PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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)
AUTHORS	Mackenzie, Isla; MacDonald, Thomas; Wei, Li; Hawkey, Christopher; Ford, Ian

VERSION 1 - REVIEW

REVIEWER	Stephen J.W. Evans Professor of Pharmacoepidemiology Dept of Medical Statistics London School of Hygiene & Tropical Medicine Keppel Street, London WC1E 7HT, UK No competing interests
REVIEW RETURNED	17-Dec-2012

THE STUDY	There are no supplemental documents and no CONSORT statement is necessary as it is a protocol only. It might be interesting to see how much of a CONSORT checklist can be completed at this stage. There will be an update to the CONSORT Non-inferiority paper published soon and the authors may wish to, prior to trial results being available, fill in as much of the revised checklist as possible.
REPORTING & ETHICS	As noted, even though it cannot be complete a partial CONSORT checklist may be helpful to the authors, though not necessary for publication
GENERAL COMMENTS	I think a forest plot, perhaps using a combination of the most relevant meta-analyses updated with any later results would be helpful to a reader. The use of investigator attributions of cause to decide whether to include AEs in the report/analysis is begging the question. I appreciate regulators use this type of thinking but i it is better to report all AEs other than the trivial. The randomisation is the mechanism for attributing cause, not just opinion. At page 15 line 37 it refers to "related to study treatment" - this aspect should be changed if possible. In some senses the protocol is for a trial that is running so comments may be ftile, but this should be addressed via an amendment if possible- it requires changes to be made in scanning the EHR which can be done retrospectively so should be possible to implement.

REVIEWER	Cannon, Christopher Brigham & Women's Hospital, Harvard Medical School

	Research grants/support from the following companies: Accumetrics AstraZeneca Essentialis GlaxoSmithKline Merck Regeneron Sanofi Takeda Advisory Board (but funds donated to charity and education) Alnylam Bristol-Myers Squibb Pfizer CSL Clinical Advisor, equity in Automedics Medical Systems.
REVIEW RETURNED	17-Dec-2012

THE STUDY	The abstract should include the number of patients in it. It should also have the hypothesis begin tested. I believe it is non-inferiority, but this needs to be specified clearly and the revised boundary included. That is a key aspect of the trial design.
GENERAL COMMENTS	Do they have a PPI subgroup? would be important for the GI outcomes.

VERSION 1 – AUTHOR RESPONSE

Reviewer: Stephen J.W. Evans
Professor of Pharmacoepidemiology
Dept of Medical Statistics
London School of Hygiene & Tropical Medicine Keppel Street, London WC1E 7HT, UK

No competing interests

There are no supplemental documents and no CONSORT statement is necessary as it is a protocol only. It might be interesting to see how much of a CONSORT checklist can be completed at this stage. There will be an update to the CONSORT Non-inferiority paper published soon and the authors may wish to, prior to trial results being available, fill in as much of the revised checklist as possible.

We have not provided a CONSORT statement at this stage, as the reviewer agrees, because this manuscript describes the protocol rather than the results of the study. We agree that it would be an interesting exercise to complete as much of the revised CONSORT checklist as possible prior to trial results being available and will do this.

I think a forest plot, perhaps using a combination of the most relevant meta-analyses updated with any later results would be helpful to a reader.

With respect to the reviewer, we do not feel that we should synthesise a forest plot combining the results of different studies in this manuscript as we believe that this would be incomplete and confusing for readers as most of the studies of NSAID safety to date differ greatly in design, are mainly observational in nature, with varying endpoints and are difficult to compare without significant additional explanation. This is beyond the scope of this manuscript which aims to describe the protocol of the SCOT study. We hope that you will agree with this.
We have, however, referenced the recent network meta-analysis published in the BMJ which includes

forest plots of the relative safety of different NSAIDs and is one of the most relevant and recent updates on NSAID safety (Trelle S, Reichenbach S, Wandel S, Hildebrand P, Tschannen B, Villiger PM, Egger M, Juni P. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. BMJ 2011;342:c7086).
Further data will also be available soon from the SOS study (a large European meta-analysis of NSAID safety). European Medicines Agency press release regarding SOS results: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/10/news_detail_001637.jsp&mid=WC0b01ac058004d5c1 (Accessed online 7.1.13)

The use of investigator attributions of cause to decide whether to include AEs in the report/analysis is begging the question. I appreciate regulators use this type of thinking but i it is better to report all AEs other than the trivial. The randomisation is the mechanism for attributing cause, not just opinion. At page 15 line 37 it refers to "related to study treatment" - this aspect should be changed if possible.
In some senses the protocol is for a trial that is running so comments may be ftile, but this should be addressed via an amendment if possible- it requires changes to be made in scanning the EHR which can be done retrospectively so should be possible to implement.

The SCOT trial was designed to be a streamlined safety study. We collect and will report information on all Serious Adverse Events (SAEs) (ie serious events), whether they are related to study treatment or not, but at the design stage decided only to collect information on ‘Treatment-related’ Adverse Events (ie non-serious events) to avoid collecting a lot of trivial AEs. We would not be able to detect all AEs from the electronic health record as most of our SAEs are based on hospitalizations and deaths and the study was designed to collect the endpoint data primarily through electronic record-linkage with supplementary reporting of any additional serious adverse events not captured via record-linkage (which is rare and may for example occur if a patient has an event outwith the UK while on holiday) via the GP or study staff.
Any SUSARs and SARs are reported within the study.

Reviewer: Christopher Cannon
Brigham & Women's Hospital, Harvard Medical School

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Merck
Regeneron
Sanofi
Takeda

Advisory Board (but funds donated to charity and education) Alnylam Bristol-Myers Squibb Pfizer CSL

Clinical Advisor, equity in Automedics Medical Systems.

The abstract should include the number of patients in it.
It should also have the hypothesis begin tested. I believe it is non-inferiority, but this needs to be specified clearly and the revised boundary included. That is a key aspect of the trial design.

The number of patients in the trial is not absolute because the end of the trial is driven by accrual of endpoints and patient years’ exposure rather than the recruitment of an exact number of patients. The original target of patient recruitment was 13682 patients but fewer patients will now be required

(probably around 9000) as the time of each patient's participation in the trial has been longer than originally predicted, increasing the patient years' exposure. We have therefore not added the number of patients to the abstract, but this is explained in the text of the main manuscript.

We have added the non-inferiority hypothesis to the abstract as suggested and included the revised boundary of 1.4.

Do they have a PPI subgroup? would be important for the GI outcomes.

We collect information on 'current use of ulcer-healing drug' at the screening visit and also collect participants' prescribing information electronically so will be able to access this information for participants. We do not have a formal PPI subgroup.

We have tracked all changes in the revised manuscript. Thank you.