COXIB AND TRADITIONAL NSAID TRIALISTS' (CNT) COLLABORATION:

A collaborative meta-analysis of individual participant data from all randomised trials with at least one unconfounded comparison involving a selective cyclo-oxygenase-2 inhibitor (coxib) or a traditional non-steroidal anti-inflammatory drug (tNSAID).

Background

Traditional non-steroidal anti-inflammatory drugs (tNSAIDs) and newer selective cyclo-oxygenase-2 inhibitors (coxibs) are widely used for analgesia, but they have potentially serious vascular and gastrointestinal risks. A meta-analysis of tabular data from randomised trials of at least 4 weeks' duration involving a coxib versus placebo, or a coxib versus a traditional NSAID, has provided some limited information about the risk of vascular events associated with these drugs.[1] Although this has been used by regulatory authorities in informing treatment choices for the public, a meta-analysis of individual participant data from these trials would be substantially more informative. The pharmaceutical sponsors of coxib trials and their investigators have agreed to provide data to form a collaboration (the Coxib and traditional NSAID Trialists' [CNT] Collaboration), in order to assemble and maintain a database of individual participant data from all unconfounded trials, published and unpublished, of at least four weeks duration which have involved a coxib or tNSAID. The chief aim of this Collaboration will be to conduct analyses of the effects of coxibs and tNSAIDs on the most common adverse effects of coxibs and tNSAIDs, namely "major vascular events" and "upper gastrointestinal (GI) complications". We aim to update the results of this meta-analysis when the results of new trials become available.

The main benefits of an individual participant data meta-analysis include an ability to address some important outstanding questions, suggest new hypotheses and help identify future research questions. Some of the outstanding questions about anti-inflammatory drugs that will be informed by this collaborative meta-analysis include:

- Do the proportional effects on serious vascular events and upper GI complications vary amongst patient subgroups, for example by age, gender and other clinical features which influence the risk of vascular and upper gastrointestinal disease?
- Do cardiovascular hazards occur soon after drug initiation, or do they require prolonged exposure?
- Do different coxib and tNSAID regimens differ clearly in their vascular and upper gastrointestinal toxicity? In particular, do these analyses support the hypothesis, first raised by the Cross Trial Safety Assessment Group in celecoxib versus placebo trials, that there is a trend towards larger proportional increases in vascular risk with higher coxib dose and higher baseline risk of vascular disease?[2]
- What is the balance of benefit and risk of different coxibs and tNSAIDs in terms of absolute effects on vascular events and gastrointestinal effects among different types of patients?

Methods

Study eligibility: Eligible studies will be randomised trials of at least four weeks' duration in which there is a comparison of a coxib versus placebo, a coxib versus tNSAID, one coxib versus another coxib, a dose-comparison of a particular coxib, tNSAID versus placebo, one tNSAID versus another tNSAID, or a dose comparison of a particular tNSAID. We aim to collect information on all available tNSAIDs, including those with additional properties (e.g., variable inhibition of COX-1, nitric oxide [NO] release, etc.) The first cycle of analyses will include all trials for which final clinical study reports are available before January 1st 2009.

Trials of less than 4 weeks duration will not be included in the primary comparisons, because most such studies are small, early phase trials, and will contribute few events but consume a disproportionately large proportion of the project's resources. However, there have been a few short-term studies among patients at high risk of vascular disease (for example, two studies of valdecoxib among patients receiving a coronary artery bypass graft[3,4]), which involved enough vascular events to warrant sensitivity analyses of the early vascular risks associated with coxibs derived from these trials as well. We will therefore seek data from all short-term trials among patients with established vascular disease (in addition to data from longer term trials).

Identification of eligible trials: Potentially eligible trials will be identified using electronic literature searches.[1] The manufacturers of coxibs (Merck, Pfizer and Novartis) and tNSAIDs (including the manufacturers of newer nitric oxide-donating agents such as NicOx) will be asked to identify any additional trials involving their own drug, published or unpublished, of which they are aware.

Data collection and checking: We will seek individual participant data for all randomised individuals in relevant trials, irrespective of whether they actually took allocated treatment. The requested data will comprise: baseline characteristics and concomitant medications recorded at randomisation, details of randomly allocated treatments (and the dates they commenced), dates of major vascular and gastrointestinal outcomes; dates of treatment discontinuation. The data will be checked carefully for internal consistency and completeness of individual participant records, and for other indicators of possible anomalies. All queries regarding particular trials will be referred back to the sponsors or principal investigators of the trials, and computer generated outputs consisting of detailed summary tabulations and consistency checks will be returned to each collaborator for review and confirmation.

Outcomes & Adjudication

Data will be sought on definite or probable cardiovascular and upper gastrointestinal outcomes, as defined and adjudicated in each trial (or adjudicated independently after trial completion [see Sections C and D of the data request]). If adjudicated cardiovascular and/or gastrointestinal outcomes are not available, then the best available information on these outcomes will be recorded. In those trials where outcomes were not adjudicated but MedDRA codes have been used to code serious adverse events, those codes will used to identify particular vascular and GI outcomes from pre-specified coding lists (see Appendices 1 & 2).

Analytical strategy

The available trials involve a number of different designs. Electronic literature searches have already established that, prior to the development of the coxibs, there were relatively few placebo controlled trials of traditional NSAIDs, or trials comparing one traditional NSAID with another, and most of these were small and short-term (typically less than 12 weeks). A majority of these trials were published over 25 years ago, and it is likely to be difficult to obtain individual participant data. It is probable, therefore, that trials that precede the development of coxibs will provide little reliable information on the effects of particular tNSAIDs on specific vascular and GI outcomes.

By contrast, there is an order of magnitude more information on these outcomes recorded in more recently completed trials involving a comparison of a coxib vs placebo or a coxib vs a tNSAID (or both).

Given this distribution of information on particular outcomes in the available trials, the primary analysis strategy will be to conduct meta-analyses of all trials involving the following comparisons:

- Coxib versus placebo
- Coxib versus tNSAID
- One coxib versus another coxib
- tNSAID versus placebo
- One tNSAID versus another tNSAID
- Dose comparisons for particular coxibs or tNSAIDs

Details of the analysis strategy are provided in the Statistical Appendix. Briefly, estimates of the effects of particular coxibs will be obtained from comparisons of a coxib versus placebo. Estimates of the effects of each tNSAID will be derived by combining *direct comparisons* (i.e., trials comparing the particular tNSAID versus placebo, which will involve small numbers of events) and *indirect comparisons* (i.e., estimates derived indirectly by combining the more statistically precise results of trials comparing a coxib versus placebo with those of trials of a coxib versus the particular tNSAID under study). In exploratory analyses, we will use a variety of model-based approaches (sometimes called “network meta-analysis”) to derive estimates of the relative effects of each tNSAID and coxib using all of the available trial data.

Rate ratios and their confidence intervals for each of the pre-specified comparisons will be derived using the Peto "one step" approximation. Standard methods for analysis of survival data in individual participant data meta-analyses will be used.[6]

The primary outcomes will be:

- "Major vascular events" as defined by Antiplatelet Trialists' (APT) Collaboration[5] (nonfatal myocardial infarction, nonfatal stroke or vascular death)
- "Upper gastrointestinal complication" (bleed, perforation or obstruction)

Secondary outcomes will be:

(i) Vascular
- Vascular mortality
- Myocardial infarction
- Stroke (subdivided into haemorrhagic and non-haemorrhagic causes)
- Heart failure requiring hospitalisation
- Pulmonary embolus
- Peripheral arterial event
- Coronary revascularisation
- Resuscitated cardiac arrest
- Unstable angina requiring hospitalisation

(ii) Upper gastrointestinal
- Upper gastrointestinal complication (bleed)
- Upper gastrointestinal complication (perforation)
- Upper gastrointestinal complication (obstruction)
- Upper gastrointestinal symptomatic uncomplicated ulcer

(iii) Cause-specific mortality
- Vascular causes (coronary heart disease, other cardiac, stroke, other vascular)
- Upper gastrointestinal causes (bleed, perforation, obstruction, other)
- Other non-vascular causes (cancer, other)

Secondary analyses will also include assessments of effects on individual components of the primary outcomes. A Poisson model will be devised to assess independent determinants of major vascular and upper gastrointestinal events, using a method employed previously by the Cholesterol Treatment Trialists' (CTT) Collaboration.[7] Subgroup analyses will include assessments of effects on specific outcomes among categories defined by:

(i) baseline demographic features
(ii) concomitant treatments at baseline (e.g. aspirin, gastroprotectants etc.)
(iii) participants at low-, intermediate-, and high-risk of vascular events (as defined by a Poisson model)
(iv) participants at low-, intermediate-, and high-risk of gastrointestinal events (as defined by a Poisson model)
(v) particular indications for an anti-inflammatory drug (e.g. osteoarthritis, rheumatoid arthritis, cancer prevention etc.)
(vi) adjudicated and non-adjudicated trials
(vii) trials of painful and non-painful conditions
(viii) cancer prevention and treatment trials

Where possible, assessments of dose-response will be made for particular coxibs or tNSAIDs, using all available data. These will include, in particular, any period involving multiple dose comparisons from "extension trials" (where a short-term placebo-controlled period, sometimes with several different doses, was followed by a longer comparison of a coxib vs tNSAID).

In addition, exploratory analyses will be carried out to assess, where possible, the evolution in rate ratios after drug discontinuation. We will also assess differences between analyses that exclude events occurring prior to the first drug dose and those involving all post-randomisation follow-up.

Publication policy

All publications will be in the name of the Coxib and traditional NSAID Trialists' (CNT) Collaboration, with the names of collaborators listed at the end of the paper. Publications will be circulated for comments and approval before submission to peer review.

Confidentiality

All trial data will be regarded as strictly confidential, and will not be provided to any third party without the prior written permission of the owners of the data.

Funding

Collaborators will be asked to fund their own travel costs for meetings (accommodation and meals will be provided), although a fund will be set up to assist those who would not otherwise be able to attend.

Proposed timeline

3rd quarter, 2008	Circulation of protocol and data request
3rd to 4th quarter, 2008	Discussions with trial sponsors
	Electronic searches and trial selection
1st to 3rd quarter, 2009	Steering Group teleconference (Oxford)
	Final protocol and data request circulated
	Data collection commences
Up to 3rd quarter, 2010	Data checking and analysis
1st quarter, 2011	Preliminary results meeting (Oxford)
Remainder of 2011	Additional analyses suggested by collaborators
	Circulation and revision of manuscript(s)
	Submission of primary manuscript

Additional substudies

In addition, to the unconfounded comparisons of coxibs and traditional NSAIDs which are detailed above, we will collect tabular data on other therapeutic and confounded comparisons. These include coxib versus paracetamol; NSAID versus paracetamol; coxib versus aspirin; NSAID versus aspirin; NSAID and gastroprotectant (eg, proton pump inhibitor [PPI], histamine-2 receptor antagonist [H2-RA] or misoprostol) versus coxib alone; coxib and gastroprotectant versus coxib alone; and NSAID and gastroprotectant versus NSAID alone.

References

1). Kearney P, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. BMJ 2006; 332: 1302-5.
2). Cross Trial Safety Assessment Group. Solomon SD, Wittes J, Finn PV, et al. Cardiovascular risk of celecoxib in 6 randomized placebo-controlled trials: the cross trial safety analysis. Circulation. 2008 Apr 22;117(16):2104-13.
3). Multicenter Study of Perioperative Ischemia (McSPI) Research Group; Ischemia Research and Education Foundation (IREF) Investigators. Ott E, Nussmeier NA, Duke PC, et al. Efficacy and safety of the cyclooxygenase 2 inhibitors parecoxib and valdecoxib in patients undergoing coronary artery bypass surgery. J Thorac Cardiovasc Surg. 2003 Jun;125(6):1481-92.
4). Nussmeier NA, Whelton AA, Brown MT, et al. Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. N Engl J Med. 2005 Mar 17;352(11):1081-91.
5). Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy - I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. BMJ 1994;308:81-106.
6). Early Breast Cancer Trialists' Collaborative Trial. Treatment of early breast cancer: worldwide evidence 1985-1990. Oxford: Oxford University Press, 1990.
7). Cholesterol Treatment Trialists' (CTT) Collaborators. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005 Oct 8;366(9493):1267-7

How to send data to the CNT secretariat

Reminder of confidentiality

All data sent to the secretariat will be held securely and treated in the strictest confidence. The data will not be used in any publication without the explicit permission of the responsible trialist.

Ways of sending data

As long as it will not cause delay the easiest way for us to receive the data is by encrypted email (cnt@ctsu.ox.ac.uk). If you choose to use a different medium for sending data, please accompany it with

1. a full description of the format
2. the software package (including version number) used to write the file
3. the number of data records included

Preferred data format

Please record ALL patients originally randomised, i.e. include any who were ineligible, withdrawn, unevaluable, lost or "protocol-deviant".

Please provide data as an *ASCII text file* and not the storage format used by any proprietary software package. The preferred format is comma separated variable (CSV) file, or similar text file delimited by a suitable character (*tabs* for example). We can also accept the data as a SAS transport file. If you are providing data in your own format (i.e. different to that described below) then it is very useful if variable names are included as column headings in the file.

If particular data are not available, simply leave the relevant columns blank: it is not necessary to include a "missing data" code. However, if it is easier for you to include a code for missing data, please tell us precisely what that code is: it is particularly important that we can differentiate between the codes for "no event" and "missing data".

If you are unable to provide actual dates (for example, due to privacy laws), then please provide the number of days since randomisation (and omit the date of randomisation). Otherwise, please use the convention DDMMYYYY (or similar day-month-year ordered format) for dates. If a date is incompletely known, either leave the day blank and give month and year, or leave the day and month blank and just give year. Please leave dates of specific events blank when a patient did not experience such an event.

A. Baseline data recorded PRIOR to randomisation	**Coding**
Patient identifier note 1	
Gender	1 = male 2 = female
Ethnicity	1 = caucasian 2 = other
Date of birth *or* age at randomisation note 2	
Indication for treatment note 3	1 = rheumatoid arthritis 2 = osteoarthritis 3 = back pain 4 = gout 5 = cancer treatment 6 = cancer prevention 7 = treatment/prevention of Alzheimer's disease 8 = other condition 9 = unknown
History of atherosclerosis (coronary heart disease note 4, cerebrovascular disease note 5, or other arterial disease note 6)	1 = yes 0 = no
History of diabetes mellitus	1 = yes 0 = no
History of upper gastrointestinal ulcer note 7	1 = yes 0 = no
Helicobacter pylori status at baseline note 8	1 = positive 0 = negative
Height (cm)	
Weight (kg)	
Current cigarette smoker note 9	1 = yes 0 = no
Current drinker of alcohol note 10	1 = yes 0 = no
Current user of aspirin	1 = yes 0 = no
Current user of gastroprotective agent note 11	1 = proton pump inhibitor 2 = histamine 2 receptor blockers 3 = misoprostol 9 = other 0 = no
Baseline haemoglobin (g/dl) note 12	

Baseline total cholesterol (mmol/L) note 12	
Baseline creatinine (µmol/l) note 12	
Baseline systolic blood pressure (mm Hg) note 13	
Baseline diastolic blood pressure (mm Hg) note 13	
B. Randomisation and treatment allocation	
Date of randomisation note 14	
Date commenced *first* treatment note 14	
First randomised treatment allocation note 14	
Date ended first treatment note 14	
Date commenced *second* treatment note 14	
Second randomised treatment allocation note 14	
Date ended second treatment note 14	

C. Cardiovascular events occurring AFTER randomisation (record information on first event of each type)

Only the first cardiovascular event occurring in each category is to be recorded. Please record all events that occurred on or before the pre-specified censoring date for that event type (in some trials, this was some time after treatment ended [e.g. 28 days]). *Definite or probable* events should be included, but please exclude "possible" events. Please use the trialists' definition of an outcome – although there will inevitably be minor differences in definition between trials, all comparisons are within trial, and heterogeneity between trials will be explored. Record either adjudicated events or, if a specific event was not adjudicated, the best available matching event from your file (and give us details of how this has been done). Where the MedDRA system has been employed, please use the list of terms in Appendix 1 to define events.

First myocardial infarction (MI) *after* randomisation	1 = yes 0 = no
Date of first MI note 15	
Whether MI was fatal or non-fatal note 16	1 = fatal 0 = non-fatal
First stroke *after* randomisation note 17	1 = yes 0 = no
Type of stroke *after* randomisation	1 = intracerebral haemorrhage 2 = subarachnoid haemorrhage 3 = subdural haematoma 4 = ischaemic (including embolic) stroke 9 = unknown
Date of first stroke note 15	
Whether stroke was fatal or non-fatal note 16	1 = fatal 0 = non-fatal
First episode of heart failure requiring hospitalisation *after* randomisation note 18	1 = yes 0 = no
Date of first heart failure event note 15	
Whether heart failure event was fatal or non-fatal note 16	1 = fatal 0 = non-fatal
First pulmonary embolus (PE) *after* randomisation note 19	1 = yes 0 = no
Date of first PE note 15	
Whether PE was fatal or non-fatal note 16	1 = fatal 0 = non-fatal
First peripheral arterial disease event *after* randomisation note 20	1 = yes 0 = no

Date of first peripheral arterial disease event note 15	
Whether peripheral arterial disease event was fatal or non-fatal note 16	1 = fatal 0 = non-fatal
First coronary revascularisation *after* randomisation note 21	1 = yes 0 = no
Date of first coronary revascularisation note 15	
Whether coronary revascularisation was fatal or non-fatal note 16	1 = fatal 0 = non-fatal
First resuscitated cardiac arrest *after* randomisation note 22	1 = yes 0 = no
Date of first resuscitated cardiac arrest note 15	
Whether resuscitated cardiac arrest was fatal or non-fatal note 16	1 = fatal 0 = non-fatal
First episode of unstable angina *after* randomisation note 23	1 = yes 0 = no
Date of first unstable angina event note 15	
Whether unstable angina was fatal or non-fatal note 16	1 = fatal 0 = non-fatal

D. Upper gastrointestinal (UGI) events occurring AFTER randomisation (record information on first event of each type)

Only the first UGI event occurring in each category is to be recorded. Please record all events that occurred on or before the pre-specified censoring date for that event type (in some trials, this was some time after treatment ended [e.g. 28 days]). *Definite or probable* events should be included, but please exclude "possible" events. Please use the trialists' definition of an outcome – although there will inevitably be minor differences in definition between trials, all comparisons are within trial, and heterogeneity between trials will be explored. Record either adjudicated events or, if a specific event was not adjudicated, the best available matching event from your file (and give us details of how this has been done). Where the MedDRA system has been employed, please use the list of terms in Appendix 2 to define events.

First symptomatic (but uncomplicated) UGI ulcer *after* randomisation note 24	1 = yes 0 = no
Date of first symptomatic (but uncomplicated) UGI ulcer note 25	
First upper gastrointestinal UGI ulcer complication *after* randomisation note 24	1 = yes 0 = no
Date of first UGI ulcer complication note 25	
Type of UGI ulcer complication	1 = UGI haemorrhage 2 = UGI obstruction 3 = UGI perforation 4 = other 9 = unknown
Whether UGI ulcer complication was fatal or non-fatal note 26	1 = fatal 0 = non-fatal

E. Study discontinuation	
Study treatment discontinued permanently prior to scheduled end	1 = yes 0 = no
Date study treatment discontinued if prior to scheduled end note 27	
F. Follow-up information	
Date of scheduled end of treatment note 28	
Date of last follow-up for cardiovascular events note 29	
Date of last follow-up for gastrointestinal events note 30	
Date of last follow-up for vital status note 31	
Vital status on that date	1 = dead 0 = alive
ICD (or other code) for death note 32	

Explanatory notes

A. Baseline data recorded prior to randomisation

1 Please use a unique code that will enable you to retrieve a patient's data if the secretariat requests clarification.

2 Please provide either the date of birth *or* age (in complete years) at randomisation.

3 Please provide primary indication for drug treatment.

4 This consists of a history of myocardial infarction, unstable angina, heart failure, resuscitated cardiac arrest or coronary revascularisation.

5 This is defined as a history of stroke (ischaemic, haemorrhagic [including subarachnoid haemorrhage or subdural haematoma], or unknown).

6 This consists of a history of peripheral arterial disease, peripheral arterial intervention, or other arterial disease (e.g., aortic aneurysm, ischaemic colitis, splenic infarction).

7 This consists of a history of symptomatic UGI ulcer or UGI ulcer complication (i.e. perforation, obstruction or haemorrhage), defined anatomically as being including and proximal to the duodenum (i.e., the ligament of Treitz).

8 If known, please record *H. pylori* status at randomisation. Otherwise please leave blank.

9 Please record 'yes' if patient reports that they are a current smoker, 'no' otherwise (and leave blank if unknown).

10. Please record 'no' if patient reports that they are currently teetotal, 'yes' otherwise (and leave blank if unknown).

11 If using the World Health Organisation (WHO) Anatomical Therapeutic Chemical (ATC) Classification System, please use Appendix 3.

12 Please use either serum or plasma measurements. Where several blood results are available, please record the last prior to randomisation.

13 Where several measurements are available, please record the last prior to randomisation.

B. Randomisation and treatment allocation

14 Each patient's trial medication should be recorded with a simple character string: date of randomisation; date commenced first randomised treatment; code for first treatment; date ended first treatment. Then, if the trial involved a second randomised comparison: date commenced second treatment; code for second allocated treatment; date ended second treatment. (For example, a trial involving a single comparison of coxib vs. placebo would involve 4 items for each patient, whilst a trial involving an initial comparison of coxib vs. placebo followed by coxib vs. NSAID would involve 7 items).

If you are unable to provide actual dates (for example, due to privacy laws), then please provide the number of days since randomisation instead (and omit the date of randomisation).

C. Cardiovascular events occurring after randomisation

15 If a cardiovascular event did not occur, please leave the corresponding “date of event” blank.

16 A cardiovascular event (after randomisation) is defined to be fatal if death was primarily attributed to that event, but otherwise an event should be recorded as non-fatal.

17 This can be either ischaemic, haemorrhagic (including subdural haematoma or subarachnoid haemorrhage), or of unknown aetiology. Stroke is defined clinically as 'a neurological deficit of cerebrovascular cause that persists beyond 24 hours or is interrupted by death within 24 hours'.

18 This consists of an episode of heart failure or pulmonary oedema requiring hospitalisation.

19 This consists of a pulmonary embolus or pulmonary thrombosis.

20 This consists of a peripheral arterial disease event, peripheral arterial intervention, or other arterial disease event (e.g., aortic aneurysm, ischaemic colitis, splenic infarction).

21 This consists of a coronary angioplasty (with or without a stent), coronary artery bypass graft, or other coronary revascularisation.

22 This consists of a confirmed resuscitated cardiac arrest, occurring in or out of hospital.

23 This consists of an episode of unstable angina requiring hospitalisation.

D. Upper gastrointestinal (UGI) events occurring after randomisation

24 UGI complicated events are defined as perforation, obstruction or haemorrhage (bleed). If patient has had a symptomatic ulcer diagnosed without these occurring, it is uncomplicated.

25 If an UGI event did not occur, please leave the corresponding “date of event” blank.

26 An UGI event (after randomisation) is defined to be fatal if death was primarily attributed to that event, but otherwise an event should be recorded as non-fatal.

E. Study discontinuation

27 If a permanent study treatment discontinuation did not occur, please leave the corresponding “date of event” blank.

F. Vital status at last follow-up

28 Please record the date that a patient was scheduled to complete study treatment.

29 Please record the last date of follow-up (i.e. censoring date) for cardiovascular events.

30 Please record the last date of follow-up (i.e. censoring date) for gastrointestinal events.

31 Please record the date of death, or the last date on which the patient was known to be alive.

32 If possible, code the cause of death using the 9th or 10th revision of the International Classification of Diseases. If this is not possible, please provide details of your coding scheme.

Coxib and traditional NSAID Trialists' (CNT) collaboration

APPENDIX 1

MedDRA Terms for unadjudicated cardiovascular endpoints

Confirmed Endpoint	**Investigator Reported Term (MedDRA PT, LLT or SMQ)**
Myocardial Infarction	Myocardial infarction Acute myocardial infarction Myocardial infarction, Coronary artery disease Non-Q wave MI Acute non-Q wave MI Post procedural myocardial infarction
Haemorrhagic Stroke	Haemorrhagic stroke Intracranial haemorrhage Haemorrhagic transformation stroke Haemorrhagic cerebral infarction Haemorrhage intracranial Haemorrhagic infarction Cerebral haemorrhage Cerebral haemorrhage traumatic Pituitary haemorrhage Thalamus haemorrhage Brain stem haemorrhage Intraventicular haemorrhage Basal ganglia haemorrhage Cerebellar haemorrhage Brain stem haemorrhage Haemorrhagic cerebrovascular conditions (SMQ)
Subarachnoid Haemorrhage	Subarachnoid haemorrhage
Subdural Haematoma	Subdural haematoma Subdural haemorrhage

Ischaemic Stroke	Ischaemic stroke Brain stem infarction Cerebral infarction Cerebral thrombosis Cerebrovascular accident Stroke Embolic stroke Thrombotic stroke Thromboembolic stroke Cerebral artery occlusions Cerebral artery thrombosis Ischaemic cerebral infarction Thrombotic cerebral infarction Embolic cerebral infarction Lacunar infarction Pituitary infarction Thalamic infarction Cerebellar infarction Cerebral thrombosis Cerebral artery thrombosis Cerebral artery embolism Post procedural stroke Ischaemic cerebrovascular conditions (SMQ)
Heart Failure	Cardiac failure Pulmonary oedema Acute pulmonary oedema Heart failure Cardiac failure acute Cardiac failure congestive Left ventricular failure Acute left ventricular failure Cardiopulmonary failure Ventricular failure
Pulmonary Embolus	Pulmonary embolus Pulmonary thrombosis

Peripheral Arterial Disease	Arterial thrombosis Peripheral occlusive disease Arterial thrombosis limb Arterial occlusive disease Arterial embolism limb Iliac artery thrombosis Subclavian artery thrombosis
Peripheral Arterial Intervention	Peripheral revascularisation Vascular operation Vascular stent insertion
Other Arterial Disease	Colitis ischaemic Infarction, Splenic infarction Aortic aneurysm Aortic aneurysm repair Aortic aneurysm rupture Intra-thoracic aortic aneurysm repair
Coronary Revascularisation	Coronary revascularisation Coronary artery bypass Coronary angioplasty Coronary arterial stent insertion Coronary endarterectomy Percutaneous coronary intervention Arterial bypass operation Angioplasty CABG/coronary artery bypass graft Percutaneous coronary (intervention) Balloon (in context of angioplasty) PTCA/Percutaneous transluminal coronary angioplasty
Resuscitated Cardiac Arrest	Cardiac arrest Cardio-respiratory arrest Circulatory collapse
Unstable angina	Angina unstable Angina pectoris Postinfarction angina Microvascular angina

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APPENDIX 2

MedDRA Terms for unadjudicated upper gastrointestinal (UGI) endpoints

Confirmed Endpoint	**Investigator Reported Term (MedDRA PT, LLT or SMQ)**
Symptomatic UGI Ulcer	Peptic ulcer Duodenal ulcer Gastroduodenal ulcer Gastric ulcer Gastric ulcer helicobacter Oesophageal ulcer Stress ulcer Gastrointestinal ulcer, site unspecified
UGI Perforation	Peptic ulcer perforation Duodenal ulcer perforation Duodenal perforation Gastric ulcer perforation Gastric perforation Oesophageal ulcer perforation Oesophageal perforation Gastrointestinal ulcer perforation, site unspecified Gastrointestinal perforation, site unspecified Perforated ulcer Perforated duodenal ulcer repair
UGI Obstruction	Peptic ulcer perforation, obstructive Peptic ulcer, obstructive Duodenal ulcer perforation, obstructive Duodenal ulcer, obstructive Duodenal obstruction Duodenal stenosis Gastric ulcer perforation, obstructive Gastric ulcer, obstructive Gastric ulcer haemorrhage, obstructive Obstruction gastric Pyloric stenosis

UGI Haemorrhage	Peptic ulcer haemorrhage Duodenal ulcer haemorrhage Gastric ulcer haemorrhage Oesophageal ulcer haemorrhage Gastrointestinal ulcer haemorrhage Gastric haemorrhage Gastroduodenal haemorrhage Oesophageal haemorrhage Upper gastrointestinal haemorrhage Gastrointestinal haemorrhage Intra-abdominal haemorrhage

Coxib and traditional NSAID Trialists' (CNT) collaboration

APPENDIX 3

WHO ATC codes for concomitant medications
[Current user of gastroprotective agent]

Medication	**ATC Term**	**ATC Code**
Proton pump inhibitors	Proton pump inhibitors	A02BC
Histamine 2 receptor blockers	H2-receptor antagonists	A02BA
Misoprostol	Prostaglandins	A02BB
Other	Combination for eradication of *Helicobacter pylori* Other drugs for peptic ulcer and gastro-oesophageal reflux disease	A02BD A02BX