STANDARD OPERATING PROCEDURE FOR:

ADVERSE EVENT REPORTING

SOP Details:

Number: SOP-OSAC-0002	Version: 1.1	
Author(s): Harriet Downing / Sue Harris Title: Trial Manager / Trial Research Nurse		Date: 18/06/2013
Authorised by: Dr Alastair Hay Title: Chief Investigator		Date: 19/04/2013
Authorised by: Dr Birgit Whitman Title: Sponsor		Date: 04/05/2013
Date operational:	4 May 2013	
Date to be reviewed:	4 November 2013	

Review History:

Review Date:		Reviewed By:	
Review amendments:			
Amended date:		Amended by:	
Authorised date:		Authorised by:	

Review Date:		Reviewed By:	
Review amendments:			
Amended date:		Amended by:	
Authorised date:		Authorised by:	

Review Date:		Reviewed By:	
Review amendments:			
Amended date:		Amended by:	
Authorised date:		Authorised by:	

Contents

1 Document History

Revision	Date	Author	Changes
1.0	19/04/2013	Harriet Downing / Sue Harris	None, this is the first version
1.1	18/06/2013	Harriet Downing	8.2.8 (5) Addition - process for SAE reconciliation set out in the OSAC trial database specification. 8.2.10 (1a) Clarification - DMC will undertake trend analysis for the summary SAE data.

2 Background

It is important that research-related adverse incidents are treated in the same way as non-research related adverse incidents. The OSAC trial is sponsored by the University of Bristol. The University

of Bristol has delegated oversight of all drug safety events within the OSAC trial to the University Hospitals Bristol monitoring team.
The Medicines for Human Use (Clinical Trials) Regulations 2004 came into force on the 1st May 2004. These regulations apply to all clinical trials involving investigational medicinal products (CTIMPs) and specify the reporting requirements for research-related adverse events. To breach these requirements constitutes a breach in criminal law. The requirements have been incorporated within this SOP.

3 Purpose

This SOP describes all of the procedures to be followed in the OSAC clinical trial to ensure that drug safety events are reported in line with all governance and regulatory requirements. This is the reference document for the trial and should be used by all recruiting site staff, and all members of research and administrative staff working on the trial.

4 Scope

This SOP refers to recording and reporting of Adverse Events; including Adverse Reactions, Serious Adverse Events, Serious Adverse Reactions and Suspected Unexpected Serious Adverse Reactions for the OSAC Trial only. These will be managed in line with the reporting policy of the UH Bristol monitoring team acting on behalf of the sponsor.

5 Definitions & Abbreviations

5.1 Abbreviations

AE	Adverse Event
AI	Adverse Incident
AR	Adverse Reaction
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unsuspected Serious Adverse Reaction
BRTC	Bristol Randomised Trials Collaboration
CI	Chief Investigator
CTIMP	Clinical trial of an Investigational Medicinal Product
DMC	Data Monitoring Committee
IMP	Investigational Medicinal Product
MHRA	Medicines and Healthcare products Regulatory Agency
PI	Principal Investigator
PID	Patient Identification Number
PP	Patient Pack
REC	Research Ethics Committee
RN	Research Nurse
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
TSF	Trial Site File
UH Bristol	University Hospitals Bristol NHS Foundation Trust
UoB	University of Bristol

5.2 Definitions

The definitions below are taken from the UH Bristol Research Safety Reporting Standard Operating Procedure, version 4.1, March 2012.

5.2.1 An **adverse event** is any untoward medical occurrence in a subject to whom a medicinal product/medical device/intervention has been administered, including occurrences which are not necessarily caused by or related to that product.

Comment: An adverse event can therefore be any unfavourable and unintended sign (including abnormal lab results), symptom or disease temporally associated with the use of the medicinal product/medical device/intervention, whether or not considered to be related to the medicinal product/medical device/intervention.

5.2.2 An **adverse reaction** is any untoward and unintended response in a subject to an investigational medicinal product/medical device/intervention which is related to any dose administered to that subject.

Comment: Any adverse event judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a medicinal product/medical device/intervention qualifies as an AR; there is evidence or argument to suggest a causal relationship. All adverse reactions are adverse events.

5.2.3 An **unexpected adverse reaction** is an adverse reaction the nature and severity of which is not consistent with the information about the medicinal product/medical device/intervention in question set out: –

a) in the case of a product with a marketing authorisation, in the summary of product characteristics for that product,

b) in the case of any other investigational medicinal product, in the investigator's brochure.

Comment: When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected. All unexpected adverse reactions are adverse events.

5.2.4 An **adverse event, adverse reaction** or **unexpected adverse reaction** is defined as serious if it:

a) results in death,
b) is life-threatening,
c) requires hospitalisation or prolongation of existing hospitalisation,
d) results in persistent or significant disability or incapacity, or
e) consists of a congenital anomaly or birth defect.

Comment: Life threatening in the definition of an SAE or SAR refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe. Medical judgement should be exercised in deciding whether an SAE/SAR is serious in other situations. Important SAE/SARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one or the other outcomes listed in the definition above, should also be considered serious.

5.2.5 A **suspected serious adverse reaction (SSAR)**, is any **serious adverse reaction** that is suspected (possibly or probably) to be related to the investigational medicinal product/medical device/intervention.

5.2.6 A **suspected unexpected serious adverse reaction (SUSAR)** is an SSAR which is also "unexpected", meaning that its nature and severity are not consistent with the information about the medicinal product in question set out:

a) in the case of a product with a marketing authorisation, in the summary of product characteristics for that product
b) in the case of any other investigational medicinal product, in the investigator's brochure relating to the trial in question.

5.2.7 Not all adverse events are adverse reactions but all adverse reactions are adverse events.

5.2.8 An **Investigational Medicinal Product** is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial including a medicinal product which has a marketing authorisation but is, for the purposes of the trial being used or assembled (formulated or packaged) in a way different from the approved form or being used for an unapproved indication or when used to gain further information about an approved use.

NB: In addition to the above definitions of SAEs, the OSAC trial will report as potentially serious any AE, the nature or severity of which is not consistent with the known information on the IMP, as provided in the Summary of Medicinal Product Characteristics, and set out in the trial protocol and Patient Information Booklet.

6 Pre-Requisites

6.1 Pre-Requisite Knowledge & Training

- Certified training in ICH-GCP (Good Clinical Practice)
- OSAC Trial recruitment training

6.2 Pre-Requisite Equipment & Systems

N/A

7 Roles & Responsibilities (Actors)

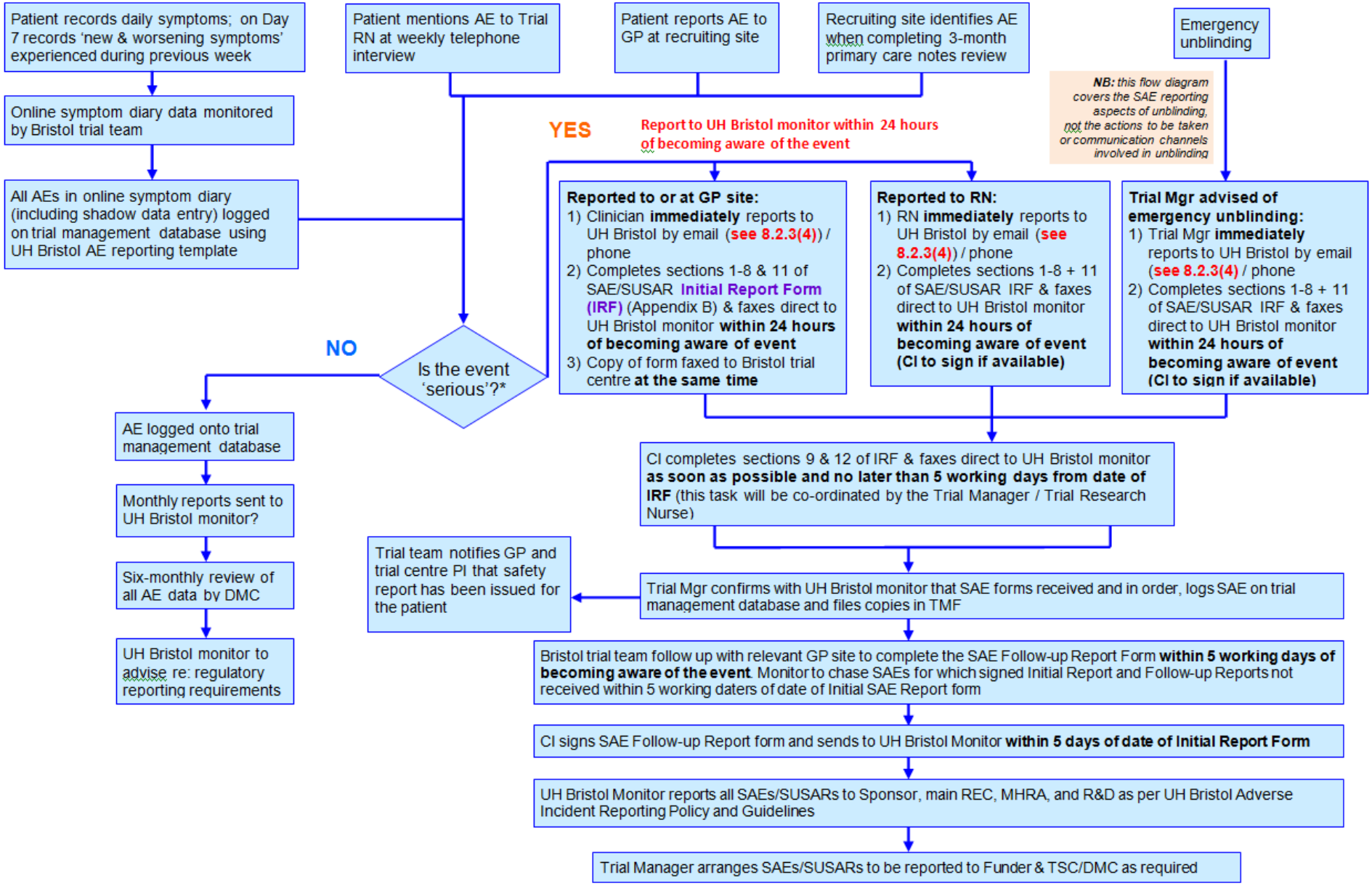
Who	What & Why
Chief Investigator	• Authorises this SOP jointly with the trial sponsor. • Reviews all SAE/SUSAR Initial Report Forms for OSAC trial patients and assigns causality level (completing sections 9 and 12 of the Initial Report Form) **as soon as possible, and no later than within 5 working days** after receipt of the form at the trial centre. • Signs SAE Follow-up Report forms and sends them to UH Bristol Monitor **within 5 working days** after receipt of the form at the trial centre. • Delegates responsibility for assigning causality and signing SAE Initial Report Forms, and for signing and sending the completed SAE Follow-up Report form to UH Bristol Monitor **within 5 working days** from the date of the SAE Initial Report Form, to another academic GP within the OSAC team or within the School of Social and Community Medicine in the event

Who	What & Why
	of the CI being away from their OSAC trial duties. • Signs off annual safety reports submitted to MHRA and main REC (reports co-ordinated by Trial Manager and UH Bristol monitoring team) jointly with Trial Sponsor.
Principal Investigator	• Ensures SOP is adhered to in all local sites. • Ensures local researchers maintain log of all safety events, and log sent regularly to the Trial Manager.
Bristol Randomised Trials Collaboration	• Provides 'unblinding' function for the DMC only (for safety monitoring purposes).
UH Bristol Monitor	• **Acts on behalf of Trial Sponsor in receiving all reports of SAEs and SUSARs from GP sites and from the Bristol trial centre.** • Logs all reported SAEs and SUSARs and reviews each to confirm appropriate course of action. • Follows up signed Initial Report Forms where these are not received within 5 working days of the Initial Report Form being faxed. • Instructs trial team regarding follow-up of SAEs / SUSARs where required. • Monitors progress of any required regulatory notification; ensures all SUSARs are submitted to MHRA and REC within required timelines. • Ensures all OSAC SAE and SUSAR reports are reviewed by the Trust.
UH Bristol Pharmacy	• Responsible for actioning all unblinding requests from healthcare professionals according to UH Bristol unblinding SOP. • Reports all unblinding incidents (but not outcomes) to Trial Manager / CI (see OSAC Trial Unblinding SOP). • Has access to the unblinded data.
Trial Sponsor (UoB)	• Authorises this SOP jointly with CI. • Delegates reporting of safety events to UH Bristol monitor. • Signs off annual safety reports to MHRA and main REC (jointly with CI).
Trial Manager	• Co-ordinates, with the Trial Research Nurse, completion of SAE/SUSAR Initial Report Forms and Follow-up Forms by recruiting clinicians and co-ordinates signing of these forms by the CI and faxing to UH Bristol monitor. Liaises with the Trial Research Nurse to ensure that trial centre PIs and GPs are informed of any SAE/SUSAR reports issued for patients recruited within their centre / at their GP practice respectively. • Maintains central log of all safety events; on paper and trial management database. • Monitors online symptom diary data for potential side-effects experienced by patients. • Ensures safety data is stored in-line with data protection requirements and GCP. • Forwards all safety reports to UH Bristol monitor for review. • Tracks submission of annual safety reports to MHRA and main REC and drafts these when they are due, with the assistance of UH Bristol Monitor where necessary. • Provides safety data to TSC and DMC in pre-determined formats. • Maintains 'blinding' of whole trial research team.

Who	What & Why
Trial Research Nurse	• Identifies potential AEs, SAEs and SUSARs in telephone interviews with patients. • Reports safety events according to this SOP. • May be called on to support GP practices in completion and submission of safety reporting documentation. • Supports the Trial Manager in ensuring that trial centre PIs and GPs are informed of any SAE/SUSAR reports issued for patients recruited within their centre / at their GP practice respectively. • Reviews primary care notes review data to identify any SAEs which may have been overlooked, and reports these accordingly.
Trial Administrator	• Assists with monitoring, logging and secure storage of patient safety data throughout the trial.
GP Practices	• Report any safety events reported by patients using the trial SAE reporting form according to this SOP. • Perform a weekly check of the records of their patients who have been recruited to the OSAC trial to identify any SAEs. • Report any SAEs identified retrospectively during the 3-month primary care notes reviews.
Data Monitoring Committee	• Reviews clinical data for the first 5 patients for whom SAEs are reported, and thereafter for each group of five SAE reports, then also collated every six months. • Reviews any potential side-effect data recorded in the online symptom diary or through shadow symptom diary data entry by trial Research Nurse every 6 months.
Trial Steering Committee	• Reviews data as recommended by the DMC. • Makes decisions regarding trial safety and whether trial should at any time be stopped.
Trial Management Group	• Members aware of all safety reporting mechanisms and the progress of trial safety monitoring.

8 Procedure

8.1 Procedure Diagram (see also Appendix A, Safety Reporting)



8.2 Procedure Narrative

Each of the points within the trial at which safety events may be identified are described below, along with the correct reporting documentation and communication channels to be used on each occasion.

8.2.1 Adverse events in OSAC

An AE within OSAC may come to the attention of the research team in one of the following ways:

1. Side-effects of the medication: the likelihood and expectedness of side-effects from the active treatment are documented in the trial protocol. There are three potential sources for information as to whether patients may experience side-effects:-

   - The patient may report a 'new or worsening' symptom to their GP.
   - The patient may record a 'new or worsening' symptom in the online Symptom Diary (Day 7 questions).
   - The patient may report a 'new or worsening' symptom to the Research Nurse during the weekly telephone interview at which the Research Nurse will ask the patient about his or her symptoms.

   As documented in the trial protocol, the side-effects that have been observed in previous trials suggest that it is very unlikely that any patients recruited to OSAC will experience SAEs as a result of taking the active treatment. However, the trial team will monitor all new and worsening symptoms recorded by patients on Day 7 of the Symptom Diary.

2. AEs reported by patients to their GP.

3. The patient may report an AE to the Research Nurse during the weekly telephone interview.

4. An AE, e.g. hospitalisation, serious ill health or death, identified during data collection for the 3-month primary care notes review.

5. A SAE may occur resulting in emergency unblinding.

Specific instructions regarding the steps to be followed in each of the above situations are set out below. This is followed by explanation of the standard procedures for recording and reporting AEs and SAEs in OSAC.

8.2.2 Adverse events recorded via online symptom diary or reported to Research Nurse

1. Patients are asked to record the severity of their symptoms on a daily basis in the online symptom diary.

2. On Day 7 patients are asked to record whether they have experienced any new or worsening symptoms during the first week of trial participation. This is designed to establish whether they have experienced any potential ARs, the nature or severity of which is not consistent with what is known about the drug.

3. The trial team will log and review all daily and Day 7 'new and worsening' symptom data in the trial management database by means of a regular download from the clinical database. The trial team will complete SAE initial report forms (Appendix B) for any potential SAEs.

4. The trial Research Nurse will collect any daily and 'new and worsening' data as part of the shadow data collection entry system during the weekly telephone interviews. These data will be logged / double-checked on the trial management database and SAE initial report forms completed for any events which appear to be serious.

5. The trial team will notify GPs of any safety reports issued on behalf of the patient and/or recommend to the patient that they consult their GP.

6. 'New or worsening' reported symptoms that correspond to previously known side-effects as per the trial protocol, that are not classified as unduly severe, will not be unexpected and therefore will not be reported to UH Bristol.

8.2.3 Adverse Events reported or notified to GPs by patients or via hospital admission/A&E letters

1. The OSAC trial team will train participating clinicians when and how to complete the SAE Initial Report Form.

2. It will be the responsibility of the delegated clinician to decide which AEs require reporting to UH Bristol monitor and the local trial centre.

3. The delegated clinician must notify UH Bristol monitor **immediately** (by email to **research@uhbristol.nhs.uk** or telephone, see 8.2.5(10)) of reported / notified SAEs. This report can be brief – the purpose is simply to notify UH Bristol monitor (acting on behalf of the trial sponsor) that the event happened. If notifying by email, the instructions below must be followed.

4. Email notifications of SAE reports should be sent only to **research@uhbristol.nhs.uk** and the format of the message should be as follows:

- OSAC trial
- Advance notice of SAE report to follow by fax
- Participant Identification Number: XXXXXX (**DO NOT include the patient's name or any other patient identifiable information)**
- (Include brief details of SAE if known)

5. They must complete **all sections 1-8** of the SAE Initial Report Form (Appendix B) and submit it by fax to UH Bristol monitor **within 24 hours of becoming aware of the event (see 8.2.5(10).**

6. The delegated clinician will ensure that the recording and submission of the Initial Report Form is logged on the patient's electronic medical record.

8.2.4 SAEs identified at 3-month primary care notes review

1. The trial team will train participating clinicians to complete the primary care notes review form, which indicates when an Initial Report Form may need to be completed retrospectively,

2. It will be the responsibility of the delegated clinician at the primary care site to decide which events require reporting to UH Bristol monitor.

3. They must complete **all sections 1-8** of the Initial Report Form (Appendix B) and submit it by fax to UH Bristol monitor **within 24 hours of becoming aware of the event** (see 8.2.5)**.**

4. The Bristol trial centre will log all retrospective SAE reports onto the trial management database.

8.2.5 Reporting and completion of SAE Initial Report Form (Appendix B)

1. Responsibility for reporting SAEs and SUSARs:
   - Healthcare professionals involved in trial recruitment at GP practices (Responsible Clinician; Recruiting Clinician)
   - Local trial staff (Research Assistants, Research Administrators)
   - Chief Investigator
   - Trial centre staff (Trial Manager, Trial Research Nurse and Trial Administrator).

2. Staff reporting a SAE will, **as soon** as they become aware of the event, **immediately** contact UH Bristol monitor (by email to **research@uhbristol.nhs.**uk [see **8.2.3(4)**] or telephone **0117 342 0233**) to briefly report that the event happened.

3. They will then complete the Initial Report Form sections 1-8, and section 11 if necessary, and fax the form **directly to UH Bristol monitor within 24 hours of becoming aware of the event**.

4. **Reporting staff in GP practices** must fax a copy of the **unsigned** Initial Report Form to the Bristol trial centre **at the same time** as sending it to UH Bristol monitor, then email the Bristol trial centre, who must reply to confirm the report has been received (see contact details below).

5. **The CI** will review the Initial Report Form to establish causality, complete sections 9 and 12 and sign the form.

6. Once causality is established by the CI, **the Bristol trial centre** is responsible for sending the **signed** Initial Report Form by fax direct to UH Bristol monitor **as soon as possible (and within 5 working days) after receiving it from the GP practice**.

7. This task should take priority and be done immediately on receipt at the Bristol trial centre, and at the latest within 5 working days after the date of the Initial Report Form.

8. **The CI will delegate responsibility for completing and signing the Initial Report Form, and for signing and sending the Follow-up Report Form, to another academic GP in the event of them being away from the OSAC trial duties.**

9. If the SAE/SUSAR is reported to the trial Research Nurse or Administrator (by the patient) or to the Trial Manager (via the emergency unblinding process) at the Bristol trial centre, they will follow the same procedure as in points 2, 3 and 5 above. Original report forms will be kept in the Trial Master File.

10. Contact details for UH Bristol monitor and Bristol trial centre are:-

UH Bristol monitor	**fax: 0117 342 0239** **tel: 0117 342 0233** **email: research@uhbristol.nhs.uk**
Bristol trial centre	**fax: 0117 928 7341** **email: osac-trial@bristol.ac.uk**

UNDER NO CIRCUMSTANCES SHOULD SAFETY REPORTING PAPERWORK BE FAXED, EMAILED OR POSTED TO ANY OTHER DESTINATIONS

11. Reporting staff at GP practices and the Bristol trial centre should file the original Initial Report Form paperwork in the Trial Site File / Trial Master File respectively.

12. The Bristol trial centre will log all SAEs on behalf of the local trial centres and confirm with UH Bristol monitor that the Initial Report Form has been received.

13. On behalf of OSAC, UH Bristol monitor will review all SAEs/SUSARs to determine whether any event requires immediate reporting to the sponsor, MHRA and main REC. **Fatal SUSARs must be reported within 7 days and non-fatal SUSARs within 14 days of becoming aware of the event** (see 12.1, Appendix A, Collection and Reporting of Adverse Events after MHRA Good Clinical Practice 2012).

14. The review of the SAE will be documented by UH Bristol monitor using the SAE / SUSAR Sponsor Report Form (as per UH Bristol Research Safety Reporting Standard Operating Procedure, see Related Documents).

8.2.6 Follow-up of SAEs

1. All SAEs need to be followed up until they are resolved.

2. A follow up report is NOT necessary if the SAE is resolved at the time of the Initial report.

3. The Bristol trial centre will be responsible for ensuring that SAEs are followed up within the required timescales.

4. If any SAEs remain unresolved beyond the required timescales, UH Bristol monitor will instruct the CI / Trial Manager accordingly.

5. The Trial Manager and Trial Research Nurse will co-ordinate with GP practices in completing the SAE Follow-up Report Form (Appendix C).

6. Ideally, the same person who completed the Initial Report Form should complete the Follow-up Report Form, **as soon as possible**, and **at the latest within 5 working days** of becoming aware of event.

7. Reporting staff must ensure that for **SUSARS all sections** on the Follow-up Report form have been completed, and for **other SAEs sections 1, 2 and 3** have been completed.
8. **Reporting staff in GP practices** will fax a copy of the Follow-up Report to the Bristol trial centre and then email the centre, who must reply to confirm the report has been received.

9. **The CI** is responsible for signing and sending the Follow-up Report form by fax direct to UH Bristol monitor **immediately on receiving the report, or within 24 hours so as to ensure that the Follow-up Report is sent to UH Bristol no later than 5 working days from the Initial Report Form** (see 8.2.5(8) for contact details).

    The Initial Report and the Follow-up Report Forms may be done together, if within 24 hours of becoming aware of the event.

10. Reporting staff at both GP practices and the Bristol trial centre should file the original document in the Trial Site File / Trial Master File respectively.

11. The Trial Manager will co-ordinate with GP practices for the completion and return (as above) of further Follow-up Report Form(s) for data collected **later than 5 days post-SAE** until the

SAE has resolved or a decision for no further follow-up has been taken (UH Bristol monitor will co-ordinate with Trial Manager / CI).

8.2.7 Development Safety Update, annual progress and end of study reports to trial sponsor and regulatory bodies

1. UH Bristol monitor will take responsibility for recording all SAEs and to report these to the trial Sponsor.

2. In addition UH Bristol will take responsibility for recording, assessing and reporting all SUSARs to the trial Sponsor and the MHRA within the required timescale (as per UH Bristol Research Safety Reporting Standard Operating Procedure, see Related Documents).

3. The UH Bristol team will ensure that research teams report SUSARs to the NHS REC on the appropriate form but the report to the NHS REC will be sent by the research team.

4. UH Bristol monitor will advise on the annual safety reports to the MHRA and REC produced by the Trial Manager.

5. The Trial Manager will draft the Development Safety Update, annual progress and end of study reports in collaboration with UH Bristol monitoring team, and arrange for sign-off by the CI / trial sponsor.

8.2.8 Data management for SAEs and SUSARs

1. The Bristol centre trial team is responsible for maintaining paper records of all SAEs (including copies of all SAE Initial Report and Follow-up forms and any associated emails) which will be filed in the Trial Master File and kept in a secure location.

2. The Bristol centre will maintain a comprehensive electronic log of all safety events (including AEs and SAEs) in the trial management database.

3. All safety events will also be recorded in the OpenClinica clinical database.

4. The process for reconciliation of SAE data logged by UH Bristol Monitor, entered on OpenClinica and recorded in the Trial Master File, is described in the OSAC trial database specification (see 7.7.4, SAE reporting).

8.2.9 Emergency unblinding

- Where a SAE occurs resulting in emergency unblinding, access to the unblinded data is restricted to Bristol Randomised Trials Collaboration and to UH Bristol Pharmacy (see Related Documents: OSAC Trial Emergency Unblinding SOP).

8.2.10 Provision of data to the Data Monitoring Committee

1. The independent DMC will review the first 5 SAEs that are reported:-

   a) The Trial Manager will provide the DMC with summary event data from the SAE reporting forms for ongoing trend analysis.

   b) Clinical data belonging to the patients for whom these SAEs have been reported will be provided to the DMC via a download from the clinical database.

c) The Bristol trial team will forward this clinical dataset to the BRTC. BRTC will identify the patients by treatment group but still blinded to allocation, i.e. Group 1 and Group 2.

d) If the DMC so request, BRTC will provide the DMC with the same information as above, but unblinded, i.e. Group 1 = active; Group 2 = placebo. The BRTC will forward these data directly to the DMC so as to maintain blinding of the trial team.

2. All DMC requests for unblinded data must be channelled through the CI (or Trial Manager) but the request itself will be handled only by the relevant member of staff within BRTC and/or UH Bristol Pharmacy so as to maintain blinding of the trial team.

9 Quality Control Measures

As per UH Bristol Research Safety Reporting Standard Operating Procedure.

10 Related Documents

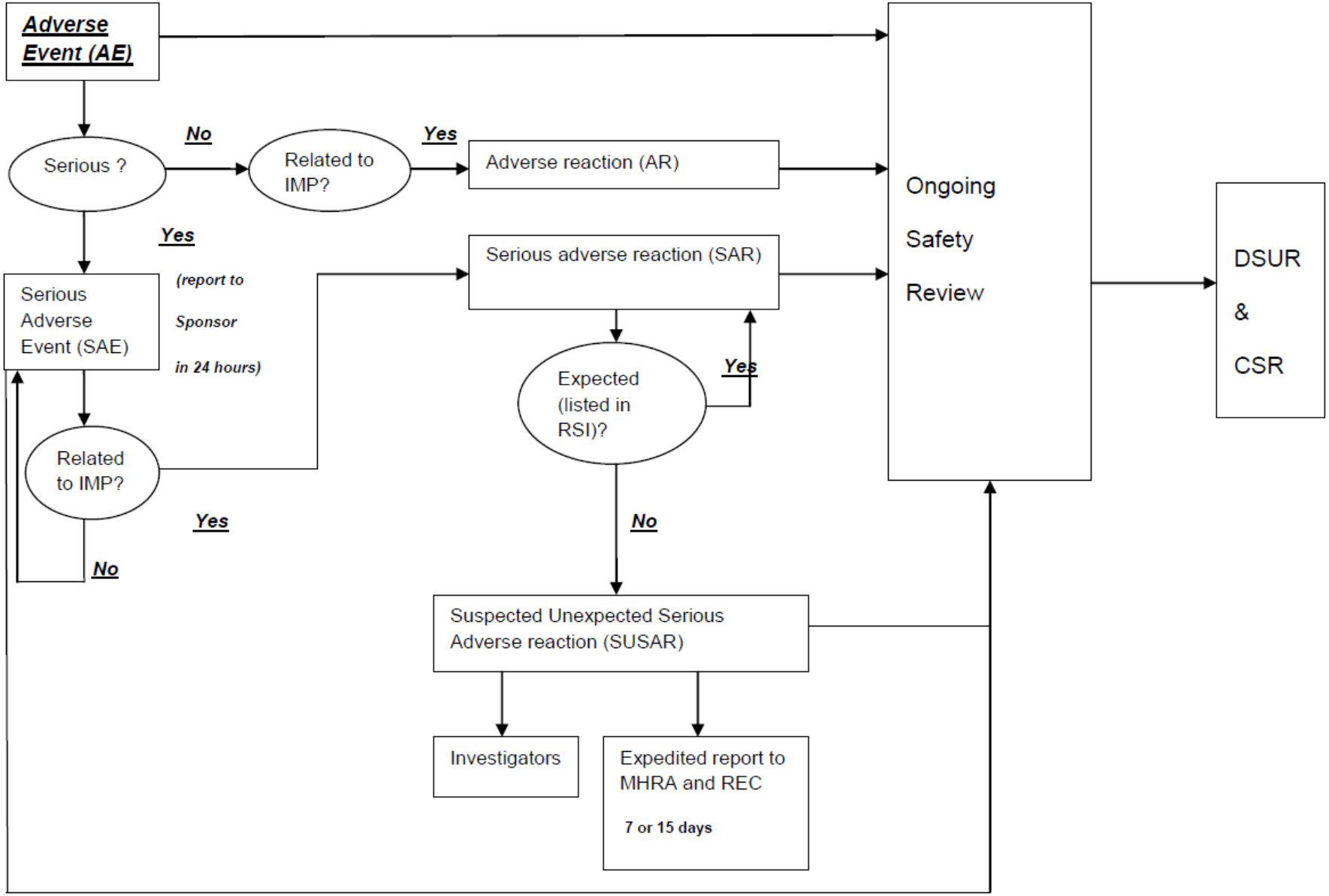
- UH Bristol Research Safety Reporting Standard Operating Procedure, version 4.0, February 2012 http://www.uhbristol.nhs.uk/research-innovation/are-you-a-researcher/information-for-researchers/forms-and-templates/
- UH Bristol Pharmacy Unblinding Procedure (UH Bristol Emergency Code Break Procedure, version CT 5 02)
- OSAC Trial Emergency Unblinding SOP, v1.0, 26/03/2013
- OSAC Trial Fax Transmissions SOP, v1.0, 13/03/2013
- OSAC trial database specification, current version

11 Additional Guidelines

N/A

12 Appendices

12.1 Appendix A: collection and reporting of adverse events (after MHRA Good Clinical Practice Guide 2012)



12.2 Appendix B

OSAC Trial SAE initial report form **v1.0 13/03/2013**

R&I use only: case reference number		Date report received by R&I	

OSAC TRIAL - SAE/SUSAR INITIAL REPORT FORM

Please complete for any SAE/SUSAR affecting any OSAC trial participants which:

- Results in death
- Is life threatening
- Results in persistent or significant disability / incapacity
- Requires hospitalisation
- Prolongs a current hospitalisation
- Results in a congenital abnormality or birth defect
- Other: an adverse event the nature or severity of which is not consistent with the known information about the drug provided in the Summary of Medicinal Product Characteristics (which is also summarised in the trial protocol and in the Full Patient Information Booklet)

1. Person making report (please complete all asterisked fields)	
Name: *	
Job title/role in study: *	
Contact address: *	
Email address: *	
Telephone No: *	
Fax number: *	

2. Details of study	
Full Title of Study: OSAC (Oral Steroids for Acute Cough) Trial Chief Investigator: Dr Alastair Hay ISRCTN #: 57309858 MHRA ref #: 03299/0015/001-0001	Study site, e.g. GP practice name:* UH Bristol R&I Project Registration No: UoB1581 Ethics No: 12/SW/0180 EudraCT No. (IMP studies only): 2012_000851-15

3. Details of subject affected by SAE/SUSAR					
Subject study ID (PID)*	Initials*	DoB*	Gender*	Weight*	Height*

4. Details of SAE/SUSAR (further space available in section 12)
Full description of event/reaction, including body site, reported signs and symptoms and diagnosis where possible:*

<table>
<tr><td colspan="3">Event is defined as serious because it (tick as many as apply) *:
☐ resulted in death
☐ is/was life-threatening
☐ resulted in persistent or significant disability/incapacity
☐ required hospitalisation
☐ prolonged an ongoing hospitalisation
☐ resulted in a congenital anomaly or birth defect
☐ other – please specify (see right)
Please give further details in section 6 ‘Outcome’</td><td colspan="2">If ‘Other’, please specify:</td></tr>
<tr><td colspan="2">Maximum intensity (up until time of initial report)*</td><td>Mild ☐</td><td>Moderate ☐</td><td>Severe ☐</td></tr>
<tr><td>Onset Date* (when event became serious):</td><td>Onset Time:*</td><td>End date:*</td><td>End time:*</td><td>OR Duration:*</td></tr>
</table>

Signature of person making report: _____Date:____/____/____

R&I use only: case reference number	

To be completed by the person filling in the SAE form:					
UH Bristol R&I number:	UoB 1581	Subject ID/initials:*		Onset date of SAE: *	

OSAC TRIAL - SAE/SUSAR INITIAL REPORT FORM

Sheet number: _____ of_____

5. Details of IMP (further space available in section 11)									
Brand name	**Indication**	**Patient ID no. ***	**Route (e.g. oral)**	**Form (e.g. tablet)**	**Total dose/24h (specify units)**	**Regimen (e.g. od or b.d)**	**Start date & time***	**Stop date & time***	**Suspected cause of SAE /SUSAR? (Y/N) ***
Prednisolone	acute cough (OSAC trial entry)		oral	tablet	2 x 20mg	od x 5 days (sooner if symptoms resolve)			
For blinded studies, was the randomisation code broken? *				Yes (see below) ☐		No ☐			
If yes, give details:									

Continue on new sheet if necessary; please identify how many sheets have been used

Signature of person making report: _____ Date: ____/____/____

R&I use only: case reference number	

To be completed by the person filling in the SAE form:					
UH Bristol R&I number:	UoB 1581	Subject ID/initials:*		Onset date of SAE: *	

6. Outcome (further space available in section 11)		
☐ Resolved*	☐ Ongoing*	☐ Died* (give cause and PM details if available)
Please give details:*		
Was the patient withdrawn from the study?	Yes ☐	No ☐

7. Location of (onset of) SAE (further space available in section 11)
Setting (e.g. hospital, home, GP, nursing home – name/address):

8. Action taken and further information (further space available in section 11)
Please describe action taken (including details of IMP where applicable e.g. drug withdrawn etc…):
Other information relevant to assessment of case e.g. medical history, family history, test results.

9. Causality and Expectedness (to be completed by OSAC Chief Investigator or Deputy)		
Is the SAE related to the drug/device/intervention? ☐ Not related ☐ Unlikely to be related ☐ Possibly related* ☐ Probably related* ☐ Definitely related*	***If possibly, probably or definitely related, was the SAE unexpected?** ☐ Yes[1] ☐ No[2] (Unexpected means not described in the protocol or other product information)	**In addition to this form, and within 5 working days:** **1 - Please complete and return all sections of the follow up report form.** **2 - Please complete and return sections 1, 2 and 3 of the follow-up report form.**

10. Sponsor notification (only complete where sponsor is not UH Bristol)	
Has the Sponsor been notified of the SAE/SUSAR?	☐ Yes, give date: ☐ No[+]
[+]Please note, you must inform the Sponsor within 24 hours of becoming aware of the event.	

Signature of person making report: _____Date:____/____/____

R&I use only: case reference number	

To be completed by the person filling in the SAE form:					
UH Bristol R&I number:	UoB 1581	Subject ID/initials:*		Onset date of SAE: *	

11. Additional information (refer to section number)	
Section no.	**Further information**

12. OSAC Chief Investigator or Deputy	
Name:	
Job title/role in study:	
Contact address:	
Email address:	
Telephone No:	
Fax number:	
Signature:	
I confirm that the contents of this form (pages 1, 2, 3, 4 ± 5) are accurate and complete	

Please tick this box if additional pages have been used: ☐

Signature of person making report: _____ **Date:____/____/____**

FOR ALL REPORTING STAFF: Please fax this form directly to UH Bristol Monitor within 24 hours of becoming aware of event. Fax: 0117 324 0239.

FOR GP SITES ONLY: Please fax a copy of the form to the Bristol trial centre at same time as sending report to UH Bristol Monitor, file original in your trial site file and email Bristol to confirm receipt of fax. Fax: 0117 928 7341 / email: osac-trial@bristol.ac.uk

FOR BRISTOL TRIAL CENTRE: Please fax this form directly to UH Bristol Monitor as soon as possible after CI has completed and signed sections 9 and 12. File original/copy in the Trial Master File.

12.3 Appendix C

OSAC Trial SAE follow-up report form **v1.0 13/03/2013**

To be completed by UH Bristol Monitor / Trial Manager					
R&I use only: case reference number				Date received:	
UH Bristol R&I no:	UoB1581	Subject ID/initials:*		Onset date of SAE:*	

OSAC TRIAL - SAE/SUSAR FOLLOW-UP REPORT FORM

To be completed by person filling in the initial SAE report form (please complete all asterisked fields)			
1. Further details of SAE/SUSAR			
Further details of event/reaction, including body site, reported signs and symptoms and diagnosis where possible: *			
Maximum intensity (up until time of follow up report)	Mild ☐	Moderate ☐	Severe ☐
	End date*	**End time***	***OR* Duration***
2. Outcome			
☐ Resolved*	☐ Ongoing*	☐ Died* (give cause and PM details if available)	
Give details:*			
Was the patient withdrawn from the study?	Yes ☐	No ☐	
3. Additional action taken and further information since initial report			
Please describe further action taken:*			
Further information or missing data relevant to assessment of case e.g. medical history, family history, test results:*			

Signature of person making report: _____ Date: ____/____/____

Name (please print):_____ Job title:_____

Signature of OSAC Chief Investigator or Deputy: **Name (print please):** **I confirm that the contents of this form (pages 1± 2/3) are accurate and complete**

R&I use only: case reference number	

To be completed by UH Bristol Monitor / Trial Manager					
UH Bristol R&I number:	UoB1581	Subject ID/initials:*		Onset date of SAE:*	

Sheet number: _____ of _____

To be completed by the person filling in the SAE form (please complete all asterisked fields)								
4. CONCOMITANT MEDICATION (details of administration of other medication concurrent with the IMP):								
Brand name*	**Indication***	**Route (e.g. oral)***	**Form (e.g. tablet)***	**Total dose/24h (specify units)***	**Regimen (e.g. b.d)***	**Start date & time***	**Stop date & time***	***Or* duration of treatment***

Continue on new sheet if necessary; please identify how many sheets have been used.

Signature of person making report: _____ Date: ____/____/____

R&I use only: case reference number	

To be completed by UH Bristol Monitor / Trial Manager					
UH Bristol R&I number:	UoB1581	Subject ID/initials:*		Onset date of SAE:*	

Sheet number: _____ of _____

To be completed by the person filling in the SAE form (please complete all asterisked fields)									
5. STUDY IMP – details of administration (NB: complete for IMP studies only)									
Brand name	**Indication**	**Patient ID***	**Route (e.g. oral)**	**Form (e.g. tablet)**	**Total dose/24h (specify units)**	**Regimen (e.g. b.d)**	**Start date & time***	**Stop date & time***	***Or* duration of treatment***
Prednisolone	Acute cough (recruitment to the OSAC clinical trial)		Oral	Tablet	2 x 20 mg	Daily x 5 days (sooner if symptoms resolve)			
For blinded studies, was the randomisation code broken?*				Yes (see below)* ☐		No ☐			
***If yes,** give details**:**									

Continue on new sheet if necessary; please identify how many sheets have been used

Name of person making report: _____

Signature of person making report: _____Date: ____/____/__