Reference Number: *UHB 406* **Version Number:** 3	**Date of Next Review: 18/04/2027** **Previous Trust/LHB Reference Number: N/A**

REPORTING REQUIREMENTS FOR CARDIFF AND VALE HEALTH BOARD SPONSORED RESEARCH : STANDARD OPERATIONAL PROCEDURE

INTRODUCTION AND AIM

The purpose of this procedure is to outline the periodic progress and safety reporting requirements for research studies sponsored by Cardiff and Vale University Health Board (CAVUHB). It also details the activities and reporting requirements for closing, suspending and terminating research.

After a research study has received all necessary approvals to proceed, various bodies and organisations will be interested in its progress. This is particularly the case for Clinical Trials of Investigational Medicinal Products (CTIMPS). Annual reports must be reported to the Research Ethics Committee for all studies, and for CTIMPS an annual Development Safety Update Report must be submitted to the Medicines and Healthcare Products Regulatory Agency (MHRA). The Sponsor is accountable for ensuring periodic reports are submitted within appropriate timelines. Where CAVUHB is the Sponsor, responsibility for compiling and submitting these reports has been delegated to the Chief Investigator and the CTU.

The Sponsor is accountable for notifying the REC, MHRA, and other relevant bodies of the end of a trial. There are also a number of circumstances when it may be necessary to suspend or terminate research trials. This procedure also explains the steps to be taken in such situations. Regulation 31 of the Medicines for Human Use (Clinical Trials) Regulations 2004 affords the MHRA power to suspend or terminate CTIMPs if there are objective grounds. This procedure does not cover situations where trials are suspended or terminated by the MHRA. The time frame for publishing the summary of results is within one year of the end of trial. End of trial summary reports need to be submitted to REC. There is no requirement to submit summary reports to the MHRA, just a confirmatory email that the information has been uploaded to the public register is required. For studies conducted in the UK that are already registered in the European Union Drug Regulating Authorities Clinical Trials database (EudraCT) results should be submitted. Steps to follow are described in the EMA webpage 'Tutorials on posting results' Where C&V UHB is the Sponsor, responsibility for submitting these notifications is delegated to the Chief Investigator and/or the CTU.

OBJECTIVES

- To outline the periodic reporting requirements for research studies
- To outline the end of trial reporting requirements and activities for research studies
- To describe the procedure for suspending and terminating research studies
- To ensure compliance with regulatory requirements

SCOPE

This procedure applies to Chief Investigators and research staff in all locations including those with honorary contracts. This procedure is applicable for all studies that are sponsored by Cardiff and Vale University Health Board.

Equality Health Impact Assessment	An equality impact assessment has been carried out on the Research Governance Policy under which this Procedure falls. No adverse impact has been identified.
Documents to read alongside this Procedure	Research Governance Policy (UHB 099) Managing breaches of GCP or the study protocol (UHB 235) Archiving of Clinical Trials Data and Research Study Data SOP *(UHB 121)*
Approved by	Joint Research Governance Group (JRGG)
Accountable Executive or Clinical Board Director	Medical Director
Author(s)	Research Governance Team

Disclaimer

If the review date of this document has passed please ensure that the version you are using is the most up to date either by contacting the document author or the Governance Directorate.

SUMMARY OF REVIEWS/AMENDMENTS

Version Number	Date of Review Approved	Date Published	Summary of Amendments
1	24/04/18	21/06/18	New document
2	28/04/21	24/06/21	Updates to reflect new guidance information following end of transition period including submission procedures for DSURs. Clarification that Progress Reports for REC are only required for studies that are more than two years in duration and for Research Tissue Bank and Research Databases. There is no requirement for a Progress Report for Proportionate Review studies. Information added regarding the use of shortened DSURs Reporting requirements for CAG

			Update on end of study reporting to the MHRA
3	18/04/2024	18/07/2024	Minor changes – to reflect national updates

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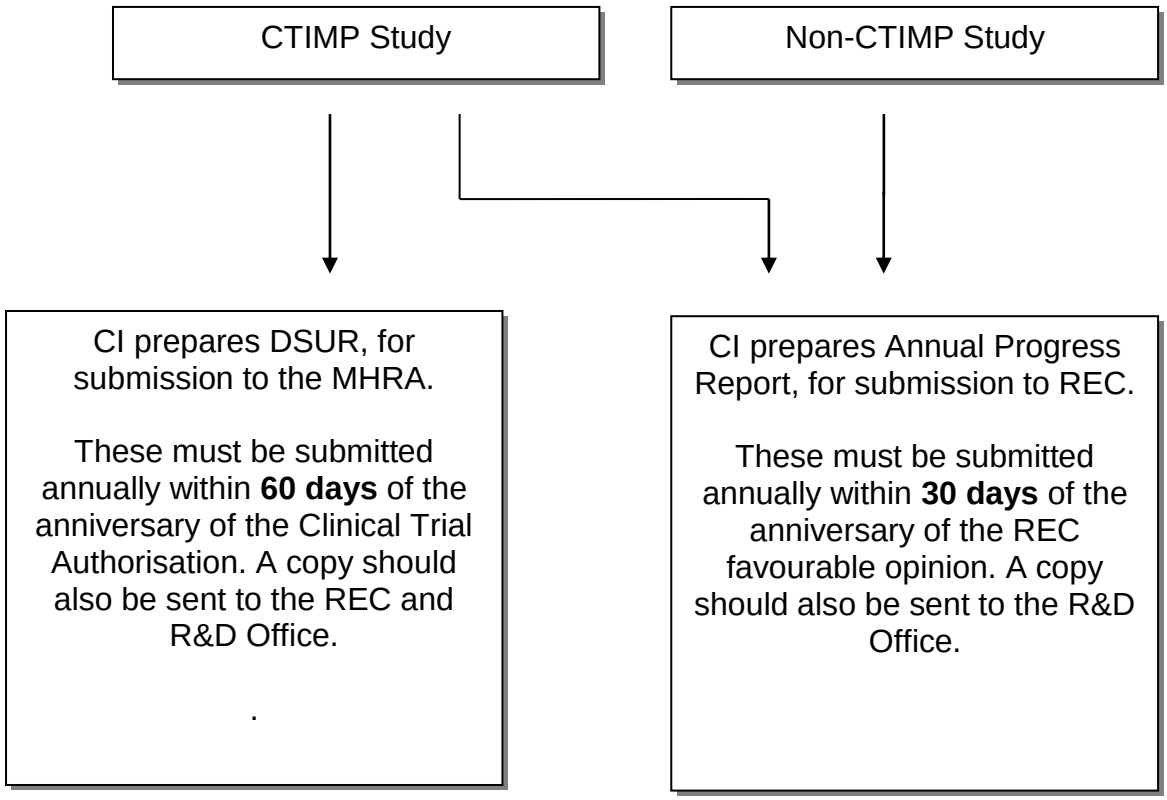
1. SOP FLOWCHART

Periodic reporting requirements



2. DEFINITIONS/ABBREVIATIONS

CAVUHB	Cardiff and Vale University Health Board
CAG	Confidentiality Advisory Group
CI	Chief Investigator
CTIMP	Clinical trials of Investigational Medicinal Products
CTU	Clinical Trials Unit
DSUR	Development Safety Update Report
EudraCT	European Union Drug Regulating Authorities Clinical Trials. This is the European Clinical Trials Database of all clinical trials commencing in the European Union after 1 May 2004
HCRW	Health and Care Research Wales
HRA	Health Research Authority
JRO	Cardiff Joint Research Office
R&D	Research and Development
REC	Research Ethics Committee
MHRA	Medicines and Healthcare Products Regulatory Agency
SOP	Standard Operating Procedure
Sponsor	The individual, company, institution or organisation, which takes on ultimate responsibility for the initiation, management (or arranging the initiation and management) of and/or financing (or arranging the financing) for that research
Suspension	Suspension is a temporary cessation of some or all of the research activities at a particular site or across all research sites. A decision not to recommence a suspended trial amounts to termination of the trial.
Termination	Termination is a permanent cessation of all research activities across all research sites.

3. PROCEDURES

3.1 PERIODIC REPORTING PROCEDURE

Responsibilities when C&V UHB is Sponsor

The CI and CTU where applicable is delegated the responsibility for compiling and submitting periodic reports to both the REC and the MHRA.
In the event that the CI fails to provide a copy of the reports submitted within the regulatory timeframes, this will constitute a breach of Good Clinical Practice and the procedure will be followed accordingly., Detailed guidance regarding how to prepare and submit reports is outlined in the remainder of this SOP.

Annual Progress Reporting to REC - (Studies requiring REC approval)

REC has a duty to monitor research that has been granted a favourable ethical opinion by it. In order to do so, periodic progress reports are required to be submitted.

Progress reports must be submitted to the REC which granted the favourable opinion. The due date for reports is **12 months** after the date on which the favourable opinion was given and each year thereafter until the end of the trial.

Where a REC regards a trial as particularly high-risk, they may require quarterly or even monthly reports to be submitted. This will be detailed in the approval letter and must be adhered to.

Progress Reports are only required for studies that are more than two years in duration and for Research Tissue Bank and Research Databases. There is no requirement for a Progress Report for Proportionate Review studies and where the study is two years or less in duration.

The HRA has produced templates which must be used. The latest versions of the forms and completion/submission instructions areavailable via the HRA website: https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/progress-reports/ There are separate forms for submitting progress reports, depending on the type of research.

Forms should be completed in typescript and signed by the CI. An electronic copy should be emailed to the REC within **30 days** of the due date, and a copy emailed to the R&D Office, which forms part of the JRO.

Once the first progress report has been received by the REC, the chair has discretion to waive the requirement for further reports upon request. This must be agreed in writing by REC and forwarded to the R&D Office. This may be appropriate where a study has completed recruitment and intervention but has a long period of follow-up with minimal participant involvement.

For multicentre trials the CI must provide a copy of the annual progress report to all Principal Investigators at all sites

HRA/HCRW Approval

Research in receipt of HCRW Approval which has also been reviewed by a REC should make regular progress reports to the HCRW in line with the arrangements for RECs.

For research projects with HCRW Approval which were not required to be reviewed by a REC progress reports are not required.

Confidentiality Advisory Group (CAG) annual review

All approvals are reviewed annually to assess the need for continuing approval and to ensure that progress towards, or achievement of, any conditions of approval is in place. This review is carried out following submission of an annual review report.

At this stage consideration should be given to whether if it would be possible to reduce the amount of confidential patient information being processed.

To allow sufficient time for processing, an annual review report should be submitted to the Confidentiality Advice Team by email **four weeks** before the approval expires (i.e. no later than 11 months following the final approval date) using the report template. This will be assessed by the Confidentiality Advice Team in the first instance. Please refer to HRA website for further guidance and templates***.*** The CAG remit only extends to England and Wales. If studies process confidential patient information generated within Scotland, Investigators should follow guidance from the Public Benefit and Privacy Panel https://www.informationgovernance.scot.nhs.uk/
For Northern Ireland, contact r.j.mcclelland@qub.ac.uk

Development Safety Update Report (DSURs) -CTIMPs only

For CTIMPS, an annual DSUR should be submitted to the MHRA and REC which granted approval for the trial to proceed. The DSUR should takeinto account all new available safety information received during the reporting period. The main objective of a DSUR is to present a comprehensive annual review and evaluation of pertinent safety information collected during the reporting period related to a drug under investigation, whether or not it is marketed.
The DSUR must be compiled annually for the duration of the clinical trial until the regulator has been notified of the end of the trial.

The DSUR due date is the anniversary of the first international regulatory approval regardless of the approval status in the UK. The DSUR must be submitted **within 60 days** of the due date.
The data lock point of the DSUR should be the last day of the one-year reporting period.
One DSUR should be submitted for the IMP rather than submitting individual reports for each trial including that IMP. This should occur on the anniversary of the first regulatory approval anywhere in the world and this date is classed as single data lock point. If there is a valid reason for submitting separate reports this should be clearly explained on the DSUR. DSURs are IMP specific therefore for trials involving multi-drug therapy (i.e. combinations of

drugs that are not fixed) R&D, in conjunction with the CI will need to decide to either prepare a DSUR for the multi-drug therapy, or DSURs for one or more of the individual components; in this case information on the multi-drug therapy trials can be included in the DSURs of one or all of the components.

The DSUR should include:

- a cover letter listing all EudraCT numbers of trials covered by the DSUR, including any trials approved via the VHP process including an email address for correspondence.
- an analysis of the subjects' safety in the concerned clinical trial(s) with an appraisal of its ongoing risk/benefit
- a line listing of all suspected serious adverse reactions (including all SUSARs) that occurred in the trial(s), including all SUSARs from third countries
- an aggregate summary tabulation of SUSARs that occurred in the concerned trial(s)
- Region-specific information on how to increase transparency

Details of what to include in a DSUR can be found in the ICH E2F guidance

In order to increase the transparency of the data included in DSURs prepared by manufacturers and/or marketing authorisation holders of an investigational drug the MHRA and Health Canada are asking that the region-specific information section of the DSUR is used to explain how safety data were reviewed during the reporting period.

Please see Guidance document for more details.

The DSUR must be submitted to both the MHRA and REC and a copy must be sent to the R&D office.

DSUR can be submitted to MHRA using MHRA Submissions via the Human Medicines Tile. Please select 'Development Safety Update Report' as the Regulatory Activity and 'Original Submission' from the Regulatory sub activity dropdown list. Acknowledgements of receipt for DSUR submissions are generated by MHRA Submissions where a confirmation of submission is emailed to the reporter.

If at least one of the trials covered by the DSUR has gone through the Combined Review process, then the report should be submitted via the Integrated Research Application System (IRAS). More information can be found on the Health Research Authority (HRA) website

Copies of all UK related safety information supplied to MHRA must also be emailed to the main REC, accompanied by a CTIMPs Safety Report form. Submissions to REC should be made by email

Shortened DSUR available for Notification Scheme approved trials

This is suitable for:

- individual trials authorised under the Notification Scheme which are not part of a multi-study development programme.
- phase 4 national (UK only) trials of licensed products that commanded a low fee from the MHRA and where all participants have completed treatment and are only in follow-up.

As an alternative to producing a full DSUR for these trials you may use the Health Research Authority Annual Progress Report.

Researchers must indicate in the cover letter that this is an Annual Progress Report (APR) in lieu of a full DSUR and include the EudraCT number and CTA reference number. You should include a list of all serious adverse reactions in section 6 of the APR.

.At the end of the DSUR reporting period the Sponsor may assess the new safety information that has been generated and submit any proposed safety changes to the Investigator's Brochure as a substantial amendment. This amendment must be supported by the DSUR and approved before the reference safety information (RSI) is changed.

3.2 PROCEDURE FOR CLOSING, SUSPENDING AND TERMINATING RESEARCH

The definition of the end of a trial should be described in the protocol (and any subsequent amendments). In the majority of trials, completion will be the date of the last patient's last visit (LPLV) or the completion of any follow-up monitoring and data collection described in the protocol.
For studies involving human tissue, the analysis of the samples should be undertaken as part of the data collection **before** the end of study is declared.

Any retained tissue for possible future evaluation after the end of study has been declared should be with the appropriate licence, and should be undertaken as described in the protocol and within the terms of consent from

the donors. Otherwise a new proposal for REC review would need to be submitted.

Any change to the end of study definition after approval has been given for the research should be notified as an amendment to the appropriate review bodies.

There are a number of actions that need to be completed upon trial completion. For CAVUHB sponsored trials, responsibility for undertaking these actions is delegated to the CI.

(a) REC and MHRA must be notified of the trial ending within **90 days** of it ending. Notification should be submitted using the 'Declaration of the end of a Clinical Trial' forms, and copies of these forms sent to R&D:

For trials submitted through combined review, you should complete and submit the end of trial form in the new part of Integrated Research Application System (IRAS). This automatically submits the notification to the REC and MHRA. For CTIMP and IMP/Device trials that were not submitted through combined review, you will need to complete the form available on the MHRA website and email this to the MHRA and REC.

For all other research, the end of study declaration form should be completed and emailed to the REC.

The REC form is available via: www.hra.nhs.uk/approvals-amendments/managing-your-approval/ending-your-project/

This can be submitted to REC via email A 'Declaration of the end of a Clinical Trial' form should be sent to the MHRA within 90 days of the global end of the trial and within 15 days of the global premature end of the trial. The submission must include an end of trial form (Annex 3) and a covering letter. You must submit your end of trial declarations using MHRA Submissions via the Human Medicines Tile.
. Where a project has HRA/HCRW Approval and has been reviewed by a REC you need only inform the REC when your study has ended. Where a project has HRA/HCRW Approval and was not reviewed by an NHS REC, you will need to tell HCRW when the project has ended. You should send this notification by email to Research-permissions@wales.nhs.uk including your IRAS ID and your contact information (phone and email).

Notifying the MHRA (medical devices)
Manufacturers or sponsors are required to email the MHRA at ctdhelpline@mhra.gov.uk when a clinical investigation of a medical device comes to an end

Notifying the Confidentiality Advisory Group (CAG)

For studies which have an application with the Confidentiality Advisory Group (CAG), when the study is complete, the CI or CTU should email the confidentiality advice team as soon as possible. The confidentiality advice team will review the information provided, update the approval register and email to confirm they have received the notice.

The application will remain on the approval register on the website for at least 12 months following notification of closure.

(b) A final research report must be submitted to the following bodies within 12 months of the date of the end of the trial: (within 6 months for Paediatric studies). Where applicable summary results should be published within this timeframe in the public register (or registers) where the clinical trial was registered.

REC: For studies submitted via combined review, the CI and CTU where applicable should complete and submit the final report form in the new part of Integrated Research Application System (IRAS).
All other research reviewed by a REC, should use the webform on the HRA website. There is no need to submit a CSR to the REC for any CTIMP. The information relevant for the REC is captured in the final report form.

MHRA Clinical Trials: It is not a requirement to submit the clinical trial summary report to the MHRA. Instead a short confirmatory email to CT.Submission@mhra.gov.uk should be sent. The subject line of the email notification must state 'End of trial: result-related information: EudraCT XXXX-XXXXXX-XX' once the result-related information has been uploaded to the public register. If the clinical trial is not on a public register or the results will not be published in the register, summary results should be submitted via MHRA Submissions. Sponsors of trials conducted in UK that are already registered in the EU Register are able to submit results to EudraCT. Steps to follow are described in the EMA webpage
A copy should also be sent to R&D. The R&D office will send a reminder to the CI.
MHRA Devices: CIs should email a copy of the final report the MHRA at ctdhelpline@mhra.gov.uk

(c) The CI should notify other stakeholders of trial completion, including R&D departments of other NHS Trusts where the trial took place and any other bodies, as required under separate agreements (such as funding bodies, universities or specialist committees).

(d) At the end of trial, the CI must ensure close-out monitoring activities are conducted. Support departments (e.g. pharmacy) should also be notified in order that they can prepare for close-out. For CTIMPs and Clinical Investigations of Medical Devices the R&D office (or CTU staff if trial monitoring has been delegated) will undertake close-out activities, including:

- Checking that the Trial Master File (TMF) and/or Site file is organised, and ensuring all necessary documents are present.
- Ensuring that archiving procedures have been initiated by the CI in line with the Archiving of Clinical Trials Data and Research Study Data SOP *(UHB 121)*
- Ensuring pharmacy close-out has been undertaken in accordance with Pharmacy procedures, if applicable.

For non CTIMPs it is the CIs responsibility to ensure the necessary close out activities are conducted.

e) The CI should also ensure arrangements are made for the following:

i. Data-lock of the database prior to analysis.

ii. Resolving any outstanding financial obligations including ensuring any outstanding invoices payable or to be raised.

iii. Documents should be archived in accordance with the Archiving of Clinical Trials Data and Research Study Data SOP *(UHB 121)*

Suspending and/or terminating Research Studies

- Suspended or terminated by CAVUHB:
  Where CAVUHB is the Sponsor, all the rights, powers and duties of a Sponsor will be exercised in relation to the suspension and termination of any research study where necessary. Decisions to suspend or terminate a study may only be taken by the JRO Director (or delegated authority in their absence).

- Suspended or terminated by the CI/PI: For CTIMPs while the Medicines for Human Use (Clinical Trials) Regulations 2004 do not expressly provide a CI/PI with the power to suspend or terminate a clinical trial, ICH-GCP paragraph 4.12 sets out the process for doing so. If a trial is prematurely terminated or suspended for any reason by the CI/PI, then the trial subjects must be promptly notified and appropriate therapy and follow-up must be arranged for the subjects.

- If the study is suspended or terminated without the prior agreement of the Sponsor then the CI/PI must inform R&D office immediately with a detailed written explanation of the reasons for termination or suspension. The CI/PI would not be expected to terminate or suspend a study without prior discussion with R&D unless in an emergency, where there are immediate safety concerns.

Suspending research - The MHRA (for CTIMPs) and REC must be notified immediately or at least within 15 days from when the study is temporarily halted. R&D will liaise with the CI regarding submission of notification. The notification must be made in the form of a substantial amendment using the 'amendment tool and explain what has been suspended (such as patient recruitment or interruption in treatment) and the reasons for the suspension. For further information on substantial amendments see SOP on Managing amendments for UHB Sponsored Research (UHB 302). Substantial amendments relating to temporary suspension must be submitted using MHRA Submissions via the Human Medicines Tile. To restart a trial that has been temporarily suspended, the request must be made as a substantial amendment using the amendment tool, providing evidence that it is safe to restart the trial.

Restarting research - If the JRO Director is satisfied that any concerns or issues have been appropriately addressed then permission may be given to continue with suspended studies. Research must not re-start without this permission. A substantial amendment will need to be sent to the MHRA (for CTIMPs) and REC to recommence activity. R&D will liaise with the CI regarding submission of these.

Terminating Research - If the R&D office decides not to recommence a suspended study, the MHRA (for CTIMPs) and REC should be notified by the CI within 15 days of the decision. In particular, the following information must be provided:

- Justification of the premature ending of the study and the number of patients still receiving treatment at the time of termination
- Proposed management of patients receiving treatment at the time of termination
- Consequences for the evaluation of results.

4. DISSEMINATION AND TRAINING

SOPs are reviewed by the JRO Quality Management Group (QMG) and presented to the JRGG for information. Once approved, they are published on the CAVUHB Intranet, AMAT and sent to the R&D Leads and JRGG members to disseminate appropriately. The Clinical Board R&D Leads should facilitate implementation by ensuring that all relevant research active personnel within their Boards are aware of the Procedure and the implications for their practice. Education and support should be available from the R&D Office for researchers who are involved in conducting clinical research studies.

5. RELATED SOPS AND DOCUMENTS

National Research Ethics Service (NRES)
Annual Progress Reports
https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/progress-reports

Medicines & Healthcare products Regulatory Agency (MHRA)
Safety Reporting: SUSARs & ASRs
www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Safetyreporting-SUSARSandASRs/index.htm

Health Research Authority Notifying the end of study https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/ending-your-project/

Medicines and Healthcare products Regulatory Agency Clinical trials for medicines: manage your authorisation, report safety issues https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues

UK Government Medicines for Human Use (Clinical Trials) Regulations 2004 http://www.legislation.gov.uk/uksi/2004/1031/pdfs/uksi_20041031_en.pdf