STANDARD OPERATING PROCEDURE FOR:

Recording and Reporting of Deviations, Violations, Potential Serious Breaches, Serious Breaches and Urgent Safety Measures

SOP Details:

Number: SOP-OSAC-XXXX	Version: 1.0
Author(s): Harriet Downing / Sue Harris Title: OSAC Trial Manager /Research Nurse	Date: 17/06/2013
Authorised by: Dr Alastair Hay Title: Chief Investigator	Date: 19 June 2013
Date operational:	19 June 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:	

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

CONFIDENTIAL: UNAUTHORISED COPYING PROHIBITED

Contents

1 Document History

Revision	Date	Author	Changes
1.0	17/06/2013	Harriet Downing / Sue Harris	None, this is the first draft

2 Background

Regulation 29 "Conduct of trial in accordance with clinical trial authorisation etc." of the UK regulations (SI 2004/1031) 'The Medicines for Human Use (Clinical Trials) Regulations 2004' stipulates that all Clinical Trials of Investigational Medicinal Products (CTIMPs) must be conducted in accordance with a protocol that has been approved by a Research Ethics Committee (REC) and the Competent Authority (Medicines and Healthcare products Regulatory Agency).

It is the Sponsor's responsibility to oversee the conduct of all CTIMPs and to ensure compliance with the approved protocol and prevailing UK regulations.

The Investigator/Institution should only conduct the trial in accordance with the **approved protocol** unless an urgent safety measure must be taken, according to SI 2004/1031 under Regulation 30.

The Investigator, or person designated by the Investigator (in the trial delegation log), should **document and explain any deviation** from the approved protocol.

3 Purpose

This SOP specifies the procedures for **Investigators** to follow for the OSAC clinical trial in the event of a **protocol and/or GCP deviation** and describes the procedure for **local investigators** to record the event and notify the Chief Investigator, Sponsor and/or the MHRA/REC as and when necessary. The procedures include assessing the impact of the **deviation** in light of the definition of **a potential serious breach** and /or **an urgent safety measure.**

It describes what consideration must be taken into account to assess whether the deviations and violations also meet the definition of a **potential serious breach** or **urgent safety measure and the reporting requirements.**

4 Scope

This SOP applies to the recording and reporting of all protocol and GCP deviations for the OSAC trial only.

The requirement to follow this SOP cannot be substituted by the use of a **"protocol waiver" or departure from the approved inclusion/exclusion criteria of the protocol.** An occurrence of this type may constitute a serious breach reportable to the MHRA and therefore must be reported according to this SOP.

5 Definitions & Abbreviations

5.1 Key definitions

Event	Description / definition
Deviation	A deviation is usually an **unintended** departure from the expected conduct of the trial (protocol/SOPs), e.g. a protocol visit date deviation (a common deviation in clinical trials) which does not need reporting to the Sponsor.

Event	Description / definition
	These events will be identified by the trial team during trial conduct and must be continually monitored by the CI/PI and site team. Minor deviations from approved clinical trial protocols and GCP occur commonly in CTIMPs and do not result in Serious Breaches (see definition below). The majority are technical deviations that do no harm to the trial subjects or significantly affect the scientific value of the reported trial results (see MHRA "Guidance for the notification of serious breaches of GCP or the trial protocol", version 2.0). These cases should be **documented in the CRF and/or in a file note** and **appropriate corrective and preventative action taken in order to ensure they do not recur**. They do not require reporting to the Sponsor. The CRF and the Centre Log of Protocol and/or GCP Deviations etc. (Appendix 1) should be used to record each case.
Violation, Major	**A violation can occur when there is a variation in practice from trial protocol/SOPs. A violation can be classified as major if there is a significant occurrence which affects participant safety or scientific integrity of the research.** Any violations that may impact on the subjects' safety or affect the integrity of the study data **must** be reported to the Sponsor. Examples include but are not limited to: • Failure to obtain informed consent, i.e. no documentation in source data or an Informed Consent form • Enrolment of subjects not meeting the inclusion/exclusion criteria • Undertaking a trial procedure not approved by the REC and/or the MHRA (unless for immediate safety reasons) • Failure to report an SAE/R/SUSAR to the UH Bristol Monitor • IMP dispensing/dosing error
Violation, Minor	A violation that does not impact on subjects' safety or compromise the integrity of study data. Examples may be: • Missing original signed consent form (only photocopy present)
Serious Breaches of the protocol and/or GCP	Please consider whether the violation that has occurred on site meets the following definitions. These cases must be reported to the Sponsor **as soon as the Investigator (CI, centre PI or a member of the trial research teams reporting to them) has become aware of the event.** Under Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 [SI 2004/1031], as amended by SI 2006/1928, there is a requirement for the notification of "serious breaches" of GCP and/or the trial protocol: ***"*** *(1) The sponsor of a clinical trial shall notify the licensing authority in writing of any serious breach of -* *(a)* ***the conditions and principles of GCP*** *in connection with that trial; or* *(b)* ***the protocol*** *relating to that trial, as amended from time to time in accordance with regulations 22 to 25,* ***within 7 days*** *of becoming aware of that breach.* *(2) For the purposes of this regulation, a "serious breach" is a breach which is* ***likely*** *to effect to a significant degree –* *(a) the safety or physical or mental integrity of the subjects of the trial; or* *(b) the scientific value of the trial".* Examples include but are not limited to: • **Systematic** failure to adhere to the schedule of events relating to patient

Event	Description / definition
	visits; • **Routinely** failing to follow instructions for handling of trial medication; • **Systematically** incorrect Patient Information Sheets and/or Consent Forms • **Routinely** failing to follow safety instructions given in the protocol • **Routinely** failing to adhere to data recording / handling instruction given in the Protocol.
Potential Serious Breach	An event which is investigated as a breach potentially meeting the definition of "serious breach" above.
Urgent Safety Measures (Implementing a Protocol Deviation under an emergency)	The Investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects **without** prior approval from the REC/MHRA. This is defined as an Urgent Safety Measure under UK Regulation 30: *"The sponsor and investigator may take appropriate urgent safety measure to protect clinical trial subjects from any immediate hazard to their health and safety. The measures should be taken immediately".* However, in order to meet the legal timelines **the investigator must inform the MHRA and the Sponsor (in parallel) in writing immediately and within 3 days.** See section 8.2.6 below.
Further definitions	
Trust Reportable Incident	The Research Governance Framework 2005 reminds investigators to report any Incident to the Trust as per their local Trust Incident reporting policy. These incidents should also be notified to the local R&D office in line with their local reporting requirements. This will be done by the Trial Manager.

5.2 Abbreviations

CAPA	Corrective and preventative actions
CI	Chief Investigator
CRF	Case Report Form
CTIMP	Clinical Trial of Investigational Medicinal Product
GCP	Good Clinical Practice
ISF	Investigator Site File
MHRA	Medicines and Healthcare products Regulatory Agency
PI	Principal Investigator
REC	Research Ethics Committee
SOP	Standard Operating Procedure
TMF	Trial Master File
TMG	Trial Management Group
N/A	Not Applicable

6 Pre-Requisites

6.1 Pre-Requisite Knowledge & Training

- Good Clinical Practice training.
- Trial specific training in OSAC recruitment and data collection procedures, including knowledge of the OSAC trial protocol and associated SOPs.

6.2 Pre-Requisite Equipment & Systems

N/A

7 Roles & Responsibilities (Actors)

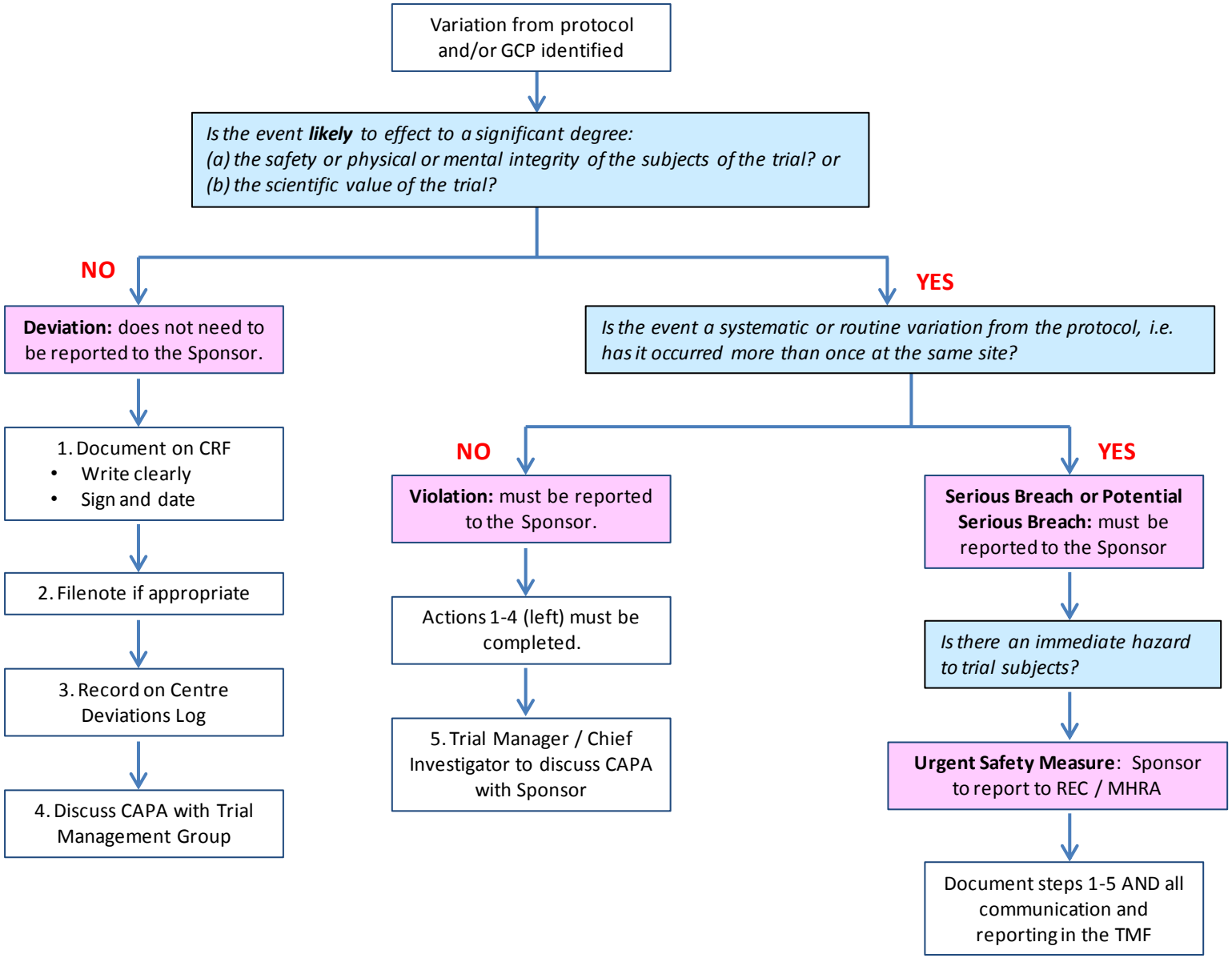
Who	What & Why
Chief Investigator	Assess all protocol violations, potential and actual serious breaches and discuss with Sponsor as per protocol deviation reporting requirements (this SOP). Assess with Sponsor if Serious Breaches require Urgent Safety Measures.
Principal Investigator	Assess all protocol deviations occurring at the local trial centre. Record and report any violations, via the Bristol-based Trial Manager to the Sponsor within agreed timeframes and in accordance with this SOP if deemed a potential serious breach/urgent safety measure. Ensure CAPA are put in place. Discuss events with TMG where appropriate.
Trial Manager	Report Trust Reportable Incidents as per R&D approval conditions for the site. Maintain Master Log of protocol deviations (etc.). Monitor CAPA and ensure they are built into data quality monitoring procedures.
Trial Research Nurse	Be aware of content of the Master Log of protocol deviations (etc.). Ensure CAPA are built into trial training.
Trial centre RAs	Be aware of definitions of protocol deviations and violations. Record all events in the Centre Deviations Log. Ensure the PI is aware of all non-trivial events.
Trial Administrators	Be aware of definitions of protocol deviations and violations. Record all events in the Centre Deviations Log. Ensure Centre RA is aware of all non-trivial events.
Sponsor	With the CI, be informed of all protocol violations and assess whether event is a Serious Breach. Assess if Serious Breaches require Urgent Safety Measures. Report Serious Breaches / Urgent Safety Measures to REC / MHRA.
UH Bristol Monitor	Advise Sponsor/CI on reporting of Serious Breaches/Urgent Safety Measures to REC/MHRA.
DMC	To be informed of Serious Breaches/Urgent Safety Measures
TSC	To be informed of Urgent Safety Measures

8 Procedure

Please check the latest version of this SOP on **http://www.osactrial.org.uk/researchers.php**

8.1 Procedure Diagram

See next page.


Variation from protocol and/or GCP identified
Is the event likely to effect to a significant degree:
(a) the safety or physical or mental integrity of the subjects of the trial? or
(b) the scientific value of the trial?
NO
YES
Deviation: does not need to be reported to the Sponsor.
1. Document on CRF
• Write clearly
• Sign and date
2. Filenote if appropriate
3. Record on Centre Deviations Log
4. Discuss CAPA with Trial Management Group
Is the event a systematic or routine variation from the protocol, i.e. has it occurred more than once at the same site?
NO
YES
Violation: must be reported to the Sponsor.
Actions 1-4 (left) must be completed.
5. Trial Manager / Chief Investigator to discuss CAPA with Sponsor
Serious Breach or Potential Serious Breach: must be reported to the Sponsor
Is there an immediate hazard to trial subjects?
Urgent Safety Measure: Sponsor to report to REC / MHRA
Document steps 1-5 AND all communication and reporting in the TMF

8.2 Procedure Narrative

The following sections explain how the different types of protocol and GCP deviations will be recorded, addressed and reported.

Judgments must be made on whether a breach is likely to have a significant impact on the scientific value of the trial and if it constitutes a deviation, violation or potential serious breach.

The Sponsor and/or CI/PI must report serious breaches to the MHRA within the regulatory timelines and consider the following actions:

- Receipt and Assessment, i.e. assessment of deviations/violations by Sponsor/delegate, isolated/systematic incident, patient(s) harmed or put at risk and data credibility etc.
- Investigation
- Corrective and Preventative Actions (CAPA)
- Reporting to MHRA
- Compliance with 7-day reporting timescale.

The regulatory timeline will only commence once the Sponsor has been notified of an event and has assessed the event as being a serious breach.

8.2.1 Deviations

- **Recording**: recorded in the CRF, deviations and violations log and file noted if necessary.
- **Reporting**: minor deviations do not require notification to the sponsor. Where a deviation is reoccurring and may result in identification of a serious breach, this should be notified to the sponsor.
- **Escalation:** CAPA should be implemented for deviations.
- It is recommended that reoccurring deviations be discussed at any trial meetings and if required detailed in the clinical study report.

8.2.2 Violations

- **Recording**: recorded in the CRF, deviations and violations log and file noted if necessary.
- **Reporting:** violations of GCP, protocol and regulations **must** be notified to the sponsor **within 3 calendar days** of becoming aware of that violation.
- **Escalation:** CAPA must be implemented for violations:
    - If a violation is determined to be a potential serious breach (as defined by UK Clinical Trials Regulation 29A) this must be reported to the MHRA and REC within regulatory timelines.
    - Reoccurring violations will be discussed at any trial meetings and, if required, detailed in the clinical study report.
    - The Sponsor must discuss an identified deviation/violation with the UH Bristol monitor **as soon as possible.**
    - If required, the Sponsor will instruct the UH Bristol Monitor to undertake a triggered monitoring visit.
    - All major violations must be resolved to conclusion.
    - If a violation constitutes a Serious Breach of GCP - further follow-up and reporting may be required by the Sponsor.

8.2.3 Potential Serious Breach

1. Site team to complete the "Notification of Serious Breaches of GCP or Trial Protocol form, Appendix 3: all available details should be documented on the form.

2. Completed notification forms to be sent to the Sponsor.

3. **If the CI/PI is unsure whether a deviation or violation is a potential serious breach notify the Sponsor as soon as possible and provide as much information as possible.**

4. Sponsor to assess and collate data relating to the potential serious breach and report to the MHRA **within 7 calendar days**.

5. Violation/serious breach to be noted on the Master Log of Protocol and/or GCP Deviations (etc.), Appendix 2.

6. The local PI must log the "Potential serious breach" in the Centre Log of Protocol and/or GCP Deviations (etc.), Appendix 1.

8.2.4 Assessment by the Trial Sponsor

1. The Chief Investigator and Sponsor to discuss potential serious breach internally:
   - Discussion with appropriate team members, e.g. local PI, trial centre staff.
   - Assess in which relevant GCP, regulatory or protocol section the breach was identified.
   - Evaluate if it fulfils the MHRA definition of a serious breach. The Sponsor may contact the GCP Inspectorate for email clarification from the MHRA.
   - Phone conversations with the MHRA are discouraged; a clear trail of information passed to and received from the MHRA **must** be maintained.
   - **Best practice - send the case as a POTENTIAL serious breach, detail available information and request the MHRA to assess the event.**
   - Compile all supporting documentation and submit to the MHRA **within 7 days** of assessing the event as a serious breach.
   - **NB:** If necessary, the Sponsor might have to submit a substantial amendment/ urgent safety measure report.

2. The CI / Sponsor should consider:
   - If the breach constitutes an Urgent Safety Measure, is a substantial amendment required due to a temporary halt in the study OR
   - If the breach involves defective medicines or IMP recall AND
   - Whether the REC needs to be notified.

3. If the Sponsor obtains clear and unequivocal evidence a serious breach has occurred the Sponsor **must:**
   - notify the MHRA first **within 7 days**,
   - investigate AND
   - take action simultaneously/ or after notification AND
   - should **not** wait to obtain all details of the breach before notification.

4. Only one report is required for a deviation/violation occurring at more than one site with copies filed in the ISFs.

8.2.5 Corrective and Preventative Actions (CAPA)

1. The Sponsor and the CI/PI must agree on the appropriate corrective and preventative action to be taken, documenting the details in the notification report.

2. Sites must also document any actions taken and file in the ISF.

8.2.6 Notification to the MHRA

1. The Sponsor **must** send the completed notification form (Appendix 3) to the GCP Inspectorate **within 7 days** of assessing a serious breach.

2. Report updates are accepted if details of the breach are incomplete; plans for completion of follow-up reports should be included.

3. Email completed form to: **GCP.SeriousBreaches@mhra.gsi.gov.uk**
   OR
   Fax/post notifications to any of the three MHRA Inspectorate offices (see MHRA website).

4. If a "potential serious breach" is investigated but is **not** a serious breach, log as a "Potential serious breach".

5. Routine review of the log must be done to identify any trends, particularly relating to recurrent findings requiring additional site training or monitoring visits.

8.2.7 Follow-up reports

1. Follow-up reports should be made in writing (the Serious Breaches form can be used) and **must**:
   - be clearly identified as a follow-up report;
   - include the unique GCP ID allocated when the MHRA acknowledged initial report;
   - be forwarded to the initial Inspector dealing with the case.

8.2.8 Escalation and dissemination process

Internally:

1. The Site Investigator where the breach occurred must be informed by their line manager(s) (both Trust and University) that the MHRA has been sent a "notification of serious breach" and which CAPA is in place.

2. The line manager(s) **must** inform their QA and senior management if necessary and according to their own SOPs.

3. The serious breach should be notified to the DMC and TSC as deemed appropriate.

4. The R&D Department of the site where the serious breach occurred must be informed which CAPA is in place.

Externally:

1. Depends on the nature of the breach and may include other sites affected.

2. The breach should be circulated to appropriate staff for inclusion in the study report or publication.

3. Serious breaches relating to investigator sites etc. should be available to those selecting study sites (including local PCRNs), i.e. careful assessment should be made before using a non-compliant site in future studies.

4. The PCRN GCP-training teams should be regularly informed of serious breaches reported to the MHRA.

8.2.9 Notification of Urgent Safety Measure (SI 2004/1031, Regulation 30, p31) by a site

1. The CI/PI should phone the MHRA Clinical Trial Unit to discuss the issue with a medical assessor **immediately** an urgent safety measure is taken at a site.

2. The CI/PI must send an email to the MHRA assessor spoken to, summarising the information exchanged and advice provided, and requesting the assessor to confirm the email content is correct.

3. The CI/PI must notify the MHRA, REC and Sponsor in writing of the measure taken and reason **within 3 days.** The local R&D Department might need to be informed, depending on their site letter.

4. **If a substantial amendment is required, the CI/PI must:**
   - **inform the sponsor and**
   - **submit a** notification of substantial amendment to the REC and MHRA
   - the substantial amendment must include a cover letter detailing the measures taken and reasons, a Notification of Amendment form and supporting documentation.

5. The urgent safety measure notification must be:
   - faxed to MHRA Clinical Trials Unit on **020 7084 2443** or sent by e-mail to clintrialhelpline@mhra.gsi.gov.uk **marked 'Urgent Safety Measure'** AND
   - sent as PDF documents on disk to:

     Information Processing Unit
     Area 6
     Medicines and Healthcare products Regulatory Agency
     151 Buckingham Palace Road
     Victoria
     London
     SW1W 9SZ
   - the PI/Trial Manager will file a copy of this notification in the Centre Trial File and log the event in the **Centre Log of Protocol Deviations (etc.),** Appendix 1.

6. Acknowledgements from the MHRA and REC must be filed.

9 Quality Control Measures

The advice and opinion of the University Hospitals Bristol NHS Foundation Trust Research and Innovation Team (Independent Monitor, on behalf of the Trial Sponsor, for the OSAC trial) will be sought on the processes and reporting formats set out in this SOP.

10 Related Documents and References

1. UCL Standard Operating Procedure for the Recording and Reporting of Deviations, Violations, Potential Serious breaches, Serious breaches and Urgent Safety Measures, SOP ID Number: JRO/SPON/S15/04 (http://www.ucl.ac.uk/jro/standingoperatingprocedures/document-library)

2. MHRA Serious Breaches Guidance Version 2.0 dated 15/10/09

3. The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031)

4. The Medicines for Human Use (Clinical Trials) Amended Regulations 2006 (SI 2006/1928)

5. The Medicines for Human Use (Clinical Trials) Amended Regulations 2009 (SI 2009/1164)

6. http://www.mhra.gov.uk/Howweregulate/Medicines/Inspectionandstandards/GoodClinicalPractice/CON009678

7. NIHR Introduction to Good Clinical Practice (GCP): A practical guide to ethical and scientific quality standards in clinical research, Consolidated Version 2.1, August 2012.

11 Additional Guidelines

N/A.

12 Appendices

12.1 Appendix 1: OSAC Trial Centre Protocol / GCP Deviations Log

THE OSAC (ORAL STEROIDS FOR ACUTE COUGH) TRIAL	**OSAC** **TRIAL CENTRE LOG FOR: PROTOCOL &OR GCP DEVIATIONS, VIOLATIONS, POTENTIAL SERIOUS BREACHES, SERIOUS BREACHES, URGENT SAFETY MEASURES**

Trial Title:	OSAC (Oral Steroids for Acute Cough) Trial		
Sponsor ID:	1580	**Centre:**	
EudraCT:	2012-000851-15	**Centre PI:**	

Date of event	Date of research team becoming aware of event	Name of site (trial centre or GP practice) where the event took place	Type of event: 1. Deviation 2. Violation 3. "Potential Serious breach" 4. "Serious breach" 5. "Urgent Safety measure" (See definitions below)	Description of event (use additional filenote if necessary)	Corrective actions taken	Preventative actions taken	PI signature and date	If a protocol violation, breach or urgent safety measure, date on which this was reported to Bristol trial centre

A copy of this log must be kept in the Centre trial file. For all events defined as type 2-5, the log must be faxed to the Bristol trial centre on 0117 928 7341.

DEFINITIONS OF PROTOCOL DEVIATION EVENTS

Event	Source	Definition
Deviation	SOP-OSAC-0005	*An un-intended departure from the expected conduct of the trial (protocol, SOPs)*
Violation	SOP-OSAC-0005	*A violation can occur when there is a consistent variation in practice from trial protocol, SOPs. A violation can be classified as major if there is a significant occurrence which affects participant safety or integrity of the research.*
Serious Breach	Regulation 29A (SI 2006/1928)	*(2) For the purposes of this regulation, a "**serious breach**" is a breach which is likely to effect to a significant degree –* *(a) the safety or physical or mental integrity of the subjects of the trial; or* *(b) the scientific value of the trial".*
Potential serious breach		*A breach which is investigated as a breach potentially meeting the definition of "serious breach" above.*
Urgent safety measures	Regulation 30 (SI 2004/1031)	*The sponsor and investigator may take appropriate 'urgent safety measures' in order to protect the subjects of a clinical trial against any immediate hazard to their health or safety. The sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the licensing authority and the relevant ethics committee of the measures taken and the circumstances giving rise to those measures.* Regulation 30 of the Medicines for Human Use (Clinical Trials) Regulations 2004(SI 2004/1031) was amended by (SI 2009/1164): *For paragraph 2 of regulation 30 of the Medicines for Human Use (Clinical Trials) Regulations 2004 (urgent safety measures) (a), substitute the following paragraphs—* *"(2) If measures are taken pursuant to paragraph (1), the sponsor shall—* *(a) where paragraph (3) applies, as soon as possible; and* *(b) in any other case, immediately, and in any event no later than 3 days from the date the measures are taken, give written notice to the licensing authority and the relevant ethics committee of the measures taken and the circumstances giving rise to those measures.* *(3) This paragraph applies for any period during which a disease—* *(a) is pandemic; and* *(b) is a serious risk to human health or potentially a serious risk to human health."*

12.2 Appendix 2: OSAC Master Protocol / GCP Deviations Log

THE OSAC (ORAL STEROIDS FOR ACUTE COUGH) TRIAL	**OSAC** **MASTER LOG FOR: PROTOCOL &/OR GCP DEVIATIONS, VIOLATIONS, POTENTIAL SERIOUS BREACHES, SERIOUS BREACHES, URGENT SAFETY MEASURES**

Trial Title:	OSAC (Oral Steroids for Acute Cough) Trial		
Sponsor ID:	1580	**EudraCT:**	2012-000851-15

Date of event	Date of research team becoming aware of event	Name of site (trial centre or GP practice) where the event took place	Type of event: 1. Deviation 2. Violation 3. "Potential Serious breach" 4. "Serious breach" 5. "Urgent Safety measure" (See definitions below)	Description of event (use additional filenote if necessary)	Corrective actions taken	Preventative actions taken	If a protocol violation, breach or urgent safety measure, date on which this was reported to the Trial Sponsor	If reported to the Trial Sponsor, CI signature and date

A copy of this log must be kept in the Trial Master File. All events defined as Type 2-4 will be reviewed by the Chief Investigator prior to reporting to the Trial Sponsor. All events defined as Type 5 will be jointly reported to the Sponsor and to the Chief Investigator.

DEFINITIONS OF PROTOCOL DEVIATION EVENTS

Event	Source	Definition
Deviation	SOP-OSAC-0005	*An un-intended departure from the expected conduct of the trial (protocol, SOPs)*
Violation	SOP-OSAC-0005	*A violation can occur when there is a consistent variation in practice from trial protocol, SOPs. A violation can be classified as major if there is a significant occurrence which affects participant safety or integrity of the research.*
Serious Breach	Regulation 29A (SI 2006/1928)	*(2) For the purposes of this regulation, a "**serious breach**" is a breach which is likely to effect to a significant degree –* *(a) the safety or physical or mental integrity of the subjects of the trial; or* *(b) the scientific value of the trial".*
Potential serious breach		*An event which is investigated as a breach potentially meeting the definition of "serious breach" above.*
Urgent safety measures	Regulation 30 (SI 2004/1031)	*The sponsor and investigator may take appropriate 'urgent safety measures' in order to protect the subjects of a clinical trial against any immediate hazard to their health or safety. The sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the licensing authority and the relevant ethics committee of the measures taken and the circumstances giving rise to those measures.* Regulation 30 of the Medicines for Human Use (Clinical Trials) Regulations 2004(SI 2004/1031) was amended by (SI 2009/1164): *For paragraph 2 of regulation 30 of the Medicines for Human Use (Clinical Trials) Regulations 2004 (urgent safety measures) (a), substitute the following paragraphs—* *"(2) If measures are taken pursuant to paragraph (1), the sponsor shall—* *(a) where paragraph (3) applies, as soon as possible; and* *(b) in any other case, immediately, and in any event no later than 3 days from the date the measures are taken, give written notice to the licensing authority and the relevant ethics committee of the measures taken and the circumstances giving rise to those measures.* *(3) This paragraph applies for any period during which a disease—* *(a) is pandemic; and* *(b) is a serious risk to human health or potentially a serious risk to human health."*

12.3 Appendix 3: Notification of a Serious Breach form

Notification of Serious Breach of Good Clinical Practice or Trial Protocol

(Ref: UK Statutory Instrument 2004/1031 Regulation 29A, as amended by 2006/1928)

Please forward this notification to **GCP.SeriousBreaches@mhra.gsi.gov.uk** OR
GCP Inspectorate, MHRA, 2a Hunter house, 57 Goodramgate, York, YO1 7FX.

Your Name:		**Your Organisation:**	
Your Contact Details:		**Date Breach Identified by Sponsor:**	
		Date Breach Notified to MHRA:	
Details of Individual or Organisation committing breach:		**Details of related study** (if applicable)**:** (e.g. EudraCT No, CTA number, study title)	
Report: Tick appropriately	**Initial Report** ☐	**Follow-up Report** ☐	
Please give details of the breach			
Potential impact to patient safety and/or data credibility: ☐ Patient safety ☐ Patient confidentiality ☐ Approval Issues ☐ IMP		☐ Scientific value / data credibility ☐ NA/None ☐ Other Non-compliances (specify)	
Background: *(continue on additional sheets if required)*			
Other relevant information: *(i.e. study status, site(s), ethics, trust, CRO /sponsor details etc.)* *(continue on additional sheets if required)*			

Please give details of the action taken:
This should include: Any investigations by your organisation, details of investigations by other organisations (e.g. CRO/ethics/trust), the results and outcomes of the investigations (if known or details of when they will be available/submitted), how it will be reported in the final report/publication, the corrective & preventative action implemented to ensure the breach does not occur again. *(continue on additional sheets if required)*

Actual impact to patient safety and/or data credibility:

☐ Patient safety	☐ Scientific value / data credibility
☐ Patient confidentiality	☐ NA/None
☐ Approval Issues	☐ Other Non-compliances (specify)
☐ IMP	

12.4 Appendix 4: Examples

Examples of protocol deviations (including examples from MHRA Guidance document version 2.0)

Event	Event type	Is it considered a Serious Breach?	Notified by	Notified to
Dosing error. Ethics Committee & MHRA informed. Subjects withdrawn. The sponsor stated that there were no serious consequences to subjects or data.	Violation	No, as there was no significant impact on the integrity of trial subjects or on scientific validity of the trial.	Investigator	Sponsor
Patient Information Leaflet and Informed Consent updated. At one trial site this was not relayed to the patients until approximately 2-3 months after approval. *More information on the potential consequences of the delay should have been provided.*	Violation (i) OR Serious Breach (ii)	(i) If this was not a systematic or persistent problem, and if no harm to trial subjects resulted from the delay, then no. (ii) However, if there was a significant impact on the integrity of trial subjects (e.g. there was key safety information not relayed to subjects in a timely manner etc.) this would constitute a Serious Breach.	Investigator	Sponsor
Visit date deviation. *A common deviation in clinical trials.*	Deviation	No – this is a minor, technical protocol deviation, which does not meet the criteria for notification.	Investigator	PI / CI
Investigator failed to report a single SAE as defined in the protocol (re-training provided).	Violation (i) OR Serious Breach (ii)	(i) No, if it did not result in this or other trial subjects being put at risk, and if it was not a systematic or persistent problem. (ii) In some circumstances, failure to report a SUSAR could have a significant impact on trial subjects. (iii) Sufficient information and context should be provided for the impact to be assessed adequately.	Investigator	Sponsor
Investigator site failed to reduce or stop trial medication, in response to certain laboratory parameters, as required by the protocol. This occurred with several patients over a one year period, despite identification by the monitor of the first two occasions. Patients were put at increased risk of thrombosis.	Serious Breach	Yes	Identified during an Inspection	MHRA
Became aware of fraud at an investigator site in the UK, which did not affect the overall scientific value of the Sponsor's trial or the integrity of trial subjects in the UK. However, the Sponsor is aware that the investigator site was also involved in trials being sponsored by other organisations.	Potential Serious Breach	Although, in this situation, not a legal requirement under 29A, MHRA encourages voluntary reporting of all fraud cases in the UK, because MHRA will need to establish the impact on the other trials in case subject integrity or the scientific value of those trials was compromised.	Sponsor	MHRA

Event	Event type	Is it considered a Serious Breach?	Notified by	Notified to
IMP temperature excursions reported.	No deviation (i) or Serious Breach (ii)	(i) No, if the excursions had been managed appropriately (i.e. IMP moved to alternative location/quarantined as necessary and it was identified by qualified personnel that there was no impact on stability of the product and therefore no impact on patient safety/data integrity). (ii) Yes, if this went unmanaged and subjects were dosed with IMP found to have become unstable and this resulted in harm or potential harm to subjects.	Sponsor ((ii) only)	MHRA
On two separate occasions sponsors identified issues with the same organisation. First with consenting issues and the second with potential fraud in recruitment and consenting. However, there was not unequivocal evidence of fraud at the time of reporting. One of the studies involved children.	Potential Serious Breach	Yes, this subsequently led to enforcement action against the organisation in question.	Sponsor	MHRA
GCP Inspectorate notified that a substantial amendment had been submitted regarding changes to dosing on a first in human study, as a result of an SAE after dosing the initial subject. The sponsor had temporarily halted the trial and only after further investigation had assigned the SAE as unrelated. The sponsor had **not** notified the CTU of the "urgent safety measure" implemented or reported the SAE as a potential SUSAR.	Serious Breach	Yes	Sponsor	MHRA
A cohort had invalid blood samples as they were processed incorrectly. As a result one of the secondary endpoints could not be met. Therefore, a substantial amendment was required to recruit more subjects to meet the endpoint. Patients were dosed unnecessarily as a result of this error.	Serious Breach	Yes	Sponsor	MHRA
A pharmacy dispensing error resulted in a non-serious adverse event. The incident was investigated and the notification from the Sponsor confirmed that training had occurred and more robust procedures were being implemented by the site.	Violation (i) or (ii) Serious Breach	(i) No, information provided by the Sponsor identified this as a single episode and the Sponsor supplied detailed corrective and preventative action. (ii) Yes, if it was persistent and systematic, occurring after the CAPA had been put in place by the Sponsor.	Investigator	Sponsor

Event	Event type	Is it considered a Serious Breach?	Notified by	Notified to
A **potential** serious breach was identified, but not reported (i.e. documentation in the Sponsor's TMF identified that there may have been fraud at an investigator site, re-use of previous time point data in later time points). The Sponsor had investigated and the issue was subsequently found to be a genuine error not fraud.	Potential Serious Breach	No, on this occasion. *However, had this been identified as fraud impacting on the integrity of the data, then this serious breach would not have been notified within the regulatory timeframe (i.e. 7 day window).*	Investigator	Sponsor
Destruction of investigator site files early (i.e. one study had only been completed a year earlier and one study was still ongoing.)	Serious Breach	Yes	Sponsor	MHRA
Concerns raised during monitoring visits about changes to source data for a number of patients in a trial, which subsequently made patients eligible with no explanation. An audit was carried out by the Sponsor and other changes to source data were noted without explanation, potentially impacting on data integrity. Follow-up reports sent to MHRA confirmed Sponsor concerns over procedures for approvals, consenting issues and data changes made to source without adequate written explanation.	Serious Breach	Yes *Note: not all information provided in original notification and Sponsor provided follow-up updates.*	Sponsor	MHRA
A study patient attended A&E, who attempted to contact pharmacy (using the phone number on the patient's emergency card) in order to break the unblinding code. Unable to break code in a timely manner, and the patient decided to withdraw from the study feeling unhappy that the pharmacy was not available for emergency situations.	Serious Breach	Yes, as this could have resulted in significant potential to harm to the subject if unblinding would have affected the course of treatment.	Sponsor	MHRA