophrenia	0	4203	1	4229
	Somatisation disorder	1	4203	0	4229
	Somatoform disorder cardiovascular	0	4203	1	4229
	Somatoform disorder gastrointestinal	0	4203	1	4229
	Suicide attempt	1	4203	1	4229
Renal and urinary disorders	Acute prerenal failure	0	4203	2	4229
	Azotaemia	1	4203	0	4229
	Bladder diverticulum	1	4203	0	4229
	Calculus ureteric	2	4203	0	4229
	Crush syndrome	1	4203	0	4229
	Cystitis erosive	0	4203	1	4229
	Cystitis haemorrhagic	1	4203	0	4229
	Cystitis noninfective	0	4203	2	4229
	Diabetic neuropathy	0	4203	2	4229
	Dysuria	0	4203	1	4229
	Haematuria	14	4513	11	4539
	Hydronephrosis	0	4203	3	4229
	Hyperuricosuria	0	149	1	152
	Incontinence	0	4203	1	4229
	Kidney fibrosis	0	4203	1	4229
	Lower urinary tract symptoms	1	4203	0	4229
	Nephrolithiasis	2	4203	4	4229
	Nephropathy	1	4203	0	4229
	Nephropathy toxic	0	4203	1	4229
	Nephrosclerosis	2	4203	0	4229
	Nephrotic syndrome	1	4203	2	4229
	Oliguria	0	4203	1	4229
	Pelvi-ureteric obstruction	1	4203	0	4229
	Prerenal failure	1	4203	3	4229
	Proteinuria	2	4203	0	4229
	Renal aneurysm	0	4203	1	4229
	Renal colic	2	4352	2	4381
	Renal cyst	1	4203	0	4229
	Renal failure	55	4662	55	4691
	Renal failure acute	76	4352	80	4381
	Renal failure chronic	9	4203	13	4229
	Renal impairment	46	4203	57	4229
	Renal injury	2	4203	0	4229
Renal tubular acidosis	0	4203	1	4229	
Renal tubular necrosis	1	4203	1	4229	
Tubulointerstitial nephritis	0	4203	3	4229	

	Urethral stenosis	2	4203	1	4229
	Urinary incontinence	0	4203	2	4229
	Urinary retention	11	4662	9	4691
	Urine flow decreased	0	4203	1	4229
Reproductive system and breast disorders	Acquired phimosis	0	4203	1	4229
	Benign prostatic hyperplasia	8	4203	9	4229
	Breast pain	1	4203	0	4229
	Cervical polyp	1	4203	1	4229
	Endometrial hyperplasia	1	4203	0	4229
	Erectile dysfunction	0	4203	1	4229
	Menorrhagia	0	4203	1	4229
	Ovarian cyst	0	4203	1	4229
	Perineal pain	1	4203	1	4229
	Postmenopausal haemorrhage	1	4203	0	4229
	Prostatic obstruction	1	4203	1	4229
	Prostatitis	4	4513	3	4539
	Uterine haemorrhage	1	4203	0	4229
	Uterine polyp	1	4203	0	4229
	Vaginal haemorrhage	0	4203	1	4229
	Vaginal relaxation	0	4203	1	4229
	Respiratory, thoracic and mediastinal disorders	Acute pulmonary oedema	20	4352	20
Acute respiratory distress syndrome		0	4203	1	4229
Acute respiratory failure		1	4203	11	4229
Asphyxia		1	4203	0	4229
Asthma		4	4203	6	4229
Atelectasis		0	4203	1	4229
Bronchiectasis		4	4352	1	4381
Bronchitis chronic		3	4203	6	4229
Bronchospasm		1	4203	1	4229
Chronic obstructive pulmonary disease		41	4513	46	4539
Chronic respiratory failure		2	4203	0	4229
Cough		3	4203	9	4229
Dysphonia		1	4203	1	4229
Dyspnoea		53	4662	62	4691
Dyspnoea exertional		5	4203	4	4229
Dyspnoea paroxysmal nocturnal		0	4203	2	4229
Emphysema		0	4203	1	4229
Epistaxis		7	4203	7	4229
Haemoptysis		4	4203	11	4229
Haemothorax		2	4203	0	4229
Hiccups	1	4203	1	4229	
Hydrothorax	3	4203	2	4229	
Hypoxia	1	4203	7	4229	
Interstitial lung disease	1	4203	0	4229	

	Laryngeal oedema	0	4203	1	4229
	Laryngospasm	1	4203	0	4229
	Lung infiltration	0	4203	1	4229
	Nasal polyps	1	4203	0	4229
	Nocturnal dyspnoea	1	4203	1	4229
	Obstructive airways disorder	2	4203	0	4229
	Orthopnoea	4	4203	3	4229
	Pleural effusion	17	4203	19	4229
	Pleurisy	2	4203	1	4229
	Pneumonia aspiration	5	4203	8	4229
	Pneumonitis	1	4203	3	4229
	Pneumothorax	6	4203	3	4229
	Pneumothorax spontaneous	0	4203	1	4229
	Productive cough	3	4352	5	4381
	Pulmonary congestion	2	4203	6	4229
	Pulmonary embolism	22	4203	23	4229
	Pulmonary fibrosis	0	4203	2	4229
	Pulmonary haemorrhage	1	4203	2	4229
	Pulmonary hypertension	3	4203	5	4229
	Pulmonary infarction	0	4203	1	4229
	Pulmonary mass	0	4203	2	4229
	Pulmonary microemboli	0	4203	1	4229
	Pulmonary oedema	21	4352	22	4381
	Rales	0	4203	4	4229
	Respiratory acidosis	1	4203	0	4229
	Respiratory arrest	2	4203	2	4229
	Respiratory distress	5	4203	1	4229
	Respiratory failure	26	4732	30	4761
	Respiratory fatigue	1	4203	0	4229
	Sleep apnoea syndrome	3	4203	2	4229
	Tachypnoea	0	4203	1	4229
	Tracheal stenosis	1	4203	0	4229
	Vocal cord leukoplakia	0	4203	1	4229
Skin and subcutaneous tissue disorders	Angioedema	4	4352	4	4381
	Angiokeratoma	0	4203	1	4229
	Cutaneous vasculitis	0	4203	1	4229
	Decubitus ulcer	0	4203	1	4229
	Dermatitis	1	4203	1	4229
	Dermatitis allergic	2	4203	0	4229
	Dermatitis contact	1	4203	0	4229
	Diabetic foot	7	4203	7	4229
	Hyperhidrosis	0	4203	2	4229
	Hypersensitivity vasculitis	0	4203	1	4229
	Lichen planus	0	4203	1	4229
	Pemphigoid	1	4203	0	4229
	Pemphigus	0	4203	1	4229
	Penile ulceration	1	4203	0	4229
	Psoriasis	1	4203	0	4229

	Rash	1	4203	0	4229
	Skin burning sensation	1	4203	0	4229
	Skin erosion	0	4203	1	4229
	Skin necrosis	1	4513	1	4539
	Skin ulcer	3	4203	6	4229
	Ski ulcer haemorrhage	1	4203	0	4229
	Stasis dermatitis	0	4203	1	4229
	Urticaria	0	4203	1	4229
Surgery and medical procedures	Cardiac pacemaker insertion	0	4203	1	4229
	Endotracheal intubation	0	4203	1	4229
	Implantable defibrillator insertion	1	4203	0	4229
	Lymphadenectomy	0	4203	1	4229
	Renal lithiasis prophylaxis	0	310	1	310
	Resuscitation	1	4203	1	4229
	Thyroidectomy	0	4203	1	4229
Vascular disorders	Accelerated hypertension	0	4203	2	4229
	Aneurysm	0	4203	1	4229
	Angiodysplasia	0	4203	1	4229
	Aortic aneurysm	8	4203	11	4229
	Aortic dilatation	1	4203	0	4229
	Aortic occlusion	1	4203	0	4229
	Aortic stenosis	6	4203	2	4229
	Arterial occlusive disease	1	4203	0	4229
	Arterial thrombosis	0	4352	2	4381
	Arteriosclerosis	3	4203	1	4229
	Arteriovenous fistula	1	4203	0	4229
	Bleeding varicose vein	0	4203	2	4229
	Blood pressure inadequately controlled	0	4203	1	4229
	Circulatory collapse	5	4203	8	4229
	Deep vein thrombosis	5	4203	5	4229
	Diabetic vascular disorder	1	4203	0	4229
	Extremity necrosis	2	4203	0	4229
	Femoral artery embolism	0	4203	1	4229
	Femoral artery occlusion	3	4352	7	4381
	Haematoma	2	4203	1	4229
	Haemorrhage	1	4203	0	4229
	Hypertension	13	4203	12	4229
	Hypertensive crisis	7	4203	2	4229
	Hypertensive emergency	0	4203	2	4229
	Hypoperfusion	0	4203	1	4229
	Hypotension	61	4352	69	4381
	Hypovolaemic shock	5	4203	2	4229
	Iliac artery occlusion	0	4203	3	4229
	Intermittent claudication	3	4513	3	4539
	Ischaemia	0	4203	1	4229
Jugular vein thrombosis	1	4203	0	4229	

Lymphatic fistula	0	4203	1	4229
Lymphocele	1	4203	0	4229
Lymphoedema	0	4203	1	4229
Orthostatic hypotension	5	4203	3	4229
Peripheral arterial occlusive disease	23	4422	14	4451
Peripheral artery aneurysm	3	4203	1	4229
Peripheral artery stenosis	4	4203	2	4229
Peripheral artery thrombosis	4	4203	3	4229
Peripheral circulatory failure	1	4203	0	4229
Peripheral coldness	1	70	0	70
Peripheral embolism	4	4352	3	4381
Peripheral ischaemia	18	4203	8	4229
Peripheral vascular disorder	7	4203	5	4229
Phlebitis	2	4203	0	4229
Polyarteritis nodosa	0	4203	1	4229
Shock	4	4203	5	4229
Shock haemorrhagic	0	4203	1	4229
Subgaleal haematoma	0	4203	1	4229
Superior vena cava syndrome	0	4203	1	4229
Thrombophlebitis	3	4203	3	4229
Thrombophlebitis superficial	0	4203	1	4229
Thrombosis	2	4513	2	4539
Varicose vein	0	4203	2	4229
Vascular compression	1	4203	0	4229
Vasculitis	2	4203	0	4229
Vein collapse	1	4203	0	4229
Venous haemorrhage	0	4203	1	4229
Venous insufficiency	0	4203	3	4229
Venous thrombosis	0	4203	1	4229
Venous thrombosis limb	1	4203	2	4229

S2 Table: Characteristics of ongoing studies

Study name (identifier)	Estimated enrollment (no.)	Participants	Control	Primary outcomes	Estimated completion	Current status
CLCZ696BDE01 (NCT02768298)	200	HFrEF	Enalapril	Peak respiratory oxygen uptake	December 2019	Recruiting
LIFE study (NCT02816736)	400	EF <35% and NYHA IV	Valsartan	NT-proBNP	March 2020	Recruiting
NCT03821701	340	HFrEF	ACEI / ARB	Cardiovascular events	January 2022	Recruiting
NEPRIExTol (NCT03190304)	52	Symptomatic heart failure EF <35%	Enalapril	Exercise tolerance	December 2019	Recruiting
PARADISE-MI (NCT02924727)	5650	LVSD or pulmonary congestion post AMI	Ramipril	CV Death, HF hospitalisations	July 2020	Recruiting
PARAGLIDE-HF (NCT03988634)	616	Acute decompensated HfpEF	Valsartan	NT-proBNP	March 2021	Not yet recruiting
PARALLAX (NCT03066804)	2500	HFmrEF or HfpEF	Continue current treatment	NT-proBNP and 6MWD	December 2019	Recruiting
PARALLEL-HF (NCT02468232)	225	HFrEF (EF <35%)	Enalapril	CV death or HF hospitalisation	August 2020	Active
PERSPECTIVE (NCT02884206)	520	HFrEF	Valsartan	CogState Global Cognitive Composite score	May 2022	Recruiting
RECOVER-LV (NCT03552575)	100	Post AMI and HFrEF	Valsartan	LV end systolic volume	August 2020	Not yet recruiting
TURKU-PET (NCT03300427)	60	EF 25-35%	Valsartan	Cardiac oxygen consumption and efficiency	September 2019	Recruiting
VASCEND (NCT03168568)	80	Symptomatic HFrEF	Valsartan	Flow-mediated vasodilatation	May 2020	Recruiting