



**Methodology of a large streamlined safety study: protocol of the Standard care versus Celecoxib Outcome Trial (SCOT trial)**

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3 **Methodology of a large streamlined safety study: protocol of the Standard care versus**  
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5 **Celecoxib Outcome Trial (SCOT trial)**  
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41 **Article summary:**  
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43 **Article focus:**  
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- 45  
46 • The SCOT trial compares the cardiovascular and gastrointestinal safety of a strategy of  
47 celecoxib therapy and a strategy of traditional NSAID therapy in patients with osteoarthritis or  
48 rheumatoid arthritis aged over 60 years without a history of cardiovascular disease.  
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53 **Key messages:**  
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- The SCOT trial is a prospective randomised trial comparing celecoxib with traditional NSAIDs in patients with arthritis without a history of cardiovascular disease.
- Cardiovascular safety of NSAIDs is an important issue where more evidence is required to guide practice.
- The SCOT trial uses electronic record-linkage to collect data on endpoints.

#### **Strengths and limitations of this study:**

The SCOT trial is a prospective randomised trial in a population of patients who take NSAIDs longterm and are therefore representative of patients who might be at risk from NSAID therapy.

The SCOT trial is a streamlined safety trial with good external validity as it is conducted in the normal care setting. Limitations of the study include the need to extrapolate from the results to guide therapy in younger patients and in patients without a history of using NSAIDs and the lack of traditional study follow-up visits although it has been shown that record-linkage can be used effectively in trial follow-up to detect events.

## Abstract

**Introduction:** Cyclooxygenase 2 (COX-2) inhibitors have less upper gastrointestinal toxicity than traditional non-steroidal anti-inflammatory drugs (NSAIDs). However, both COX-2 inhibitors and traditional NSAIDs may be associated with adverse cardiovascular side effects. Data from randomised and observational studies suggest that celecoxib has similar cardiovascular toxicity to traditional NSAIDs. The overall safety balance of a strategy of celecoxib therapy versus traditional NSAID therapy is unknown. The European Medicines Agency (EMA) requested studies of the cardiovascular safety of celecoxib within Europe. The Standard care versus Celecoxib Outcome Trial (SCOT) compares the cardiovascular safety of celecoxib with traditional NSAID therapy in the setting of the EU healthcare system.

**Methods and analysis:** SCOT is a large streamlined safety study conducted in Scotland, England, Denmark, and the Netherlands using the Prospective Randomised Open Blinded Endpoint (PROBE) design. Patients aged over 60 years with osteoarthritis or rheumatoid arthritis, who are free from established cardiovascular disease and who require chronic NSAID therapy are randomised to celecoxib or to continue their previous traditional NSAID. They are then followed up for events by record-linkage within their normal healthcare setting. The primary endpoint is the first occurrence of hospitalisation or death for the Anti-Platelet Trialists' Collaboration (APTC) cardiovascular endpoint of non-fatal myocardial infarction, non-fatal stroke or cardiovascular death. The secondary endpoints are 1) first hospitalisation or death for upper gastrointestinal ulcer complications (bleeding, perforation or obstruction); 2) first occurrence of hospitalised upper gastrointestinal ulcer complications or APTC endpoint; 3) first hospitalisation for heart failure; 4) first hospitalisation for APTC endpoint plus heart failure; 5) all cause mortality and 6) first hospitalisation for new or worsening renal failure.

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3 **Ethics and dissemination:** The SCOT trial has been approved by the relevant ethics  
4 committees. The trial results will be published in a peer-reviewed scientific journal.  
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8 **Registration:** The SCOT trial is registered on clinicaltrials.gov (NCT00447759).  
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For peer review only

## Introduction

NSAID-induced gastrointestinal toxicity is one of the most common serious drug adverse events requiring hospitalisation.<sup>1</sup> Upper gastrointestinal complications result in considerable morbidity and mortality. The COX-2 selective NSAIDs gained popularity based upon evidence that they are associated with a lower incidence of ulcer-related upper gastrointestinal tract complications compared to traditional non-selective NSAID therapy. However, the withdrawal of rofecoxib<sup>2</sup> due to cardiovascular toxicity and the suggestion that most NSAIDs are probably associated with increased cardiovascular adverse events when compared to placebo,<sup>3</sup> has led to the need for further prospective studies on the safety of other COX-2 inhibitors and traditional NSAIDs.

The cardiovascular safety profile of COX-2 inhibitors was brought into question following the results of two placebo-controlled studies designed to test the hypothesis that the COX-2 inhibitors rofecoxib and celecoxib might prevent colorectal adenomas and colorectal tumours. The Adenomatous Polyp Prevention on Vioxx (APPROVe) Trial randomised patients with a history of colorectal adenomas to rofecoxib 25mg or placebo and reported an excess of cardiovascular thrombotic events in the group treated with rofecoxib<sup>4</sup>. The Prevention of Sporadic Colorectal Adenomas with Celecoxib (APC) Trial randomised patients with previous colorectal adenomas to celecoxib 400mg twice daily, celecoxib 200mg twice daily or placebo and reported a dose-related increase in risk of cardiovascular events in the celecoxib groups<sup>5,6</sup>. However, the Prevention of Colorectal Sporadic Adenomatous Polyps (PreSAP) Trial did not show a significant increase in cardiovascular events with celecoxib 400mg given once per day versus placebo in patients with previous colorectal adenomas.<sup>7</sup> In the Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT), which was stopped early due to the findings of the

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3 APC trial, there was a suggestion of an increased risk of cardiovascular events with naproxen but  
4  
5 not celecoxib compared to placebo, although this study was underpowered and the  
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7 cardiovascular results must therefore be interpreted with caution. In a later meta-analysis of six  
8  
9 randomised double-blind placebo controlled trials of celecoxib in non-arthritis conditions, which  
10  
11 included analysis of the APC, PreSAP and ADAPT studies and three other smaller studies  
12  
13 (MA27, The Diabetic Macular Edema (CDME) Trial and the Celecoxib/Selenium Trial), there  
14  
15 was no evidence of increased cardiovascular risk with celecoxib in low risk patients but there  
16  
17 was a dose-dependent increase in cardiovascular risk in high risk patients<sup>8</sup> .  
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24 In the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme,  
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26 which compared cardiovascular outcomes with etoricoxib 60mg or 90mg daily and diclofenac  
27  
28 150mg daily in patients with osteoarthritis or rheumatoid arthritis, rates of thrombotic  
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30 cardiovascular events were similar in patients randomised to either drug<sup>9</sup> .  
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36 In trials of celecoxib versus traditional NSAIDs, no evidence of increased cardiovascular toxicity  
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38 has been seen<sup>10</sup> . In large observational studies, celecoxib has not been found to be associated  
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40 with increased cardiovascular risk versus other NSAIDs<sup>11</sup> or non-use.<sup>12,13</sup> At present, much of  
41  
42 the available data comes from observational studies and while it seems clear that rofecoxib  
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44 increased cardiovascular risk, many traditional NSAIDs may also pose considerable risk.<sup>3,11,</sup>  
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53 The recent Celecoxib versus Omeprazole and Diclofenac in patients  
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3 with Osteoarthritis and Rheumatoid arthritis (CONDOR) study found that celecoxib was  
4 associated with a lower incidence of clinically significant upper or lower gastrointestinal events  
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6 than the combination of diclofenac and omeprazole, adding further evidence to the improved  
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8 gastrointestinal safety of COX-2 inhibitors compared with non-selective NSAIDs<sup>17</sup>.  
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15 Against this background of conflicting data, the overall risk-benefit balance of celecoxib versus  
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17 traditional NSAIDs needs to be better clarified in a prospective trial design. This paper describes  
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19 the design and rationale for The Standard care versus Celecoxib Outcome Trial (SCOT), which  
20  
21 is a prospective trial randomising patients without a history of cardiovascular disease to  
22  
23 celecoxib or traditional NSAID and measuring cardiovascular outcomes that is expected to report  
24  
25 in 2014. This trial, which started recruiting in 2008, is a large streamlined safety study of  
26  
27 celecoxib versus traditional NSAIDs in patients with osteoarthritis or rheumatoid arthritis that  
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29 aims to address the relative cardiovascular and gastrointestinal safety of the two treatment  
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32 strategies in a real world setting.  
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## Methods and analysis

### Trial Design

#### *Overall Trial Design*

The SCOT trial is an active comparator, streamlined clinical trial with Prospective, Randomised, Open label, Blinded Endpoint evaluation (PROBE) design<sup>18</sup>. It aims to compare the cardiovascular and gastrointestinal safety of continuing with current traditional NSAID therapy versus switching to celecoxib therapy in patients with osteoarthritis or rheumatoid arthritis. After randomisation to celecoxib or to continue their current traditional NSAID therapy, subjects are followed up for an average of 2 years for pre-defined cardiovascular, gastrointestinal and renal events and mortality (Figure 1).

#### *Study Population*

The EMA requested that the trial population should include patients from at least two European Member States. The trial is being conducted in the UK, Denmark and The Netherlands. Patients over the age of 60 years, who are free from cardiovascular disease, and are taking chronic NSAID therapy for osteoarthritis or rheumatoid arthritis are included in the study. The trial inclusion and exclusion criteria are listed in Table 1 and Table 2 respectively.

#### *Recruitment and randomisation of participants*

Potentially suitable patients are identified from general practice populations. Written informed consent is obtained from participants. The research nurse records baseline variables, takes blood and urine for baseline biochemistry and haematology and records the medical history. Blood samples are analysed at the local health service laboratory according to usual practice. Serum for

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3 future analyses and blood for future genetic analyses are stored by regional centres. Subjects who  
4  
5 have given informed consent and meet the inclusion and exclusion criteria are randomised to  
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7 receive celecoxib or to continue on their usual traditional NSAID therapy. Randomisation is  
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9 performed by contacting a central randomisation facility based at the Robertson Centre for  
10  
11 Biostatistics, University of Glasgow by telephone or via a web-based service.  
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### 15 16 17 **Stratification of randomisation**

18  
19 Prior to the start of the study, a group of general practitioners' databases in Scotland and the  
20  
21 centralised dispensing database in Denmark were screened to identify the distribution of usage of  
22  
23 different NSAIDs. On this basis, each NSAID with a frequency of usage >12% (ibuprofen and  
24  
25 diclofenac) was assigned its own stratum. Other NSAIDs were pooled into a single stratum for  
26  
27 the purpose of randomisation. The allocated therapy is prescribed using the normal health  
28  
29 service prescription form. Thus therapy is provided to patients in an open-label fashion in order  
30  
31 to mimic normal care as closely as possible.  
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39 After randomisation, a health service prescription is issued for the randomised drug and the  
40  
41 patient's case records and computer file are marked to show that they are participating in the  
42  
43 SCOT trial. Repeat prescriptions are issued according to normal clinical practice and patients  
44  
45 take their medication according to clinical need. This method is 'naturalistic' in that it most  
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47 closely mimics the real world of NSAID use.  
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### 53 **Trial treatments**

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3 The trial treatments are either celecoxib (Celebrex®) or any other licensed non-selective  
4 traditional NSAID listed in the British National Formulary section 10.1.1 (ibuprofen,  
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The trial treatments are either celecoxib (Celebrex®) or any other licensed non-selective traditional NSAID listed in the British National Formulary section 10.1.1 (ibuprofen, aceclofenac, acemetacin, dexibuprofen, dexketoprofen, diclofenac sodium, diflunisal, etodolac, fenbufen, fenoprofen, flurbiprofen, ibuprofen, indometacin, ketoprofen, mefenamic acid, meloxicam, nabumetone, naproxen, piroxicam, sulindac, tenoxicam, tiaprofenic acid and Arthrotec® (diclofenac plus misoprostol)).

Celecoxib is prescribed at standard licensed doses of up to 200mg bd – the dose is adjusted as necessary up to this maximum limit to provide adequate symptomatic relief. Other NSAIDs are continued at their standard licensed doses and again, the dose may be adjusted as necessary to control symptoms.

### ***Compliance***

Study medication prescriptions are recorded on practice computer systems. Compliance is measured as the number of prescription doses prescribed divided by the number of days between prescriptions averaged over the time in the trial.

### ***Discontinuation of Randomised Therapy***

If a period of 56 days elapses from the estimated end of the last written prescription or if a prescription is written for a traditional NSAID or COX2 inhibitor other than that allocated at the time of randomisation, it is confirmed whether the patient has discontinued therapy and, if appropriate, the reason for study drug discontinuation is recorded.

### ***Concomitant Medications***

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2  
3 Concomitant medications are also recorded. Of particular interest are prescriptions for aspirin,  
4  
5 ulcer healing drugs and antihypertensive drugs.  
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### 10 *Rescue Medication*

#### 11 Efficacy

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13 Patients who experience the onset of inadequate therapeutic efficacy may be up-titrated in dose  
14  
15 as per normal clinical practice. Such dose escalations are tracked. Additional rescue medication  
16  
17 may be prescribed in order that the patient continues on randomised therapy. These rescue  
18  
19 medications may include paracetamol (acetaminophen), opiates such as codeine, dihydrocodeine,  
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21 tramadol etc., nefopam, low dose anti-depressant therapy and other recognised analgesic  
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23 augmenting therapies.  
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#### 32 Tolerability

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34 Patients who experience the onset of symptoms of upper gastrointestinal discomfort, dyspepsia  
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36 or heartburn may be prescribed antacid therapy or ulcer healing therapy at the discretion of their  
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38 primary care physician. Study site coordinators report such events as treatment-related adverse  
39  
40 events and specify if they lead to discontinuation of randomised study treatment.  
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### 46 **Original study design with a celecoxib run-in period (2008-2010 prior to protocol** 47 48 **amendment)**

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50 In the original trial design (for patients entering the study up to between April and August 2010  
51  
52 depending on study site), 3962 subjects underwent a celecoxib run-in period prior to  
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54 randomisation and 2545 subjects were subsequently randomised. The celecoxib run-in was done  
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3 in all patients completing screening for the study. They were asked to discontinue their current  
4 NSAID and enter a two-week (14 +/- 7 days) open-label run-in of treatment with celecoxib as  
5 two to four 100mg tablets taken daily in single or divided doses. During the run-in period the  
6 dose of celecoxib was titrated to achieve equivalent pain control to their previous NSAID  
7 therapy. At the end of this period, subjects who had taken at least one dose of celecoxib and who  
8 did not express a strong preference for either their previous treatment or celecoxib were eligible  
9 for randomisation. Preference was determined by the patient response to a questionnaire:  
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22 Which statement do you agree with?  
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- 24 1. My previous pain killer was much better than celecoxib
  - 25 2. My previous pain killer was somewhat better than celecoxib
  - 26 3. My previous pain killer and celecoxib were the same
  - 27 4. Celecoxib was somewhat better than my previous pain killer
  - 28 5. Celecoxib was much better than my previous pain killer
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39 Only subjects who responded with answers 2, 3 or 4 were eligible for randomisation. This  
40 resulted in 1,417 subjects being excluded using this run-in period.  
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46 This open-label celecoxib run-in period was originally included in the design of the SCOT trial  
47 because a major problem with previous randomised trials of NSAID toxicity had been dropout  
48 from randomised treatment during the trial. For example, in the TARGET trial, only 60% of  
49 subjects completed the trial and 31-37% of subjects withdrew from randomised therapy.<sup>19</sup> In the  
50 CLASS study, less than 50% of those randomised completed the study and there was differential  
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3 dropout between the two treatment arms.<sup>20</sup> A similar trial run-in phase was used in the Heart  
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5 Protection Study.<sup>21</sup> It was hoped that by having a celecoxib run-in period, dropouts after  
6  
7 randomisation would be avoided. However, after review of the data on the level of dropouts after  
8  
9 the first few years of the trial, it was clear that the celecoxib run-in period was resulting in  
10  
11 different rates of randomisation in different centres with hardly any being excluded in some  
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13 centres and a high proportion being excluded in others. For this reason the protocol was amended  
14  
15 to remove the run-in period and to perform randomisation on the day of screening if the subject  
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17 was eligible. This amendment was implemented in each region on different dates but was  
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19 complete by September 2010. Since then, up to October 2012, around 3500 further patients were  
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21 randomised without run-in period. We have since formally evaluated the influence of the  
22  
23 presence or absence of the celecoxib run-in period on study drop-out rates and found no  
24  
25 significant difference (adjusted odds ratio for drop-out at 180 days in patients with the celecoxib  
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27 run-in period was 1.28 (95% CI 0.76-2.14)<sup>22</sup>.  
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## 36 **Trial endpoints**

### 37 ***Primary Endpoint***

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39 The primary endpoint is the first occurrence of hospitalisation or death for the Anti-Platelet  
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41 Trialists' Collaboration (APTC) cardiovascular endpoint of non-fatal myocardial infarction, non-  
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43 fatal stroke or cardiovascular death.  
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51 The secondary and tertiary endpoints and further planned analyses are listed in Table 3.  
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### 55 **Assessment of study endpoints, adverse events, and serious adverse events**

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3 The principal mode of collection of study endpoints, adverse events and serious adverse events  
4 in the SCOT trial is by record-linkage from national population healthcare databases. Record-  
5 linkage retrieves electronic records of hospitalisations and deaths for individual patients within  
6 the study from central databases. Hospitalisation discharge diagnoses are coded and causes of  
7 death are reported. Any events of particular interest (potential study endpoints) are investigated  
8 further and confirmed by retrieving the original case records. Record-linkage has previously  
9 been demonstrated to be highly effective in the follow-up of patients for study events<sup>23</sup>. Any  
10 treatment-related adverse events and serious adverse events detected and reported by research  
11 staff or physicians manually are also collected and investigated.  
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#### 27 ***Mortality data by record-linkage***

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29 Mortality and certified cause-specific mortality are retrieved from national mortality record  
30 systems by record-linkage at approximately 3 monthly intervals.  
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#### 36 ***Morbidity data by record-linkage***

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38 Hospitalisations are retrieved by record-linkage from national systems at approximately 3  
39 monthly intervals.  
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#### 45 ***Data Abstraction for endpoint adjudication***

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47 For each death, and for each hospitalisation that is a potential endpoint, primary care and  
48 secondary care records and, if appropriate, full death certification data is retrieved. Diagnostic  
49 validation forms are filled in to supplement scanned images of original case records relating to  
50 the endpoints in question. The scanned images of case records and the data validation forms are  
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3 collated. Any record of randomised treatment is removed before these collated documents are  
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5 passed to the relevant (cardiovascular or gastrointestinal) endpoint committee for adjudication as  
6  
7 to the hospital diagnosis or the cause of death. This is the Prospective Randomised Open Blinded  
8  
9 Endpoint (PROBE) design and is similar to the design of the Anglo Scandinavian Cardiac  
10  
11 Outcomes Trial (ASCOT).<sup>24</sup>  
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### 14 15 16 17 18 ***Adjudication of Endpoints***

19  
20 Endpoint data are adjudicated by two independent endpoint committees, one for cardiovascular  
21  
22 endpoints (also adjudicate heart failure, renal and death endpoints) and one for gastrointestinal  
23  
24 endpoints. These committees are blinded to randomised treatment and have due regard of the  
25  
26 published consensus diagnostic criteria for myocardial infarction,<sup>25</sup> stroke,<sup>26</sup> vascular death,  
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28 ulcer-related upper gastrointestinal hospitalisations or death, heart failure<sup>27</sup> and renal failure.<sup>28,29</sup>  
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### 34 35 36 37 38 **Adverse Events**

39 All observed or volunteered adverse events that are considered to be serious or related to  
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41 randomised study treatment, regardless of treatment group or suspected causal relationship to the  
42  
43 investigational product(s), are recorded on the adverse event pages of the electronic case report  
44  
45 form (eCRF). Adverse events are defined as abnormal test findings, clinically significant  
46  
47 symptoms and signs, changes in physical examination findings or hypersensitivity. A serious  
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49 adverse event (SAE) or serious adverse drug reaction is any untoward medical occurrence at any  
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51 dose that: results in death, is life-threatening (immediate risk of death), requires inpatient  
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53 hospitalisation or prolongation of existing hospitalisation, results in persistent or significant  
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55 disability/incapacity or results in congenital anomaly or birth defect.  
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6 For these adverse events, further information is obtained to determine the outcome of the adverse  
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8 event and to confirm whether it meets the criteria for classification as a SAE requiring immediate  
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10 notification to the sponsor. Physicians assess causality, and expectedness for any SAE thought to  
11  
12 be related to study drug, on the web portal. Follow-up of SAEs continues until the event has  
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14 resolved or the patient has died. In this study, primary and secondary study endpoints and their  
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16 associated symptoms and laboratory abnormalities are not reported as Suspected Unexpected  
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18 Serious Adverse Drug Reactions (SUSARs). Further, adverse events that are neither considered  
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20 to be serious nor related to randomised treatment are not reported.  
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## 24 **Data Analysis/Statistical Method**

### 25 *Sample Size Determination*

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28 Originally, the study was powered at 90% to exclude a 30% poorer outcome on celecoxib  
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30 compared to traditional NSAIDs (hazard ratio=1.3) in the primary endpoint with a non-  
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32 inferiority analysis between the two treatment strategies. However, due to slower than expected  
33  
34 recruitment and lower than expected event rates, the trial steering committee made the decision  
35  
36 to revise the power of the study to 80% and the non-inferiority limit to 1.4 in October 2011.  
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43 The statistical method to be used will involve a stratified Cox proportional hazards model  
44  
45 including the randomisation strata and the randomised treatment group as covariates. Statistical  
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47 significance for the treatment differences will be based on the Wald statistics and on two-sided  
48  
49 95% confidence intervals for the estimated hazard ratio comparing celecoxib to non-selective  
50  
51 NSAIDs. The original power calculations suggested that for an average duration of 2 years  
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53 exposure to treatment with a 30% non-inferiority limit and a NSAID-exposed CV event rate of  
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3 2.0% per year the study would require 6,841 subjects in each treatment group or 13,682 subjects  
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5 in total and 611 patients with endpoints (based on an intention-to-treat analysis). Since, an on-  
6  
7 treatment analysis will result in reduced follow-up that was difficult to predict *a priori*, follow-  
8  
9 up would be continued until 611 endpoints were identified in the per-protocol population.  
10  
11 Following the revision to the power calculation made in 2011 (power 80%, non-inferiority limit  
12  
13 1.4), the number of primary endpoints required to achieve adequate power in the per-protocol  
14  
15 population decreased to 277.  
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### 22 ***Primary Analysis***

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24 A full Statistical Analysis Plan has been developed. The first analysis to be carried out will be a  
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26 non-inferiority analysis of the primary outcome based on the per-protocol population (those  
27  
28 subjects remaining on randomised therapy) with a supporting non-inferiority analysis based on  
29  
30 the intention-to-treat population. A patient will be considered to remain on the randomised  
31  
32 therapy until a period of 56 days following the last recorded prescription of the medication  
33  
34 allocated at randomisation plus 28 calendar days.  
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41 Thus the *per-protocol* analysis will censor subjects after:

- 42  
43 - Discontinuation from original randomised therapy (defined as 84 days after day of last  
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45 recorded prescription)
- 46  
47 - First primary study endpoint
- 48  
49 - Withdrawal of consent.  
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3 If non-inferiority is demonstrated, a superiority analysis will be carried out based on the  
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6 intention-to-treat population.  
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### 10 ***Sensitivity Analysis***

11  
12 A prospective sensitivity analysis will be performed adding a 90-day period to the *per-protocol*  
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14 period (or end of study) to ensure that withdrawal or crossover is not a presage of disease. This  
15  
16 will be done for both primary and secondary endpoints.  
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### 20 ***Subgroup Analyses and Prognostic Factors***

21  
22 Subgroup analyses will be conducted comparing celecoxib treatment with each of the individual  
23  
24 non-selective NSAID treatments allocated at randomisation. In addition, subgroup analyses will  
25  
26 be carried out for each of the baseline covariates described below that are significant predictors  
27  
28 of the primary endpoint in a Cox regression model including that variable alone plus the  
29  
30 stratification categorical variable.  
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35 Baseline covariates include age, sex, baseline blood pressure, baseline total cholesterol, HDL  
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37 cholesterol and LDL cholesterol, body mass index, smoking status, prior upper gastrointestinal  
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39 bleed or perforation, history of peptic ulcer, *Helicobacter pylori* serology status at baseline,  
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41 diabetes, social deprivation category, use of systemic (not inhaled) steroids at entry, indication  
42  
43 for NSAID i.e. rheumatoid arthritis or osteoarthritis diagnosis, randomised therapy and aspirin  
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45 use.  
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### 50 **Ethics and dissemination**

### ***Steering Committee and Independent Data Monitoring Committee (IDMC)***

A steering committee oversees the conduct of the trial and an independent data monitoring committee receives unblinded data and has the power to recommend to the steering committee modifications to study conduct, including early discontinuation of the study, based on a risk/benefit assessment of the study data.

### ***Study Sponsorship, Monitoring, Audit, Quality Control & Quality Assurance***

The University of Dundee is the study sponsor and supervises monitoring and undertakes quality assurance of the study.

### ***Legal and Ethical Issues***

The trial has been approved by the UK Multi-Centre Research Ethics Committee (MREC) (Reference number: 2006-005735-24) and the Medicines and Healthcare products Regulatory Agency (MHRA) (Reference number: 07/MRE00/9). It is also approved by the relevant authorities in Denmark and the Netherlands. It is registered on ClinicalTrials.gov (Reference number: NCT00447759). The trial is performed in accordance with the protocol, International Conference on Harmonization Good Clinical Practice guidelines, ISPE Good Pharmacoepidemiology Practice guidance<sup>30</sup> and applicable local regulatory requirements and laws.

### ***Dissemination***

The results of the trial will be published in a peer-reviewed scientific journal.

## Discussion

The methodology of the SCOT trial differs from many traditional trials in that follow-up is largely electronic using record-linkage techniques and treatments are prescribed within the usual healthcare setting. Such a design means that the trial more closely mimics normal care. There have been a number of publications of meta-analyses of cardiovascular risk-benefit of celecoxib compared to NSAIDs.<sup>31,32,33</sup> Most of them showed that there was no increase in cardiovascular risk in patients receiving celecoxib compared with traditional NSAIDs. Alongside the current SCOT trial, a more traditional trial is ongoing in the United States - The Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen Or Naproxen (PRECISION) trial<sup>34, 35</sup>. It is a randomized, double-blind, parallel-group study of cardiovascular safety in osteoarthritis or rheumatoid arthritis patients with, or at high risk of, cardiovascular disease comparing celecoxib with naproxen and ibuprofen.

Traditional trials have good internal validity but less external validity. A large streamlined safety trial is expected to have good external validity. However, such a trial becomes more observational with time and internal validity becomes less reliable. The PRECISION and SCOT trial results are likely to be available by around 2014 and we believe that the results will inform clinical practice in a more reliable way than previous studies of cardiovascular safety of NSAIDs. We believe that naturalistic trials such as the SCOT trial will be essential in shaping health care policy in the future.

## Funding statement

1  
2  
3 The study takes place as an academic study, grant-funded by Pfizer as an Investigator Initiated  
4  
5 Research Grant, under a full legal agreement with Pfizer, with the University of Dundee being  
6  
7 the study sponsor.  
8  
9

### 10 11 12 **Competing interests statement**

13  
14  
15 ISM and TMM have previously had part of their university salary reimbursed to the University  
16  
17 by Pfizer in connection with the SCOT trial. In the last 5 years TMM has received honoraria for  
18  
19 lectures and consulting from NiCox, Novartis and Astra Zeneca in relation to NSAID therapies  
20  
21 and from other companies regarding other therapeutic areas. MEMO holds research grants from  
22  
23 Novartis, Pfizer, Ipsen & Menarini. IF and CH have received research funding from Pfizer  
24  
25 related to the conduct of the SCOT trial.  
26  
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### 34 **Authors' contributions**

35  
36 The original study protocol was written by TM, IF, CH and EF. This paper describing the  
37  
38 protocol was written by LW, IM, TM, IF and CH with review and input from the other  
39  
40 collaborators listed below.  
41  
42  
43  
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45

### 46 **\*SCOT Study Group collaborators:**

47  
48 **\*Executive Committee** – Thomas M MacDonald (Chief Investigator), Ian Ford, Chris Hawkey;

49  
50 **\*Steering Committee** – Thomas M MacDonald, Ian Ford, Chris Hawkey, Jesper Hallas, John  
51  
52 Webster, David Reid, Isla Mackenzie, Stuart Ralston, Matthew Walters, FD Richard Hobbs, Sir  
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3 Lewis Ritchie, Mark Davis, Susana Perez-Gutthann, Frank Ruschitzka, James Scheiman, Evelyn  
4  
5 Findlay, John McMurray, Brendan Delaney & Diedrick Grobbee.  
6  
7

### 8 **Independent Data and Statistical Centre**

9  
10 Sharon Kean (IT and data management), Nicola Greenlaw and Michele Robertson (Biostatistics)

11  
12 **Consultant Epidemiologist** – Li Wei.

### 13 **Independent Data Monitoring Committee**

14  
15  
16  
17 Kim Fox (Chair), Gordon Murray, Frank Murray.

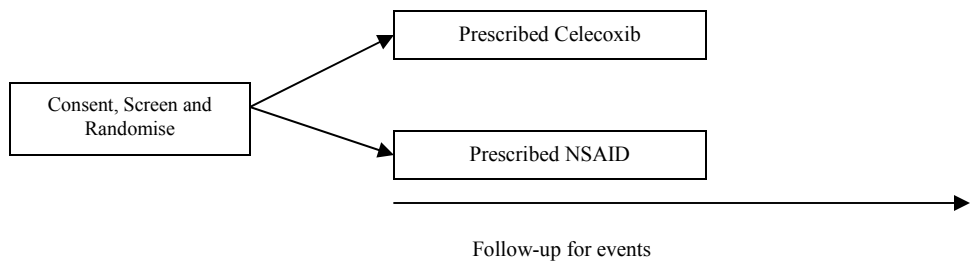
### 18 **Endpoint Adjudication Committees**

19  
20  
21 **Cardiovascular:** John McMurray (Chair), Pardeep Jhund, Mark Petrie, Michael MacDonald.

22  
23  
24 **Gastrointestinal:** James Scheiman (Chair), John Dillon, Jane Moeller, Angel Lanas.  
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**Figure 1 – Current SCOT trial design**



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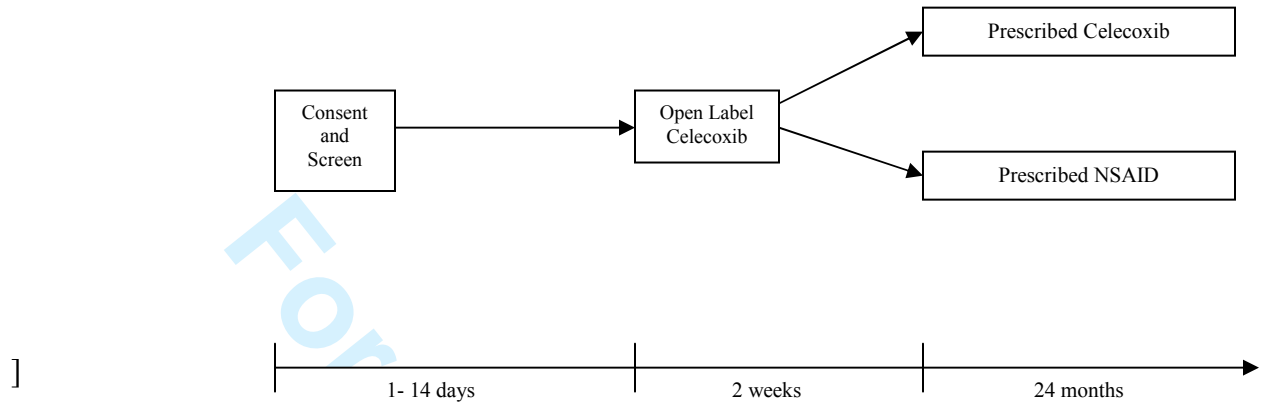


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Figure 2 - Original SCOT trial design (including 2-week celecoxib run-in period)



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3 **Table 1 – Inclusion criteria**  
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- 8 1. Age 60 or over.  
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10 2. Male and female subjects.  
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12 3. Chronic NSAID use ( $\geq 90$  days or at least 3 filled prescriptions in the last year).  
13  
14 4. Subjects who, in the opinion of the recruiting physician, have a licensed indication for  
15 chronic non-selective NSAID or celecoxib therapy (osteoarthritis (OA) or rheumatoid  
16 arthritis (RA)).  
17  
18 5. Subjects, who in the opinion of the study site coordinator, are eligible for treatment (with  
19 reference to the summary of product characteristics) with either celecoxib or an  
20 alternative traditional non-selective NSAID. In particular these subjects must be free  
21 from established cardiovascular disease (established ischaemic heart disease (IHD), heart  
22 failure, cerebrovascular disease and peripheral arterial disease).  
23  
24 6. Subjects who are willing to give permission for their paper and electronic medical  
25 records and prescribing data to be accessed and abstracted by trial investigators.  
26  
27 7. Subjects who are willing to be contacted and interviewed by trial investigators, should the  
28 need arise for adverse event assessment etc.  
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30 8. For the avoidance of doubt, there are no other specific co-morbidities, or concurrent drug  
31 therapies (including aspirin) that are contraindicated.  
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**Table 2 – Exclusion criteria**

1. Established cardiovascular disease including IHD such as myocardial infarction, angina or acute coronary syndrome, cerebrovascular disease such as a cerebrovascular accident or transient ischaemic attack, established peripheral vascular disease and moderate or severe heart failure.
2. Subject currently taking a COX-2 selective NSAID (celecoxib or etoricoxib), or having received one of the therapies within 90 days of screening.
3. Presence of a life-threatening co-morbidity (investigator opinion).
4. Presence of clinically important renal or hepatic disease (investigator opinion).
5. Subjects whose behaviour or lifestyle would render them less likely to comply with study medication (i.e. alcoholism, substance misuse, debilitating psychiatric conditions or inability to provide informed consent).
6. Subjects with known or suspected allergy to celecoxib or NSAIDs including aspirin.
7. Subjects with known hypersensitivity to sulphonamide antibiotics.
8. Subjects with active peptic ulceration or gastrointestinal (GI) bleeding.
9. Subjects scheduled to have arthritis surgery likely to modify their need for pain relief within the next year.
10. Subjects currently participating in another clinical trial or who have been in a trial in the previous three months.

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3 **Table 3 – Secondary and tertiary endpoints and further analyses**  
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8 **Secondary endpoints**  
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- 10 1. First occurrence of hospitalisation or death for upper gastrointestinal ulcer complications  
11 (bleeding, perforation or obstruction).  
12  
13 2. First occurrence of hospitalised upper gastrointestinal ulcer complications or APTC endpoint.  
14  
15 3. First hospitalisation for heart failure.  
16  
17 4. First occurrence of hospitalisation for APTC endpoint plus heart failure.  
18  
19 5. All cause mortality.  
20  
21 6. First hospitalisation for new or worsening renal failure.  
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29 **Tertiary endpoints**  
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- 31 1. First occurrence of hospitalisation or death for upper gastrointestinal bleeding, perforation or  
32 obstruction not due to ulcers.  
33  
34 2. First occurrence of hospitalisation or death for lower gastrointestinal bleeding, perforation or  
35 obstruction.  
36  
37 3. First occurrence of hospitalisation or death for all episodes of gastrointestinal bleeding,  
38 perforation or obstruction.  
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48 **Further planned analyses**  
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- 50 1. Myocardial infarction as a whole and as the components of ST segment elevation myocardial  
51 infarction and non ST elevation myocardial infarction.  
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53 2. Non-fatal stroke.  
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3 3. Cardiovascular death.  
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6 4. Analyses of GI subcomponents  
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8 (a) Hospitalisation or death for all episodes of upper gastrointestinal bleeding  
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10 (b) Hospitalisation or death for all episodes of lower gastrointestinal bleeding  
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12 (c) Hospitalisation or death for all episodes of gastrointestinal bleeding  
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14  
15 5. All uncomplicated upper gastrointestinal ulcers detected during the study  
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18 6. All upper gastrointestinal ulcers (complicated and uncomplicated) detected during the study.  
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20 7. New prescription for ulcer healing drugs.  
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22 8. All hospitalisations.  
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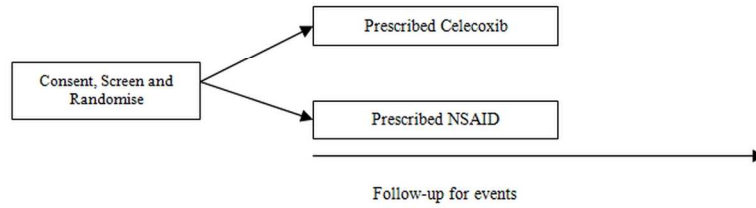


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5 Safety versus Ibuprofen Or Naproxen (PRECISION), a cardiovascular end point trial of nonsteroidal anti-  
6 inflammatory agents in patients with arthritis. Am Heart J 2009;157(4):606-12. Epub 2009 Feb 25.  
7 <sup>35</sup> <http://clinicaltrials.gov/ct/show/NCT00346216>.  
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**Figure 1 – Current SCOT trial design**

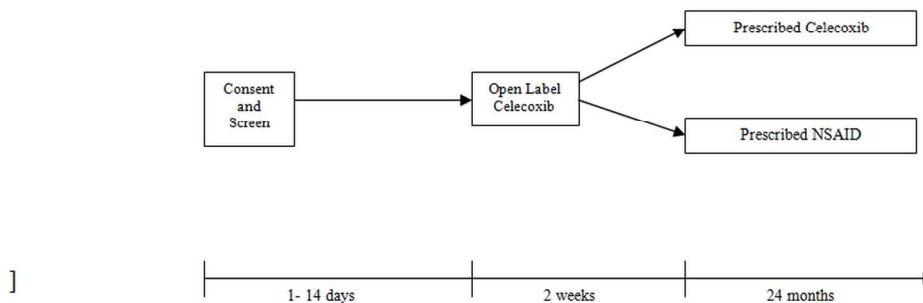


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Figure 2 - Original SCOT trial design (including 2-week celecoxib run-in period)



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**Methodology of a large prospective randomised open, blinded endpoint streamlined safety study of celecoxib versus traditional non-steroidal anti-inflammatory drugs (NSAIDs) in patients with osteoarthritis or rheumatoid arthritis: protocol of the Standard care versus Celecoxib Outcome Trial (SCOT)**

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2012-002295.R1
Article Type:	Protocol
Date Submitted by the Author:	07-Jan-2013
Complete List of Authors:	MacDonald, Thomas; University of Dundee, Clinical Pharmacology Mackenzie, Isla; University of Dundee, Clinical Pharmacology Wei, Li; UCL, School of Pharmacy Hawkey, Christopher; University of Nottingham, NDDC Ford, Ian; University of Glasgow, Robertson Centre for Biostatistics
<b>Primary Subject Heading</b>:	Pharmacology and therapeutics
Secondary Subject Heading:	Rheumatology, Gastroenterology and hepatology, General practice / Family practice, Cardiovascular medicine, Research methods
Keywords:	THERAPEUTICS, Adverse events < THERAPEUTICS, Clinical trials < THERAPEUTICS

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Manuscripts

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3 **Methodology of a large prospective randomised open, blinded endpoint streamlined safety**  
4 **study of celecoxib versus traditional non-steroidal anti-inflammatory drugs in patients with**  
5 **osteoarthritis or rheumatoid arthritis: protocol of the Standard care versus Celecoxib**  
6 **Outcome Trial (SCOT)**  
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15 **The SCOT study group collaborators\*.**  
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20 **Corresponding author:**  
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43 Word count (abstract) 297; Word count (full text) 4898; Figures 2; Tables 3  
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46 **Article summary:**  
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48 **Article focus:**  
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- 50  
51 • The SCOT trial compares the cardiovascular and gastrointestinal safety of a strategy of  
52 celecoxib therapy and a strategy of traditional NSAID therapy in patients with osteoarthritis or  
53 rheumatoid arthritis aged over 60 years without a history of cardiovascular disease.  
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**Key messages:**

- The SCOT trial is a prospective randomised trial comparing celecoxib with traditional NSAIDs in patients with arthritis without a history of cardiovascular disease.
- Cardiovascular safety of NSAIDs is an important issue where more evidence is required to guide practice.
- The SCOT trial uses electronic record-linkage to collect data on endpoints.

**Strengths and limitations of this study:**

The SCOT trial is a prospective randomised trial in a population of patients who take NSAIDs longterm and are therefore representative of patients who might be at risk from NSAID therapy.

The SCOT trial is a streamlined safety trial with good external validity as it is conducted in the normal care setting. Limitations of the study include the need to extrapolate from the results to guide therapy in younger patients and in patients without a history of using NSAIDs and the lack of traditional study follow-up visits although it has been shown that record-linkage can be used effectively in trial follow-up to detect events.

## Abstract

**Introduction:** Cyclooxygenase 2 (COX-2) inhibitors have less upper gastrointestinal toxicity than traditional non-steroidal anti-inflammatory drugs (NSAIDs). However, both COX-2 inhibitors and traditional NSAIDs may be associated with adverse cardiovascular side effects. Data from randomised and observational studies suggest that celecoxib has similar cardiovascular toxicity to traditional NSAIDs. The overall safety balance of a strategy of celecoxib therapy versus traditional NSAID therapy is unknown. The European Medicines Agency (EMA) requested studies of the cardiovascular safety of celecoxib within Europe. The Standard care versus Celecoxib Outcome Trial (SCOT) compares the cardiovascular safety of celecoxib with traditional NSAID therapy in the setting of the EU healthcare system.

**Methods and analysis:** SCOT is a large streamlined safety study conducted in Scotland, England, Denmark, and the Netherlands using the Prospective Randomised Open Blinded Endpoint (PROBE) design. Patients aged over 60 years with osteoarthritis or rheumatoid arthritis, free from established cardiovascular disease and requiring chronic NSAID therapy are randomised to celecoxib or their previous traditional NSAID. They are then followed up for events by record-linkage within their normal healthcare setting. The hypothesis is non-inferiority with a confidence limit of 1.4.

The primary endpoint is the first occurrence of hospitalisation or death for the Anti-Platelet Trialists' Collaboration (APTC) cardiovascular endpoint of non-fatal myocardial infarction, non-fatal stroke or cardiovascular death. Secondary endpoints are 1) first hospitalisation or death for upper gastrointestinal ulcer complications (bleeding, perforation or obstruction); 2) first occurrence of hospitalised upper gastrointestinal ulcer complications or APTC endpoint; 3) first

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3 hospitalisation for heart failure; 4) first hospitalisation for APTC endpoint plus heart failure; 5)  
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5 all-cause mortality and 6) first hospitalisation for new or worsening renal failure.  
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8 **Ethics and dissemination:** The SCOT trial has been approved by the relevant ethics  
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10 committees. The trial results will be published in a peer-reviewed scientific journal.  
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12 **Registration:** Clinicaltrials.gov (NCT00447759).  
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## Introduction

NSAID-induced gastrointestinal toxicity is one of the most common serious drug adverse events requiring hospitalisation.<sup>1</sup> Upper gastrointestinal complications result in considerable morbidity and mortality. The COX-2 selective NSAIDs gained popularity based upon evidence that they are associated with a lower incidence of ulcer-related upper gastrointestinal tract complications compared to traditional non-selective NSAID therapy. However, the withdrawal of rofecoxib<sup>2</sup> due to cardiovascular toxicity and the suggestion that most NSAIDs are probably associated with increased cardiovascular adverse events when compared to placebo,<sup>3</sup> has led to the need for further prospective studies on the safety of other COX-2 inhibitors and traditional NSAIDs.

The cardiovascular safety profile of COX-2 inhibitors was brought into question following the results of two placebo-controlled studies designed to test the hypothesis that the COX-2 inhibitors rofecoxib and celecoxib might prevent colorectal adenomas and colorectal tumours. The Adenomatous Polyp Prevention on Vioxx (APPROVe) Trial randomised patients with a history of colorectal adenomas to rofecoxib 25mg or placebo and reported an excess of cardiovascular thrombotic events in the group treated with rofecoxib<sup>4</sup>. The Prevention of Sporadic Colorectal Adenomas with Celecoxib (APC) Trial randomised patients with previous colorectal adenomas to celecoxib 400mg twice daily, celecoxib 200mg twice daily or placebo and reported a dose-related increase in risk of cardiovascular events in the celecoxib groups<sup>5,6</sup>. However, the Prevention of Colorectal Sporadic Adenomatous Polyps (PreSAP) Trial did not show a significant increase in cardiovascular events with celecoxib 400mg given once per day versus placebo in patients with previous colorectal adenomas.<sup>7</sup> In the Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT), which was stopped early due to the findings of the

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3 APC trial, there was a suggestion of an increased risk of cardiovascular events with naproxen but  
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5 not celecoxib compared to placebo, although this study was underpowered and the  
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7 cardiovascular results must therefore be interpreted with caution. In a later meta-analysis of six  
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9 randomised double-blind placebo controlled trials of celecoxib in non-arthritis conditions, which  
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11 included analysis of the APC, PreSAP and ADAPT studies and three other smaller studies  
12  
13 (MA27, The Diabetic Macular Edema (CDME) Trial and the Celecoxib/Selenium Trial), there  
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15 was no evidence of increased cardiovascular risk with celecoxib in low risk patients but there  
16  
17 was a dose-dependent increase in cardiovascular risk in high risk patients<sup>8</sup> .  
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25 In the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme,  
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27 which compared cardiovascular outcomes with etoricoxib 60mg or 90mg daily and diclofenac  
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29 150mg daily in patients with osteoarthritis or rheumatoid arthritis, rates of thrombotic  
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31 cardiovascular events were similar in patients randomised to either drug<sup>9</sup> .  
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37 In trials of celecoxib versus traditional NSAIDs, no evidence of increased cardiovascular toxicity  
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39 has been seen<sup>10</sup> . In large observational studies, celecoxib has not been found to be associated  
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41 with increased cardiovascular risk versus other NSAIDs<sup>11</sup> or non-use.<sup>12,13</sup> At present, much of  
42  
43 the available data comes from observational studies and while it seems clear that rofecoxib  
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45 increased cardiovascular risk, many traditional NSAIDs may also pose considerable risk.<sup>3,11,</sup>  
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53 The recent Celecoxib versus Omeprazole and Diclofenac in patients  
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3 with Osteoarthritis and Rheumatoid arthritis (CONDOR) study found that celecoxib was  
4 associated with a lower incidence of clinically significant upper or lower gastrointestinal events  
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6 than the combination of diclofenac and omeprazole, adding further evidence to the improved  
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8 gastrointestinal safety of COX-2 inhibitors compared with non-selective NSAIDs<sup>17</sup>.  
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15 Against this background of conflicting data, the overall risk-benefit balance of celecoxib versus  
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17 traditional NSAIDs needs to be better clarified in a prospective trial design. This paper describes  
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19 the design and rationale for The Standard care versus Celecoxib Outcome Trial (SCOT), which  
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21 is a prospective trial randomising patients without a history of cardiovascular disease to  
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23 celecoxib or traditional NSAID and measuring cardiovascular outcomes that is expected to report  
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25 in 2014. This trial, which started recruiting in 2008, is a large streamlined safety study of  
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27 celecoxib versus traditional NSAIDs in patients with osteoarthritis or rheumatoid arthritis that  
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29 aims to address the relative cardiovascular and gastrointestinal safety of the two treatment  
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31 strategies in a real world setting.  
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## Methods and analysis

### Trial Design

#### *Overall Trial Design*

The SCOT trial is an active comparator, streamlined clinical trial with Prospective, Randomised, Open label, Blinded Endpoint evaluation (PROBE) design<sup>18</sup>. It aims to compare the cardiovascular and gastrointestinal safety of continuing with current traditional NSAID therapy versus switching to celecoxib therapy in patients with osteoarthritis or rheumatoid arthritis. After randomisation to celecoxib or to continue their current traditional NSAID therapy, subjects are followed up for an average of 2 years for pre-defined cardiovascular, gastrointestinal and renal events and mortality (Figure 1).

#### *Study Population*

The EMA requested that the trial population should include patients from at least two European Member States. The trial is being conducted in the UK, Denmark and The Netherlands. Patients over the age of 60 years, who are free from cardiovascular disease, and are taking chronic NSAID therapy for osteoarthritis or rheumatoid arthritis are included in the study. The trial inclusion and exclusion criteria are listed in Table 1 and Table 2 respectively.

#### *Recruitment and randomisation of participants*

Potentially suitable patients are identified from general practice populations. Written informed consent is obtained from participants. The research nurse records baseline variables, takes blood and urine for baseline biochemistry and haematology and records the medical history. Blood samples are analysed at the local health service laboratory according to usual practice. Serum for

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2  
3 future analyses and blood for future genetic analyses are stored by regional centres. Subjects who  
4  
5 have given informed consent and meet the inclusion and exclusion criteria are randomised to  
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7 receive celecoxib or to continue on their usual traditional NSAID therapy. Randomisation is  
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9 performed by contacting a central randomisation facility based at the Robertson Centre for  
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11 Biostatistics, University of Glasgow by telephone or via a web-based service.  
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### 15 16 17 **Stratification of randomisation**

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19 Prior to the start of the study, a group of general practitioners' databases in Scotland and the  
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21 centralised dispensing database in Denmark were screened to identify the distribution of usage of  
22  
23 different NSAIDs. On this basis, each NSAID with a frequency of usage >12% (ibuprofen and  
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25 diclofenac) was assigned its own stratum. Other NSAIDs were pooled into a single stratum for  
26  
27 the purpose of randomisation. The allocated therapy is prescribed using the normal health  
28  
29 service prescription form. Thus therapy is provided to patients in an open-label fashion in order  
30  
31 to mimic normal care as closely as possible.  
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39 After randomisation, a health service prescription is issued for the randomised drug and the  
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41 patient's case records and computer file are marked to show that they are participating in the  
42  
43 SCOT trial. Repeat prescriptions are issued according to normal clinical practice and patients  
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45 take their medication according to clinical need. This method is 'naturalistic' in that it most  
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47 closely mimics the real world of NSAID use.  
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### 53 **Trial treatments**

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3 The trial treatments are either celecoxib (Celebrex®) or any other licensed non-selective  
4 traditional NSAID listed in the British National Formulary section 10.1.1 (ibuprofen,  
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The trial treatments are either celecoxib (Celebrex®) or any other licensed non-selective traditional NSAID listed in the British National Formulary section 10.1.1 (ibuprofen, aceclofenac, acemetacin, dexibuprofen, dexketoprofen, diclofenac sodium, diflunisal, etodolac, fenbufen, fenoprofen, flurbiprofen, ibuprofen, indometacin, ketoprofen, mefenamic acid, meloxicam, nabumetone, naproxen, piroxicam, sulindac, tenoxicam, tiaprofenic acid and Arthrotec® (diclofenac plus misoprostol)).

Celecoxib is prescribed at standard licensed doses of up to 200mg bd – the dose is adjusted as necessary up to this maximum limit to provide adequate symptomatic relief. Other NSAIDs are continued at their standard licensed doses and again, the dose may be adjusted as necessary to control symptoms.

### ***Compliance***

Study medication prescriptions are recorded on practice computer systems. Compliance is measured as the number of prescription doses prescribed divided by the number of days between prescriptions averaged over the time in the trial.

### ***Discontinuation of Randomised Therapy***

If a period of 56 days elapses from the estimated end of the last written prescription or if a prescription is written for a traditional NSAID or COX2 inhibitor other than that allocated at the time of randomisation, it is confirmed whether the patient has discontinued therapy and, if appropriate, the reason for study drug discontinuation is recorded.

### ***Concomitant Medications***

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3 Concomitant medications are also recorded. Of particular interest are prescriptions for aspirin,  
4  
5 ulcer healing drugs and antihypertensive drugs.  
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### 10 *Rescue Medication*

#### 11 Efficacy

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13 Patients who experience the onset of inadequate therapeutic efficacy may be up-titrated in dose  
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15 as per normal clinical practice. Such dose escalations are tracked. Additional rescue medication  
16  
17 may be prescribed in order that the patient continues on randomised therapy. These rescue  
18  
19 medications may include paracetamol (acetaminophen), opiates such as codeine, dihydrocodeine,  
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21 tramadol etc., nefopam, low dose anti-depressant therapy and other recognised analgesic  
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23 augmenting therapies.  
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#### 32 Tolerability

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34 Patients who experience the onset of symptoms of upper gastrointestinal discomfort, dyspepsia  
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36 or heartburn may be prescribed antacid therapy or ulcer healing therapy at the discretion of their  
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38 primary care physician. Study site coordinators report such events as treatment-related adverse  
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40 events and specify if they lead to discontinuation of randomised study treatment.  
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### 46 **Original study design with a celecoxib run-in period (2008-2010 prior to protocol** 47 48 **amendment)**

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50 In the original trial design (for patients entering the study up to between April and August 2010  
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52 depending on study site), 3962 subjects underwent a celecoxib run-in period prior to  
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54 randomisation and 2545 subjects were subsequently randomised. The celecoxib run-in was done  
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3 in all patients completing screening for the study. They were asked to discontinue their current  
4 NSAID and enter a two-week (14 +/- 7 days) open-label run-in of treatment with celecoxib as  
5 two to four 100mg tablets taken daily in single or divided doses. During the run-in period the  
6 dose of celecoxib was titrated to achieve equivalent pain control to their previous NSAID  
7 therapy. At the end of this period, subjects who had taken at least one dose of celecoxib and who  
8 did not express a strong preference for either their previous treatment or celecoxib were eligible  
9 for randomisation. Preference was determined by the patient response to a questionnaire:  
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22 Which statement do you agree with?  
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- 24 1. My previous pain killer was much better than celecoxib
  - 25 2. My previous pain killer was somewhat better than celecoxib
  - 26 3. My previous pain killer and celecoxib were the same
  - 27 4. Celecoxib was somewhat better than my previous pain killer
  - 28 5. Celecoxib was much better than my previous pain killer
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39 Only subjects who responded with answers 2, 3 or 4 were eligible for randomisation. This  
40 resulted in 1,417 subjects being excluded using this run-in period.  
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46 This open-label celecoxib run-in period was originally included in the design of the SCOT trial  
47 because a major problem with previous randomised trials of NSAID toxicity had been dropout  
48 from randomised treatment during the trial. For example, in the TARGET trial, only 60% of  
49 subjects completed the trial and 31-37% of subjects withdrew from randomised therapy.<sup>19</sup> In the  
50 CLASS study, less than 50% of those randomised completed the study and there was differential  
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3 dropout between the two treatment arms.<sup>20</sup> A similar trial run-in phase was used in the Heart  
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5 Protection Study.<sup>21</sup> It was hoped that by having a celecoxib run-in period, dropouts after  
6  
7 randomisation would be avoided. However, after review of the data on the level of dropouts after  
8  
9 the first few years of the trial, it was clear that the celecoxib run-in period was resulting in  
10  
11 different rates of randomisation in different centres with hardly any being excluded in some  
12  
13 centres and a high proportion being excluded in others. For this reason the protocol was amended  
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15 to remove the run-in period and to perform randomisation on the day of screening if the subject  
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17 was eligible. This amendment was implemented in each region on different dates but was  
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19 complete by September 2010. Since then, up to October 2012, around 3500 further patients were  
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21 randomised without run-in period. We have since formally evaluated the influence of the  
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23 presence or absence of the celecoxib run-in period on study drop-out rates and found no  
24  
25 significant difference (adjusted odds ratio for drop-out at 180 days in patients with the celecoxib  
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27 run-in period was 1.28 (95% CI 0.76-2.14)<sup>22</sup>.  
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## 36 **Trial endpoints**

### 37 ***Primary Endpoint***

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39 The primary endpoint is the first occurrence of hospitalisation or death for the Anti-Platelet  
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41 Trialists' Collaboration (APTC) cardiovascular endpoint of non-fatal myocardial infarction, non-  
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43 fatal stroke or cardiovascular death.  
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51 The secondary and tertiary endpoints and further planned analyses are listed in Table 3.  
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### 55 **Assessment of study endpoints, adverse events, and serious adverse events**

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3 The principal mode of collection of study endpoints, adverse events and serious adverse events  
4 in the SCOT trial is by record-linkage from national population healthcare databases. Record-  
5 linkage retrieves electronic records of hospitalisations and deaths for individual patients within  
6 the study from central databases. Hospitalisation discharge diagnoses are coded and causes of  
7 death are reported. Any events of particular interest (potential study endpoints) are investigated  
8 further and confirmed by retrieving the original case records. Record-linkage has previously  
9 been demonstrated to be highly effective in the follow-up of patients for study events<sup>23</sup>. Any  
10 treatment-related adverse events and serious adverse events detected and reported by research  
11 staff or physicians manually are also collected and investigated.  
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#### 27 ***Mortality data by record-linkage***

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29 Mortality and certified cause-specific mortality are retrieved from national mortality record  
30 systems by record-linkage at approximately 3 monthly intervals.  
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#### 36 ***Morbidity data by record-linkage***

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38 Hospitalisations are retrieved by record-linkage from national systems at approximately 3  
39 monthly intervals.  
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#### 45 ***Data Abstraction for endpoint adjudication***

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47 For each death, and for each hospitalisation that is a potential endpoint, primary care and  
48 secondary care records and, if appropriate, full death certification data is retrieved. Diagnostic  
49 validation forms are filled in to supplement scanned images of original case records relating to  
50 the endpoints in question. The scanned images of case records and the data validation forms are  
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3 collated. Any record of randomised treatment is removed before these collated documents are  
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5 passed to the relevant (cardiovascular or gastrointestinal) endpoint committee for adjudication as  
6  
7 to the hospital diagnosis or the cause of death. This is the Prospective Randomised Open Blinded  
8  
9 Endpoint (PROBE) design and is similar to the design of the Anglo Scandinavian Cardiac  
10  
11 Outcomes Trial (ASCOT).<sup>24</sup>  
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### 14 15 16 17 18 ***Adjudication of Endpoints***

19  
20 Endpoint data are adjudicated by two independent endpoint committees, one for cardiovascular  
21  
22 endpoints (also adjudicate heart failure, renal and death endpoints) and one for gastrointestinal  
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24 endpoints. These committees are blinded to randomised treatment and have due regard of the  
25  
26 published consensus diagnostic criteria for myocardial infarction,<sup>25</sup> stroke,<sup>26</sup> vascular death,  
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28 ulcer-related upper gastrointestinal hospitalisations or death, heart failure<sup>27</sup> and renal failure.<sup>28,29</sup>  
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### 34 35 36 37 38 **Adverse Events**

39 All observed or volunteered adverse events that are considered to be serious or related to  
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41 randomised study treatment, regardless of treatment group or suspected causal relationship to the  
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43 investigational product(s), are recorded on the adverse event pages of the electronic case report  
44  
45 form (eCRF). Adverse events are defined as abnormal test findings, clinically significant  
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47 symptoms and signs, changes in physical examination findings or hypersensitivity. A serious  
48  
49 adverse event (SAE) or serious adverse drug reaction is any untoward medical occurrence at any  
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51 dose that: results in death, is life-threatening (immediate risk of death), requires inpatient  
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53 hospitalisation or prolongation of existing hospitalisation, results in persistent or significant  
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55 disability/incapacity or results in congenital anomaly or birth defect.  
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6 For these adverse events, further information is obtained to determine the outcome of the adverse  
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8 event and to confirm whether it meets the criteria for classification as a SAE requiring immediate  
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10 notification to the sponsor. Physicians assess causality, and expectedness for any SAE thought to  
11  
12 be related to study drug, on the web portal. Follow-up of SAEs continues until the event has  
13  
14 resolved or the patient has died. In this study, primary and secondary study endpoints and their  
15  
16 associated symptoms and laboratory abnormalities are not reported as Suspected Unexpected  
17  
18 Serious Adverse Drug Reactions (SUSARs). Further, adverse events that are neither considered  
19  
20 to be serious nor related to randomised treatment are not reported.  
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## 24 **Data Analysis/Statistical Method**

### 25 *Sample Size Determination*

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28 Originally, the study was powered at 90% to exclude a 30% poorer outcome on celecoxib  
29  
30 compared to traditional NSAIDs (hazard ratio=1.3) in the primary endpoint with a non-  
31  
32 inferiority analysis between the two treatment strategies. However, due to slower than expected  
33  
34 recruitment and lower than expected event rates, the trial steering committee made the decision  
35  
36 to revise the power of the study to 80% and the non-inferiority limit to 1.4 in October 2011.  
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43  
44 The statistical method to be used will involve a stratified Cox proportional hazards model  
45  
46 including the randomisation strata and the randomised treatment group as covariates. Statistical  
47  
48 significance for the treatment differences will be based on the Wald statistics and on two-sided  
49  
50 95% confidence intervals for the estimated hazard ratio comparing celecoxib to non-selective  
51  
52 NSAIDs. The original power calculations suggested that for an average duration of 2 years  
53  
54 exposure to treatment with a 30% non-inferiority limit and a NSAID-exposed CV event rate of  
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3 2.0% per year the study would require 6,841 subjects in each treatment group or 13,682 subjects  
4  
5 in total and 611 patients with endpoints (based on an intention-to-treat analysis). Since, an on-  
6  
7 treatment analysis will result in reduced follow-up that was difficult to predict *a priori*, follow-  
8  
9 up would be continued until 611 endpoints were identified in the per-protocol population.  
10  
11 Following the revision to the power calculation made in 2011 (power 80%, non-inferiority limit  
12  
13 1.4), the number of primary endpoints required to achieve adequate power in the per-protocol  
14  
15 population decreased to 277.  
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### 22 ***Primary Analysis***

23  
24 A full Statistical Analysis Plan has been developed. The first analysis to be carried out will be a  
25  
26 non-inferiority analysis of the primary outcome based on the per-protocol population (those  
27  
28 subjects remaining on randomised therapy) with a supporting non-inferiority analysis based on  
29  
30 the intention-to-treat population. A patient will be considered to remain on the randomised  
31  
32 therapy until a period of 56 days following the last recorded prescription of the medication  
33  
34 allocated at randomisation plus 28 calendar days.  
35  
36  
37  
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41 Thus the *per-protocol* analysis will censor subjects after:

- 42
- 43 - Discontinuation from original randomised therapy (defined as 84 days after day of last
- 44 recorded prescription)
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- 46
- 47
- 48 - First primary study endpoint
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- 51 - Withdrawal of consent.
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3 If non-inferiority is demonstrated, a superiority analysis will be carried out based on the  
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6 intention-to-treat population.  
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### 10 ***Sensitivity Analysis***

11  
12 A prospective sensitivity analysis will be performed adding a 90-day period to the *per-protocol*  
13  
14 period (or end of study) to ensure that withdrawal or crossover is not a presage of disease. This  
15  
16 will be done for both primary and secondary endpoints.  
17  
18  
19

### 20 ***Subgroup Analyses and Prognostic Factors***

21  
22 Subgroup analyses will be conducted comparing celecoxib treatment with each of the individual  
23  
24 non-selective NSAID treatments allocated at randomisation. In addition, subgroup analyses will  
25  
26 be carried out for each of the baseline covariates described below that are significant predictors  
27  
28 of the primary endpoint in a Cox regression model including that variable alone plus the  
29  
30 stratification categorical variable.  
31  
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34  
35 Baseline covariates include age, sex, baseline blood pressure, baseline total cholesterol, HDL  
36  
37 cholesterol and LDL cholesterol, body mass index, smoking status, prior upper gastrointestinal  
38  
39 bleed or perforation, history of peptic ulcer, *Helicobacter pylori* serology status at baseline,  
40  
41 diabetes, social deprivation category, use of systemic (not inhaled) steroids at entry, indication  
42  
43 for NSAID i.e. rheumatoid arthritis or osteoarthritis diagnosis, randomised therapy and aspirin  
44  
45 use.  
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### 50 **Ethics and dissemination**

### ***Steering Committee and Independent Data Monitoring Committee (IDMC)***

A steering committee oversees the conduct of the trial and an independent data monitoring committee receives unblinded data and has the power to recommend to the steering committee modifications to study conduct, including early discontinuation of the study, based on a risk/benefit assessment of the study data.

### ***Study Sponsorship, Monitoring, Audit, Quality Control & Quality Assurance***

The University of Dundee is the study sponsor and supervises monitoring and undertakes quality assurance of the study.

### ***Legal and Ethical Issues***

The trial has been approved by the UK Multi-Centre Research Ethics Committee (MREC) (Reference number: 2006-005735-24) and the Medicines and Healthcare products Regulatory Agency (MHRA) (Reference number: 07/MRE00/9). It is also approved by the relevant authorities in Denmark and the Netherlands. It is registered on ClinicalTrials.gov (Reference number: NCT00447759). The trial is performed in accordance with the protocol, International Conference on Harmonization Good Clinical Practice guidelines, ISPE Good Pharmacoepidemiology Practice guidance<sup>30</sup> and applicable local regulatory requirements and laws.

### ***Dissemination***

The results of the trial will be published in a peer-reviewed scientific journal.

## Discussion

The methodology of the SCOT trial differs from many traditional trials in that follow-up is largely electronic using record-linkage techniques and treatments are prescribed within the usual healthcare setting. Such a design means that the trial more closely mimics normal care. There have been a number of publications of meta-analyses of cardiovascular risk-benefit of celecoxib compared to NSAIDs.<sup>31,32,33</sup> Most of them showed that there was no increase in cardiovascular risk in patients receiving celecoxib compared with traditional NSAIDs. Alongside the current SCOT trial, a more traditional trial is ongoing in the United States - The Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen Or Naproxen (PRECISION) trial<sup>34, 35</sup>. It is a randomized, double-blind, parallel-group study of cardiovascular safety in osteoarthritis or rheumatoid arthritis patients with, or at high risk of, cardiovascular disease comparing celecoxib with naproxen and ibuprofen.

Traditional trials have good internal validity but less external validity. A large streamlined safety trial is expected to have good external validity. However, such a trial becomes more observational with time and internal validity becomes less reliable. The PRECISION and SCOT trial results are likely to be available by around 2014 and we believe that the results will inform clinical practice in a more reliable way than previous studies of cardiovascular safety of NSAIDs. We believe that naturalistic trials such as the SCOT trial will be essential in shaping health care policy in the future.

## Funding statement

The study takes place as an academic study, grant-funded by Pfizer as an Investigator Initiated Research Grant, under a full legal agreement with Pfizer, with the University of Dundee being



1  
2  
3 the study sponsor. The study was designed by the trial executive committee (Professor Tom  
4 MacDonald, Professor Ian Ford and Professor Chris Hawkey). The sponsor (University of  
5 Dundee) and the trial steering committee are primarily responsible for data collection, trial  
6 management, analysis and interpretation of data, writing of the report and submission of the  
7 report for publication. Pfizer has provided funding for the SCOT study but has no authority over  
8 the above activities.  
9  
10

### 11 12 13 14 15 **Competing interests statement**

16  
17 ISM and TMM have previously had part of their university salary reimbursed to the University  
18 by Pfizer in connection with the SCOT trial. In the last 5 years TMM has received honoraria for  
19 lectures and consulting from NiCox, Novartis and Astra Zeneca in relation to NSAID therapies  
20 and from other companies regarding other therapeutic areas. MEMO holds research grants from  
21 Novartis, Pfizer, Ipsen & Menarini. IF and CH have received research funding from Pfizer  
22 related to the conduct of the SCOT trial.  
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### 37 **Authors' contributions**

38 The original study protocol was written by TM, IF, CH and EF. This paper describing the  
39 protocol was written by LW, IM, TM, IF and CH with review and input from the other  
40 collaborators listed below.  
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### 48 **\*SCOT Study Group collaborators:**

49  
50 **\*Executive Committee** – Thomas M MacDonald (Chief Investigator), Ian Ford, Chris Hawkey;

51  
52  
53 **\*Steering Committee** – Thomas M MacDonald, Ian Ford, Chris Hawkey, Jesper Hallas, John  
54 Webster, David Reid, Isla Mackenzie, Stuart Ralston, Matthew Walters, FD Richard Hobbs, Sir  
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3 Lewis Ritchie, Mark Davis, Susana Perez-Gutthann, Frank Ruschitzka, James Scheiman, Evelyn  
4 Findlay, John McMurray, Brendan Delaney & Diederick Grobbee.  
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### 8 **Independent Data and Statistical Centre**

9  
10 Sharon Kean (IT and data management), Nicola Greenlaw and Michele Robertson (Biostatistics)

11  
12 **Consultant Epidemiologist** – Li Wei.  
13

### 14 **Independent Data Monitoring Committee**

15  
16 Kim Fox (Chair), Gordon Murray, Frank Murray.  
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19

### 20 **Endpoint Adjudication Committees**

21  
22 **Cardiovascular:** John McMurray (Chair), Pardeep Jhund, Mark Petrie, Michael MacDonald.  
23

24 **Gastrointestinal:** James Scheiman (Chair), John Dillon, Jane Moeller, Angel Lanas.  
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3 **Table 1 – Inclusion criteria**  
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- 8 1. Age 60 or over.  
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10 2. Male and female subjects.  
11  
12 3. Chronic NSAID use ( $\geq 90$  days or at least 3 filled prescriptions in the last year).  
13  
14 4. Subjects who, in the opinion of the recruiting physician, have a licensed indication for  
15 chronic non-selective NSAID or celecoxib therapy (osteoarthritis (OA) or rheumatoid  
16 arthritis (RA)).  
17  
18 5. Subjects, who in the opinion of the study site coordinator, are eligible for treatment (with  
19 reference to the summary of product characteristics) with either celecoxib or an  
20 alternative traditional non-selective NSAID. In particular these subjects must be free  
21 from established cardiovascular disease (established ischaemic heart disease (IHD), heart  
22 failure, cerebrovascular disease and peripheral arterial disease).  
23  
24 6. Subjects who are willing to give permission for their paper and electronic medical  
25 records and prescribing data to be accessed and abstracted by trial investigators.  
26  
27 7. Subjects who are willing to be contacted and interviewed by trial investigators, should the  
28 need arise for adverse event assessment etc.  
29  
30 8. For the avoidance of doubt, there are no other specific co-morbidities, or concurrent drug  
31 therapies (including aspirin) that are contraindicated.  
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3 **Table 2 – Exclusion criteria**  
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- 8 1. Established cardiovascular disease including IHD such as myocardial infarction, angina  
9 or acute coronary syndrome, cerebrovascular disease such as a cerebrovascular accident  
10 or transient ischaemic attack, established peripheral vascular disease and moderate or  
11 severe heart failure.  
12  
13 2. Subject currently taking a COX-2 selective NSAID (celecoxib or etoricoxib), or having  
14 received one of the therapies within 90 days of screening.  
15  
16 3. Presence of a life-threatening co-morbidity (investigator opinion).  
17  
18 4. Presence of clinically important renal or hepatic disease (investigator opinion).  
19  
20 5. Subjects whose behaviour or lifestyle would render them less likely to comply with study  
21 medication (i.e. alcoholism, substance misuse, debilitating psychiatric conditions or  
22 inability to provide informed consent).  
23  
24 6. Subjects with known or suspected allergy to celecoxib or NSAIDs including aspirin.  
25  
26 7. Subjects with known hypersensitivity to sulphonamide antibiotics.  
27  
28 8. Subjects with active peptic ulceration or gastrointestinal (GI) bleeding.  
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30 9. Subjects scheduled to have arthritis surgery likely to modify their need for pain relief  
31 within the next year.  
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33 10. Subjects currently participating in another clinical trial or who have been in a trial in the  
34 previous three months.  
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**Table 3 – Secondary and tertiary endpoints and further analyses****Secondary endpoints**

1. First occurrence of hospitalisation or death for upper gastrointestinal ulcer complications (bleeding, perforation or obstruction).
2. First occurrence of hospitalised upper gastrointestinal ulcer complications or APTC endpoint.
3. First hospitalisation for heart failure.
4. First occurrence of hospitalisation for APTC endpoint plus heart failure.
5. All cause mortality.
6. First hospitalisation for new or worsening renal failure.

**Tertiary endpoints**

1. First occurrence of hospitalisation or death for upper gastrointestinal bleeding, perforation or obstruction not due to ulcers.
2. First occurrence of hospitalisation or death for lower gastrointestinal bleeding, perforation or obstruction.
3. First occurrence of hospitalisation or death for all episodes of gastrointestinal bleeding, perforation or obstruction.

**Further planned analyses**

1. Myocardial infarction as a whole and as the components of ST segment elevation myocardial infarction and non ST elevation myocardial infarction.
2. Non-fatal stroke.

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3 3. Cardiovascular death.  
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6 4. Analyses of GI subcomponents  
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8 (a) Hospitalisation or death for all episodes of upper gastrointestinal bleeding  
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10 (b) Hospitalisation or death for all episodes of lower gastrointestinal bleeding  
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12 (c) Hospitalisation or death for all episodes of gastrointestinal bleeding  
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14  
15 5. All uncomplicated upper gastrointestinal ulcers detected during the study  
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17  
18 6. All upper gastrointestinal ulcers (complicated and uncomplicated) detected during the study.  
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20 7. New prescription for ulcer healing drugs.  
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22 8. All hospitalisations.  
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32 **Figure Legends:**  
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34 **Figure 1: Current SCOT trial design**  
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36 **Figure 2: Original SCOT trial design (including 2-week celecoxib run-in period)**  
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Methodology of a large prospective randomised open, blinded endpoint streamlined safety study of celecoxib versus traditional non-steroidal anti-inflammatory drugs in patients with osteoarthritis or rheumatoid arthritis: protocol of the Standard care versus Celecoxib Outcome Trial (SCOT-~~trial~~)

The SCOT study group collaborators\*.

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Word count (abstract) ~~309~~297; Word count (full text) 4898; Figures 2; Tables 3

**Article summary:**

**Article focus:**

- The SCOT trial compares the cardiovascular and gastrointestinal safety of a strategy of celecoxib therapy and a strategy of traditional NSAID therapy in patients with osteoarthritis or rheumatoid arthritis aged over 60 years without a history of cardiovascular disease.

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9 **Key messages:**

- 10
- 11 • The SCOT trial is a prospective randomised trial comparing celecoxib with traditional
  - 12 NSAIDs in patients with arthritis without a history of cardiovascular disease.
  - 13
  - 14 • Cardiovascular safety of NSAIDs is an important issue where more evidence is required to
  - 15 guide practice.
  - 16
  - 17
  - 18 • The SCOT trial uses electronic record-linkage to collect data on endpoints.
  - 19

20 **Strengths and limitations of this study:**

21 The SCOT trial is a prospective randomised trial in a population of patients who take NSAIDs  
22 longterm and are therefore representative of patients who might be at risk from NSAID therapy.  
23  
24 The SCOT trial is a streamlined safety trial with good external validity as it is conducted in the  
25 normal care setting. Limitations of the study include the need to extrapolate from the results to  
26 guide therapy in younger patients and in patients without a history of using NSAIDs and the lack  
27 of traditional study follow-up visits although it has been shown that record-linkage can be used  
28 effectively in trial follow-up to detect events.  
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## Abstract

**Introduction:** Cyclooxygenase 2 (COX-2) inhibitors have less upper gastrointestinal toxicity than traditional non-steroidal anti-inflammatory drugs (NSAIDs). However, both COX-2 inhibitors and traditional NSAIDs may be associated with adverse cardiovascular side effects. Data from randomised and observational studies suggest that celecoxib has similar cardiovascular toxicity to traditional NSAIDs. The overall safety balance of a strategy of celecoxib therapy versus traditional NSAID therapy is unknown. The European Medicines Agency (EMA) requested studies of the cardiovascular safety of celecoxib within Europe. The Standard care versus Celecoxib Outcome Trial (SCOT) compares the cardiovascular safety of celecoxib with traditional NSAID therapy in the setting of the EU healthcare system.

**Methods and analysis:** SCOT is a large streamlined safety study conducted in Scotland, England, Denmark, and the Netherlands using the Prospective Randomised Open Blinded Endpoint (PROBE) design. Patients aged over 60 years with osteoarthritis or rheumatoid arthritis, ~~who are~~ free from established cardiovascular disease and ~~who require-requiring~~ chronic NSAID therapy are randomised to celecoxib or ~~to continue~~ their previous traditional NSAID. They are then followed up for events by record-linkage within their normal healthcare setting.

The hypothesis is non-inferiority with a confidence limit of 1.4.

The primary endpoint is the first occurrence of hospitalisation or death for the Anti-Platelet Trialists' Collaboration (APTC) cardiovascular endpoint of non-fatal myocardial infarction, non-fatal stroke or cardiovascular death. ~~The s~~Secondary endpoints are 1) first hospitalisation or death for upper gastrointestinal ulcer complications (bleeding, perforation or obstruction); 2) first occurrence of hospitalised upper gastrointestinal ulcer complications or APTC endpoint; 3) first

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9 hospitalisation for heart failure; 4) first hospitalisation for APTC endpoint plus heart failure; 5)  
10 all-cause mortality and 6) first hospitalisation for new or worsening renal failure.

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12 **Ethics and dissemination:** The SCOT trial has been approved by ~~the relevant~~ ~~the relevant~~ ethics  
13 committees. The trial results will be published in a peer-reviewed scientific journal.  
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16 **Registration:** ~~The SCOT trial is registered on e~~Clinicaltrials.gov (NCT00447759).  
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## Introduction

NSAID-induced gastrointestinal toxicity is one of the most common serious drug adverse events requiring hospitalisation.<sup>1</sup> Upper gastrointestinal complications result in considerable morbidity and mortality. The COX-2 selective NSAIDs gained popularity based upon evidence that they are associated with a lower incidence of ulcer-related upper gastrointestinal tract complications compared to traditional non-selective NSAID therapy. However, the withdrawal of rofecoxib<sup>2</sup> due to cardiovascular toxicity and the suggestion that most NSAIDs are probably associated with increased cardiovascular adverse events when compared to placebo,<sup>3</sup> has led to the need for further prospective studies on the safety of other COX-2 inhibitors and traditional NSAIDs.

The cardiovascular safety profile of COX-2 inhibitors was brought into question following the results of two placebo-controlled studies designed to test the hypothesis that the COX-2 inhibitors rofecoxib and celecoxib might prevent colorectal adenomas and colorectal tumours. The Adenomatous Polyp Prevention on Vioxx (APPROVe) Trial randomised patients with a history of colorectal adenomas to rofecoxib 25mg or placebo and reported an excess of cardiovascular thrombotic events in the group treated with rofecoxib<sup>4</sup>. The Prevention of Sporadic Colorectal Adenomas with Celecoxib (APC) Trial randomised patients with previous colorectal adenomas to celecoxib 400mg twice daily, celecoxib 200mg twice daily or placebo and reported a dose-related increase in risk of cardiovascular events in the celecoxib groups<sup>5,6</sup>. However, the Prevention of Colorectal Sporadic Adenomatous Polyps (PreSAP) Trial did not show a significant increase in cardiovascular events with celecoxib 400mg given once per day versus placebo in patients with previous colorectal adenomas.<sup>7</sup> In the Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT), which was stopped early due to the findings of the

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9 APC trial, there was a suggestion of an increased risk of cardiovascular events with naproxen but  
10 not celecoxib compared to placebo, although this study was underpowered and the  
11 cardiovascular results must therefore be interpreted with caution. In a later meta-analysis of six  
12 randomised double-blind placebo controlled trials of celecoxib in non-arthritis conditions, which  
13 included analysis of the APC, PreSAP and ADAPT studies and three other smaller studies  
14 (MA27, The Diabetic Macular Edema (CDME) Trial and the Celecoxib/Selenium Trial), there  
15 was no evidence of increased cardiovascular risk with celecoxib in low risk patients but there  
16 was a dose-dependent increase in cardiovascular risk in high risk patients<sup>8</sup>.

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26 In the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme,  
27 which compared cardiovascular outcomes with etoricoxib 60mg or 90mg daily and diclofenac  
28 150mg daily in patients with osteoarthritis or rheumatoid arthritis, rates of thrombotic  
29 cardiovascular events were similar in patients randomised to either drug<sup>9</sup>.

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35 In trials of celecoxib versus traditional NSAIDs, no evidence of increased cardiovascular toxicity  
36 has been seen<sup>10</sup>. In large observational studies, celecoxib has not been found to be associated  
37 with increased cardiovascular risk versus other NSAIDs<sup>11</sup> or non-use.<sup>12,13</sup> At present, much of  
38 the available data comes from observational studies and while it seems clear that rofecoxib  
39 increased cardiovascular risk, many traditional NSAIDs may also pose considerable risk.<sup>3,11,</sup>

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The recent Celecoxib versus Omeprazole and Diclofenac in patients

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with Osteoarthritis and Rheumatoid arthritis (CONDOR) study found that celecoxib was associated with a lower incidence of clinically significant upper or lower gastrointestinal events than the combination of diclofenac and omeprazole, adding further evidence to the improved gastrointestinal safety of COX-2 inhibitors compared with non-selective NSAIDs<sup>17</sup>.

Against this background of conflicting data, the overall risk-benefit balance of celecoxib versus traditional NSAIDs needs to be better clarified in a prospective trial design. This paper describes the design and rationale for The Standard care versus Celecoxib Outcome Trial (SCOT), which is a prospective trial randomising patients without a history of cardiovascular disease to celecoxib or traditional NSAID and measuring cardiovascular outcomes that is expected to report in 2014. This trial, which started recruiting in 2008, is a large streamlined safety study of celecoxib versus traditional NSAIDs in patients with osteoarthritis or rheumatoid arthritis that aims to address the relative cardiovascular and gastrointestinal safety of the two treatment strategies in a real world setting.

## Methods and analysis

### Trial Design

#### *Overall Trial Design*

The SCOT trial is an active comparator, streamlined clinical trial with Prospective, Randomised, Open label, Blinded Endpoint evaluation (PROBE) design<sup>18</sup>. It aims to compare the cardiovascular and gastrointestinal safety of continuing with current traditional NSAID therapy versus switching to celecoxib therapy in patients with osteoarthritis or rheumatoid arthritis. After randomisation to celecoxib or to continue their current traditional NSAID therapy, subjects are followed up for an average of 2 years for pre-defined cardiovascular, gastrointestinal and renal events and mortality (Figure 1).

#### *Study Population*

The EMA requested that the trial population should include patients from at least two European Member States. The trial is being conducted in the UK, Denmark and The Netherlands. Patients over the age of 60 years, who are free from cardiovascular disease, and are taking chronic NSAID therapy for osteoarthritis or rheumatoid arthritis are included in the study. The trial inclusion and exclusion criteria are listed in Table 1 and Table 2 respectively.

#### *Recruitment and randomisation of participants*

Potentially suitable patients are identified from general practice populations. Written informed consent is obtained from participants. The research nurse records baseline variables, takes blood and urine for baseline biochemistry and haematology and records the medical history. Blood samples are analysed at the local health service laboratory according to usual practice. Serum for



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9 future analyses and blood for future genetic analyses are stored by regional centres. Subjects who  
10 have given informed consent and meet the inclusion and exclusion criteria are randomised to  
11 receive celecoxib or to continue on their usual traditional NSAID therapy. Randomisation is  
12 performed by contacting a central randomisation facility based at the Robertson Centre for  
13 Biostatistics, University of Glasgow by telephone or via a web-based service.  
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### 20 **Stratification of randomisation**

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22 Prior to the start of the study, a group of general practitioners' databases in Scotland and the  
23 centralised dispensing database in Denmark were screened to identify the distribution of usage of  
24 different NSAIDs. On this basis, each NSAID with a frequency of usage >12% (ibuprofen and  
25 diclofenac) was assigned its own stratum. Other NSAIDs were pooled into a single stratum for  
26 the purpose of randomisation. The allocated therapy is prescribed using the normal health  
27 service prescription form. Thus therapy is provided to patients in an open-label fashion in order  
28 to mimic normal care as closely as possible.  
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37 After randomisation, a health service prescription is issued for the randomised drug and the  
38 patient's case records and computer file are marked to show that they are participating in the  
39 SCOT trial. Repeat prescriptions are issued according to normal clinical practice and patients  
40 take their medication according to clinical need. This method is 'naturalistic' in that it most  
41 closely mimics the real world of NSAID use.  
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### 48 **Trial treatments**

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9 The trial treatments are either celecoxib (Celebrex®) or any other licensed non-selective  
10 traditional NSAID listed in the British National Formulary section 10.1.1 (ibuprofen,  
11 aceclofenac, acemetacin, dexibuprofen, dexketoprofen, diclofenac sodium, diflunisal, etodolac,  
12 fenbufen, fenoprofen, flurbiprofen, ibuprofen, indometacin, ketoprofen, mefenamic acid,  
13 meloxicam, nabumetone, naproxen, piroxicam, sulindac, tenoxicam, tiaprofenic acid and  
14 Arthrotec® (diclofenac plus misoprostol)).  
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20 Celecoxib is prescribed at standard licensed doses of up to 200mg bd – the dose is adjusted as  
21 necessary up to this maximum limit to provide adequate symptomatic relief. Other NSAIDs are  
22 continued at their standard licensed doses and again, the dose may be adjusted as necessary to  
23 control symptoms.  
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### 29 ***Compliance***

30 Study medication prescriptions are recorded on practice computer systems. Compliance is  
31 measured as the number of prescription doses prescribed divided by the number of days between  
32 prescriptions averaged over the time in the trial.  
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### 39 ***Discontinuation of Randomised Therapy***

40 If a period of 56 days elapses from the estimated end of the last written prescription or if a  
41 prescription is written for a traditional NSAID or COX2 inhibitor other than that allocated at the  
42 time of randomisation, it is confirmed whether the patient has discontinued therapy and, if  
43 appropriate, the reason for study drug discontinuation is recorded.  
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### 49 ***Concomitant Medications***

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9 Concomitant medications are also recorded. Of particular interest are prescriptions for aspirin,  
10 ulcer healing drugs and antihypertensive drugs.  
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### 13 ***Rescue Medication***

#### 14 Efficacy

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18 Patients who experience the onset of inadequate therapeutic efficacy may be up-titrated in dose  
19 as per normal clinical practice. Such dose escalations are tracked. Additional rescue medication  
20 may be prescribed in order that the patient continues on randomised therapy. These rescue  
21 medications may include paracetamol (acetaminophen), opiates such as codeine, dihydrocodeine,  
22 tramadol etc., nefopam, low dose anti-depressant therapy and other recognised analgesic  
23 augmenting therapies.  
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#### 30 Tolerability

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33 Patients who experience the onset of symptoms of upper gastrointestinal discomfort, dyspepsia  
34 or heartburn may be prescribed antacid therapy or ulcer healing therapy at the discretion of their  
35 primary care physician. Study site coordinators report such events as treatment-related adverse  
36 events and specify if they lead to discontinuation of randomised study treatment.  
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### 42 **Original study design with a celecoxib run-in period (2008-2010 prior to protocol 43 amendment)**

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46 In the original trial design (for patients entering the study up to between April and August 2010  
47 depending on study site), 3962 subjects underwent a celecoxib run-in period prior to  
48 randomisation and 2545 subjects were subsequently randomised. The celecoxib run-in was done  
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9 in all patients completing screening for the study. They were asked to discontinue their current  
10 NSAID and enter a two-week (14 +/- 7 days) open-label run-in of treatment with celecoxib as  
11 two to four 100mg tablets taken daily in single or divided doses. During the run-in period the  
12 dose of celecoxib was titrated to achieve equivalent pain control to their previous NSAID  
13 therapy. At the end of this period, subjects who had taken at least one dose of celecoxib and who  
14 did not express a strong preference for either their previous treatment or celecoxib were eligible  
15 for randomisation. Preference was determined by the patient response to a questionnaire:  
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24 Which statement do you agree with?

- 25 1. My previous pain killer was much better than celecoxib
  - 26 2. My previous pain killer was somewhat better than celecoxib
  - 27 3. My previous pain killer and celecoxib were the same
  - 28 4. Celecoxib was somewhat better than my previous pain killer
  - 29 5. Celecoxib was much better than my previous pain killer
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37 Only subjects who responded with answers 2, 3 or 4 were eligible for randomisation. This  
38 resulted in 1,417 subjects being excluded using this run-in period.  
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43 This open-label celecoxib run-in period was originally included in the design of the SCOT trial  
44 because a major problem with previous randomised trials of NSAID toxicity had been dropout  
45 from randomised treatment during the trial. For example, in the TARGET trial, only 60% of  
46 subjects completed the trial and 31-37% of subjects withdrew from randomised therapy.<sup>19</sup> In the  
47 CLASS study, less than 50% of those randomised completed the study and there was differential  
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9 dropout between the two treatment arms.<sup>20</sup> A similar trial run-in phase was used in the Heart  
10 Protection Study.<sup>21</sup> It was hoped that by having a celecoxib run-in period, dropouts after  
11 randomisation would be avoided. However, after review of the data on the level of dropouts after  
12 the first few years of the trial, it was clear that the celecoxib run-in period was resulting in  
13 different rates of randomisation in different centres with hardly any being excluded in some  
14 centres and a high proportion being excluded in others. For this reason the protocol was amended  
15 to remove the run-in period and to perform randomisation on the day of screening if the subject  
16 was eligible. This amendment was implemented in each region on different dates but was  
17 complete by September 2010. Since then, up to October 2012, around 3500 further patients were  
18 randomised without run-in period. We have since formally evaluated the influence of the  
19 presence or absence of the celecoxib run-in period on study drop-out rates and found no  
20 significant difference (adjusted odds ratio for drop-out at 180 days in patients with the celecoxib  
21 run-in period was 1.28 (95% CI 0.76-2.14)<sup>22</sup>.

## 22 23 24 25 26 27 28 29 30 31 32 33 34 35 **Trial endpoints**

### 36 ***Primary Endpoint***

37 The primary endpoint is the first occurrence of hospitalisation or death for the Anti-Platelet  
38 Trialists' Collaboration (APTC) cardiovascular endpoint of non-fatal myocardial infarction, non-  
39 fatal stroke or cardiovascular death.

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46 The secondary and tertiary endpoints and further planned analyses are listed in Table 3.

### 47 48 49 50 **Assessment of study endpoints, adverse events, and serious adverse events**

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9 The principal mode of collection of study endpoints, adverse events and serious adverse events  
10 in the SCOT trial is by record-linkage from national population healthcare databases. Record-  
11 linkage retrieves electronic records of hospitalisations and deaths for individual patients within  
12 the study from central databases. Hospitalisation discharge diagnoses are coded and causes of  
13 death are reported. Any events of particular interest (potential study endpoints) are investigated  
14 further and confirmed by retrieving the original case records. Record-linkage has previously  
15 been demonstrated to be highly effective in the follow-up of patients for study events<sup>23</sup>. Any  
16 treatment-related adverse events and serious adverse events detected and reported by research  
17 staff or physicians manually are also collected and investigated.  
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#### 28 ***Mortality data by record-linkage***

29 Mortality and certified cause-specific mortality are retrieved from national mortality record  
30 systems by record-linkage at approximately 3 monthly intervals.  
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#### 35 ***Morbidity data by record-linkage***

36 Hospitalisations are retrieved by record-linkage from national systems at approximately 3  
37 monthly intervals.  
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#### 43 ***Data Abstraction for endpoint adjudication***

44 For each death, and for each hospitalisation that is a potential endpoint, primary care and  
45 secondary care records and, if appropriate, full death certification data is retrieved. Diagnostic  
46 validation forms are filled in to supplement scanned images of original case records relating to  
47 the endpoints in question. The scanned images of case records and the data validation forms are  
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9 collated. Any record of randomised treatment is removed before these collated documents are  
10 passed to the relevant (cardiovascular or gastrointestinal) endpoint committee for adjudication as  
11 to the hospital diagnosis or the cause of death. This is the Prospective Randomised Open Blinded  
12 Endpoint (PROBE) design and is similar to the design of the Anglo Scandinavian Cardiac  
13 Endpoint (PROBE) design and is similar to the design of the Anglo Scandinavian Cardiac  
14 Outcomes Trial (ASCOT).<sup>24</sup>  
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### 20 *Adjudication of Endpoints*

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22 Endpoint data are adjudicated by two independent endpoint committees, one for cardiovascular  
23 endpoints (also adjudicate heart failure, renal and death endpoints) and one for gastrointestinal  
24 endpoints. These committees are blinded to randomised treatment and have due regard of the  
25 published consensus diagnostic criteria for myocardial infarction,<sup>25</sup> stroke,<sup>26</sup> vascular death,  
26 ulcer-related upper gastrointestinal hospitalisations or death, heart failure<sup>27</sup> and renal failure.<sup>28,29</sup>  
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### 33 **Adverse Events**

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35 All observed or volunteered adverse events that are considered to be serious or related to  
36 randomised study treatment, regardless of treatment group or suspected causal relationship to the  
37 investigational product(s), are recorded on the adverse event pages of the electronic case report  
38 form (eCRF). Adverse events are defined as abnormal test findings, clinically significant  
39 symptoms and signs, changes in physical examination findings or hypersensitivity. A serious  
40 adverse event (SAE) or serious adverse drug reaction is any untoward medical occurrence at any  
41 dose that: results in death, is life-threatening (immediate risk of death), requires inpatient  
42 hospitalisation or prolongation of existing hospitalisation, results in persistent or significant  
43 disability/incapacity or results in congenital anomaly or birth defect.  
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11 For these adverse events, further information is obtained to determine the outcome of the adverse  
12 event and to confirm whether it meets the criteria for classification as a SAE requiring immediate  
13 notification to the sponsor. Physicians assess causality, and expectedness for any SAE thought to  
14 be related to study drug, on the web portal. Follow-up of SAEs continues until the event has  
15 resolved or the patient has died. In this study, primary and secondary study endpoints and their  
16 associated symptoms and laboratory abnormalities are not reported as Suspected Unexpected  
17 Serious Adverse Drug Reactions (SUSARs). Further, adverse events that are neither considered  
18 to be serious nor related to randomised treatment are not reported.  
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## 25 **Data Analysis/Statistical Method**

### 26 *Sample Size Determination*

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28 Originally, the study was powered at 90% to exclude a 30% poorer outcome on celecoxib  
29 compared to traditional NSAIDs (hazard ratio=1.3) in the primary endpoint with a non-  
30 inferiority analysis between the two treatment strategies. However, due to slower than expected  
31 recruitment and lower than expected event rates, the trial steering committee made the decision  
32 to revise the power of the study to 80% and the non-inferiority limit to 1.4 in October 2011.  
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40 The statistical method to be used will involve a stratified Cox proportional hazards model  
41 including the randomisation strata and the randomised treatment group as covariates. Statistical  
42 significance for the treatment differences will be based on the Wald statistics and on two-sided  
43 95% confidence intervals for the estimated hazard ratio comparing celecoxib to non-selective  
44 NSAIDs. The original power calculations suggested that for an average duration of 2 years  
45 exposure to treatment with a 30% non-inferiority limit and a NSAID-exposed CV event rate of  
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9 2.0% per year the study would require 6,841 subjects in each treatment group or 13,682 subjects  
10 in total and 611 patients with endpoints (based on an intention-to-treat analysis). Since, an on-  
11 treatment analysis will result in reduced follow-up that was difficult to predict *a priori*, follow-  
12 up would be continued until 611 endpoints were identified in the per-protocol population.  
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16 Following the revision to the power calculation made in 2011 (power 80%, non-inferiority limit  
17 1.4), the number of primary endpoints required to achieve adequate power in the per-protocol  
18 population decreased to 277.  
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### 22 23 24 **Primary Analysis**

25 A full Statistical Analysis Plan has been developed. The first analysis to be carried out will be a  
26 non-inferiority analysis of the primary outcome based on the per-protocol population (those  
27 subjects remaining on randomised therapy) with a supporting non-inferiority analysis based on  
28 the intention-to-treat population. A patient will be considered to remain on the randomised  
29 therapy until a period of 56 days following the last recorded prescription of the medication  
30 allocated at randomisation plus 28 calendar days.  
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39 Thus the *per-protocol* analysis will censor subjects after:

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41 - Discontinuation from original randomised therapy (defined as 84 days after day of last  
42 recorded prescription)  
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44 - First primary study endpoint  
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46 - Withdrawal of consent.  
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9 If non-inferiority is demonstrated, a superiority analysis will be carried out based on the  
10 intention-to-treat population.  
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### 12 13 14 ***Sensitivity Analysis***

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16 A prospective sensitivity analysis will be performed adding a 90-day period to the *per-protocol*  
17 period (or end of study) to ensure that withdrawal or crossover is not a presage of disease. This  
18 will be done for both primary and secondary endpoints.  
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### 22 23 24 ***Subgroup Analyses and Prognostic Factors***

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26 Subgroup analyses will be conducted comparing celecoxib treatment with each of the individual  
27 non-selective NSAID treatments allocated at randomisation. In addition, subgroup analyses will  
28 be carried out for each of the baseline covariates described below that are significant predictors  
29 of the primary endpoint in a Cox regression model including that variable alone plus the  
30 stratification categorical variable.  
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34 Baseline covariates include age, sex, baseline blood pressure, baseline total cholesterol, HDL  
35 cholesterol and LDL cholesterol, body mass index, smoking status, prior upper gastrointestinal  
36 bleed or perforation, history of peptic ulcer, *Helicobacter pylori* serology status at baseline,  
37 diabetes, social deprivation category, use of systemic (not inhaled) steroids at entry, indication  
38 for NSAID i.e. rheumatoid arthritis or osteoarthritis diagnosis, randomised therapy and aspirin  
39 use.  
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### 48 **Ethics and dissemination**

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### ***Steering Committee and Independent Data Monitoring Committee (IDMC)***

A steering committee oversees the conduct of the trial and an independent data monitoring committee receives unblinded data and has the power to recommend to the steering committee modifications to study conduct, including early discontinuation of the study, based on a risk/benefit assessment of the study data.

### ***Study Sponsorship, Monitoring, Audit, Quality Control & Quality Assurance***

The University of Dundee is the study sponsor and supervises monitoring and undertakes quality assurance of the study.

### ***Legal and Ethical Issues***

The trial has been approved by the UK Multi-Centre Research Ethics Committee (MREC) (Reference number: 2006-005735-24) and the Medicines and Healthcare products Regulatory Agency (MHRA) (Reference number: 07/MRE00/9). It is also approved by the relevant authorities in Denmark and the Netherlands. It is registered on ClinicalTrials.gov (Reference number: NCT00447759). The trial is performed in accordance with the protocol, International Conference on Harmonization Good Clinical Practice guidelines, ISPE Good Pharmacoepidemiology Practice guidance<sup>30</sup> and applicable local regulatory requirements and laws.

### ***Dissemination***

The results of the trial will be published in a peer-reviewed scientific journal.

## Discussion

The methodology of the SCOT trial differs from many traditional trials in that follow-up is largely electronic using record-linkage techniques and treatments are prescribed within the usual healthcare setting. Such a design means that the trial more closely mimics normal care. There have been a number of publications of meta-analyses of cardiovascular risk-benefit of celecoxib compared to NSAIDs.<sup>31,32,33</sup> Most of them showed that there was no increase in cardiovascular risk in patients receiving celecoxib compared with traditional NSAIDs. Alongside the current SCOT trial, a more traditional trial is ongoing in the United States - The Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen Or Naproxen (PRECISION) trial<sup>34, 35</sup> It is a randomized, double-blind, parallel-group study of cardiovascular safety in osteoarthritis or rheumatoid arthritis patients with, or at high risk of, cardiovascular disease comparing celecoxib with naproxen and ibuprofen.

Traditional trials have good internal validity but less external validity. A large streamlined safety trial is expected to have good external validity. However, such a trial becomes more observational with time and internal validity becomes less reliable. The PRECISION and SCOT trial results are likely to be available by around 2014 and we believe that the results will inform clinical practice in a more reliable way than previous studies of cardiovascular safety of NSAIDs. We believe that naturalistic trials such as the SCOT trial will be essential in shaping health care policy in the future.

## Funding statement

The study takes place as an academic study, grant-funded by Pfizer as an Investigator Initiated Research Grant, under a full legal agreement with Pfizer, with the University of Dundee being

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the study sponsor. The study was designed by the trial executive committee (Professor Tom MacDonald, Professor Ian Ford and Professor Chris Hawkey). The sponsor (University of Dundee) and the trial steering committee are primarily responsible for data collection, trial management, analysis and interpretation of data, writing of the report and submission of the report for publication. Pfizer has provided funding for the SCOT study but has no authority over the above activities.

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### Competing interests statement

ISM and TMM have previously had part of their university salary reimbursed to the University by Pfizer in connection with the SCOT trial. In the last 5 years TMM has received honoraria for lectures and consulting from NiCox, Novartis and Astra Zeneca in relation to NSAID therapies and from other companies regarding other therapeutic areas. MEMO holds research grants from Novartis, Pfizer, Ipsen & Menarini. IF and CH have received research funding from Pfizer related to the conduct of the SCOT trial.

### Authors' contributions

The original study protocol was written by TM, IF, CH and EF. This paper describing the protocol was written by LW, IM, TM, IF and CH with review and input from the other collaborators listed below.

#### \*SCOT Study Group collaborators:

\***Executive Committee** – Thomas M MacDonald (Chief Investigator), Ian Ford, Chris Hawkey;

\***Steering Committee** – Thomas M MacDonald, Ian Ford, Chris Hawkey, Jesper Hallas, John

Webster, David Reid, Isla Mackenzie, Stuart Ralston, Matthew Walters, FD Richard Hobbs, Sir

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10 Findlay, John McMurray, Brendan Delaney & Died~~e~~rick Grobbee.  
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12 **Independent Data and Statistical Centre**

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14 Sharon Kean (IT and data management), Nicola Greenlaw and Michele Robertson (Biostatistics)

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16 **Consultant Epidemiologist** – Li Wei.

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18 **Independent Data Monitoring Committee**

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20 Kim Fox (Chair), Gordon Murray, Frank Murray.

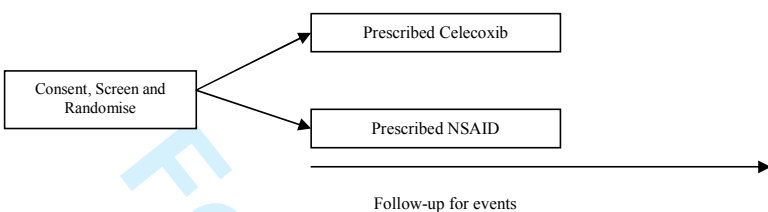
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22 **Endpoint Adjudication Committees**

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24 **Cardiovascular:** John McMurray (Chair), Pardeep Jhund, Mark Petrie, Michael MacDonald.

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26 **Gastrointestinal:** James Scheiman (Chair), John Dillon, Jane Moeller, Angel Lanas.  
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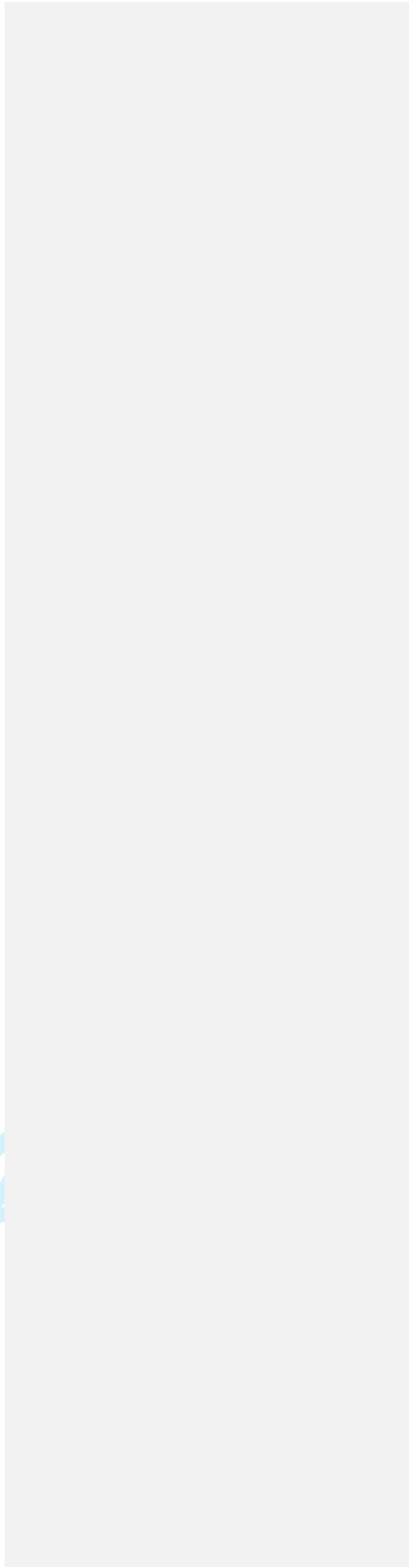
Figure 1 – Current SCOT trial design



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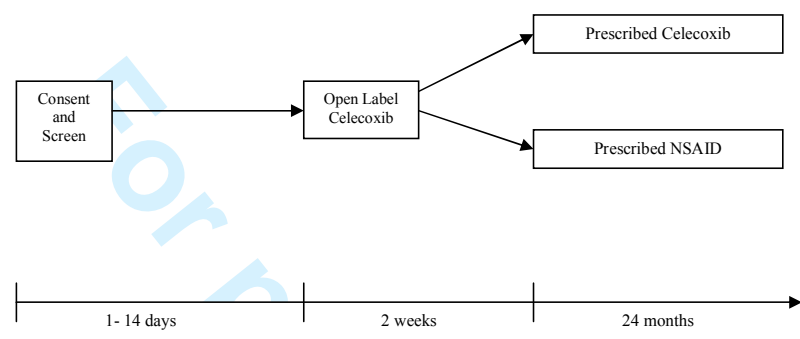
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Figure 2 - Original SCOT trial design (including 2-week celecoxib run-in period)



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9 **Table 1 – Inclusion criteria**

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13 1. Age 60 or over.
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15 2. Male and female subjects.
- 16  
17 3. Chronic NSAID use ( $\geq 90$  days or at least 3 filled prescriptions in the last year).
- 18  
19 4. Subjects who, in the opinion of the recruiting physician, have a licensed indication for  
20 chronic non-selective NSAID or celecoxib therapy (osteoarthritis (OA) or rheumatoid  
21 arthritis (RA)).
- 22  
23 5. Subjects, who in the opinion of the study site coordinator, are eligible for treatment (with  
24 reference to the summary of product characteristics) with either celecoxib or an  
25 alternative traditional non-selective NSAID. In particular these subjects must be free  
26 from established cardiovascular disease (established ischaemic heart disease (IHD), heart  
27 failure, cerebrovascular disease and peripheral arterial disease).
- 28  
29 6. Subjects who are willing to give permission for their paper and electronic medical  
30 records and prescribing data to be accessed and abstracted by trial investigators.
- 31  
32 7. Subjects who are willing to be contacted and interviewed by trial investigators, should the  
33 need arise for adverse event assessment etc.
- 34  
35 8. For the avoidance of doubt, there are no other specific co-morbidities, or concurrent drug  
36 therapies (including aspirin) that are contraindicated.
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9 **Table 2 – Exclusion criteria**

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1. Established cardiovascular disease including IHD such as myocardial infarction, angina or acute coronary syndrome, cerebrovascular disease such as a cerebrovascular accident or transient ischaemic attack, established peripheral vascular disease and moderate or severe heart failure.
  2. Subject currently taking a COX-2 selective NSAID (celecoxib or etoricoxib), or having received one of the therapies within 90 days of screening.
  3. Presence of a life-threatening co-morbidity (investigator opinion).
  4. Presence of clinically important renal or hepatic disease (investigator opinion).
  5. Subjects whose behaviour or lifestyle would render them less likely to comply with study medication (i.e. alcoholism, substance misuse, debilitating psychiatric conditions or inability to provide informed consent).
  6. Subjects with known or suspected allergy to celecoxib or NSAIDs including aspirin.
  7. Subjects with known hypersensitivity to sulphonamide antibiotics.
  8. Subjects with active peptic ulceration or gastrointestinal (GI) bleeding.
  9. Subjects scheduled to have arthritis surgery likely to modify their need for pain relief within the next year.
  10. Subjects currently participating in another clinical trial or who have been in a trial in the previous three months.

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9 **Table 3 – Secondary and tertiary endpoints and further analyses**

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13 **Secondary endpoints**

- 14 1. First occurrence of hospitalisation or death for upper gastrointestinal ulcer complications  
15 (bleeding, perforation or obstruction).  
16  
17 2. First occurrence of hospitalised upper gastrointestinal ulcer complications or APTC endpoint.  
18  
19 3. First hospitalisation for heart failure.  
20  
21 4. First occurrence of hospitalisation for APTC endpoint plus heart failure.  
22  
23 5. All cause mortality.  
24  
25 6. First hospitalisation for new or worsening renal failure.  
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30 **Tertiary endpoints**

- 31 1. First occurrence of hospitalisation or death for upper gastrointestinal bleeding, perforation or  
32 obstruction not due to ulcers.  
33  
34 2. First occurrence of hospitalisation or death for lower gastrointestinal bleeding, perforation or  
35 obstruction.  
36  
37 3. First occurrence of hospitalisation or death for all episodes of gastrointestinal bleeding,  
38 perforation or obstruction.  
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44 **Further planned analyses**

- 45 1. Myocardial infarction as a whole and as the components of ST segment elevation myocardial  
46 infarction and non ST elevation myocardial infarction.  
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48 2. Non-fatal stroke.  
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3. Cardiovascular death.

4. Analyses of GI subcomponents

(a) Hospitalisation or death for all episodes of upper gastrointestinal bleeding

(b) Hospitalisation or death for all episodes of lower gastrointestinal bleeding

(c) Hospitalisation or death for all episodes of gastrointestinal bleeding

5. All uncomplicated upper gastrointestinal ulcers detected during the study

6. All upper gastrointestinal ulcers (complicated and uncomplicated) detected during the study.

7. New prescription for ulcer healing drugs.

8. All hospitalisations.

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Investigators. Rationale, design, and governance of Prospective Randomized Evaluation of Celecoxib Integrated

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Safety versus Ibuprofen Or Naproxen (PRECISION), a cardiovascular end point trial of nonsteroidal anti-inflammatory agents in patients with arthritis. *Am Heart J* 2009;157(4):606-12. Epub 2009 Feb 25.

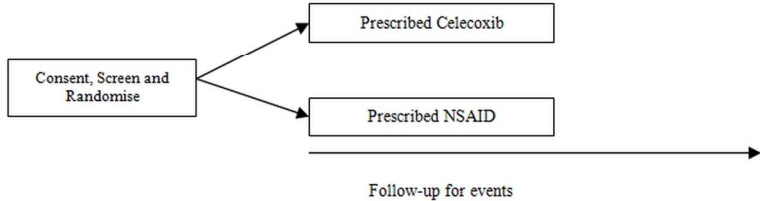
<sup>35</sup> <http://clinicaltrials.gov/ct/show/NCT00346216>.

For peer review only



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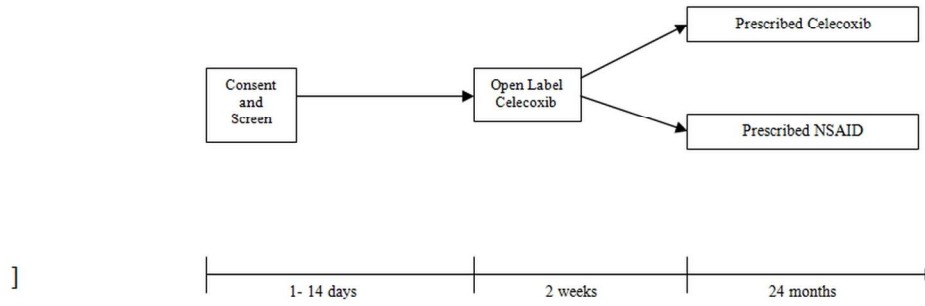
Figure 1 – Current SCOT trial design



205x90mm (300 x 300 DPI)

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Figure 2 - Original SCOT trial design (including 2-week celecoxib run-in period)



167x90mm (300 x 300 DPI)

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