EORTC
The future of cancer therapy

Avenue E. Mounier 83/11
1200 Brussels
Belgium
Tel: +32 2 774 1611
Email: eortc@eortc.be
www.eortc.org

Study Reporting

ST-006-SOP
Version 2.0
ALWAYS REFER TO THE INTRANET TO CHECK THE VALIDITY OF THIS DOCUMENT

Author *Senior Biostatistician* Catherine Fortpied	Signature: C. Fortpied	Date: 21 April 2016.
Approved by: *Head Statistics Department* Laurence Collette	Signature:	Date: 21 April 2016
Authorized by: *Director General* Denis Lacombe	Signature:	Date: 25 APR 2016

1 PURPOSE

To describe how data and results from EORTC studies are reported and released outside of the EORTC Headquarters (HQ), including to EORTC bodies such as EORTC Disease/Treatment Oriented Groups (Groups) or EORTC IDMC; pharmaceutical partners; academic collaborative groups; regulatory authorities.

2 SCOPE

This SOP applies to all study reports produced at the EORTC HQ.

3 POLICY

EORTC studies are conducted as a collaborative effort between the legal sponsor, the Study Coordinator(s) the Principal Investigators, and if applicable, external funders, subcontractors, partner groups; as well as EORTC committees such as EORTC IDMC and the EORTC HQ team allocated to the project.

When data are managed at the EORTC HQ, EORTC's policy is to prepare reports based on accumulated data that are then distributed to the various partners, either as a basis for dissemination of results as per POL009 or for monitoring of the study progress.

4 DEFINITIONS

- **Statistical Analysis Reports**: report on statistical analyses intended to serve as a basis for IDMC reviews or for publication/dissemination.
- **Trial status report (TSR):** report issued during the study conduct to inform principal investigators and other partners of study progress and protocol compliance, and to monitor treatment safety. The objective is to address and solve any arising problems that may compromise the conduct of the study and/or the statistical analysis and/or the interpretation of the study's results.
- **Interim analysis report (IAR):** report on an interim statistical analysis issued before final data maturity. IAR include but are not limited to: safety analysis reports, feasibility reports, analysis reports of intermediate steps of phase II studies. Not all IAR are intended for IDMC review; those that are submitted to the IDMC are termed IDMCR, to enable the distinction between the two.
- **IDMC analysis report (IDMCR):** confidential report on an interim statistical analysis issued before data maturity for review by the independent data monitoring committee (IDMC).
- **Final analysis report (FAR):** report on the statistical analysis that includes the principal analysis of the primary end-point defined in the protocol; this report serves as a basis for the principal publications of study results.
- **Independent data monitoring committee (IDMC):** an independent committee of clinicians and statisticians whose task is to review the status of a clinical trial and make recommendations to the clinical research group concerning the trial’s continuation, modification and/or publication.
- **Development safety update report (DSUR):** A comprehensive, thoughtful safety report which needs to be submitted once a year throughout the clinical trial to the Competent Authority and the Ethics Committee of the concerned Member States, taking into account all new available safety information received during the reporting period. The aim of the DSUR is to describe concisely all new safety information relevant for one or several clinical trial(s) and to assess the safety conditions of subjects

included in the concerned trial(s). The DSUR report as per ICH E2F is considered to be a common standard for periodic reporting on drugs under development (including marketed drugs that are under further study) among the ICH regions.

- **Result-related information to EudraCT:** information required by EMA should be provided to Health Authorities.
- **Administrative Report:** interim report issued during the conduct or follow-up of the study for the information of Health Authorities or persons involved in the study. These reports do not disclose efficacy end-point information or premature conclusions on study results.
- **Publication:** any public release or dissemination of study results (abstracts, oral presentations, posters, full length article, chapters in books, press release) or disclosure of any confidential information, including but not limited to intellectual property.

5 PROCEDURE

5.1 Trial Status Reports (TSR)

Twice a year the Data Manager (DM) prepares a TSR in collaboration with the study team, which is presented at the bi-annual EORTC Group meeting (if relevant, the TSR is prepared and distributed even if the Group does not meet twice a year). TSRs can be prepared more frequently if the contract with the pharmaceutical partner specifies so.

The DM chooses an appropriate cut-off date in agreement with the study team which should be preferably no more than 4 weeks prior to the Group meeting. All information (including new data and answers to queries) received before the cut-off date are as much as possible incorporated in the database and reviewed by the DM. All data included in the database and reviewed by the DM is used for the report, even if they are not fully validated; data entered in the database but not reviewed by the DM are not used. There is no formal database lock (as defined in DM-005-SOP) for this purpose.

The format and contents of the report follow the instruction ST-006-WIN-04. The DM generates tables, listings and graphs to be integrated in the TSR from the data available in the Clinical Data Management System. The Statistician and Clinical Research Physician (CRP) provide assistance if needed, and review the draft TSR.

Prior to the preparation of the TSR, the CRP determines which Serious Adverse Events information needs to be provided by Pharmacovigilance Unit (PVU) (in case the EORTC PVU holds the study safety database). The Pharmacovigilance Manager (PVM) generates the requested SAE information from the safety database. The cut-off date is specified in the report should it differ from the general cut-off date of the report.

The Statistician, the CRP, the Project Manager (PM) and the Study Coordinator review the TSR and provide comments and/or additional information to be included in the report (tables or graphs that cannot be generated with VISTA such as quality of life compliance tables, patients narratives, special issues that they would like to address). For these additions, the cut-off date is specified in the report if it differs from the general cut-off date of the report.

The DM provides the final report(s) to Webmaster in the Communications Office for release on the EORTC web site (restricted area), and informs the study team, the EORTC Study Coordinator and principal investigators. Other members of the Group may also have access to this report.

The PM distributes the report(s) to external partners as per contract agreement.

The DM prepares a powerpoint presentation for the EORTC Group meetings; the Statistician, the CRP and the Study Coordinator review these slides; the powerpoint show is presented by the DM, the Study Coordinator, or another member of the EORTC HQ team attending the meeting as decided by mutual agreement.

5.2 Interim analysis reports (IAR)

IAR report on safety, feasibility, intermediate steps of phase II studies, or other interim statistical analyses issued before final data maturity, that are used as benchmarks for study continuation.

In particular, a safety analysis report is produced when planned in the study protocol or can be requested by the CRP after a medical review of the study.

Database lock is performed according to DM-005-SOP.

- The contents and format of the IARs follows the WINs related to the present SOP (ST-006-WIN-01, ST-006-WIN-02 or ST-006-WIN-03). Depending on the scope of the interim analysis, some sections may be omitted. When the IAR includes an analysis of safety data, the PVM prepares SAE cumulative tables for inclusion in the IAR according to timelines discussed during the pre-analysis meeting.
- The Statistician sends the draft IAR to the study CRP, PM and DM for their comments and additions (including case narratives….).
- The Statistician addresses all comments received from the HQ study team and includes additional results as required.
- The study report must be signed off by the CRP and the Statistician and approved by the Head of Statistics Department (or delegate) (depending on reporting lines) using ST-006-AF-02.
- The IAR is not necessarily confidential and its release outside EORTC HQ is defined on a case by case in the study protocol.

If the study is blind, the IAR is a blind report and if it needs to be unblinded, it should then be prepared , in which case the process for IDMCR described in section 5.3 below needs to be followed. The preparation of unblinded reports must be requested to and approved by the IDMC Chair (see CM-011-SOP),

5.3 IDMC analysis reports (IDMCR)

Database lock is required to produce an IDMCR (DM-005-SOP).

If the study is blind, the IDMCR may be a blind or unblinded analysis report depending on the protocol specifications and whether the IDMC requests unblinding for their review. The preparation of the unblind report and the submission to IDMC is performed by the unblinded statistician and the PharmacoVigilance Physician (PVP) acting as unblind CRP, according to CM-011-SOP.

- The contents and format of the analysis report follows the WINs related to the present SOP (ST-006-WIN-02 and ST-006-WIN-03). Depending on the scope of the interim analysis, some sections may be omitted. When the IDMCR includes an analysis of safety data, the PVM prepares SAE cumulative tables for inclusion in the IDMCR according to timelines discussed during the pre-analysis meeting.
- The (unblinded) statistician and the (unblinded) CRP/PvP prepare and send the draft IDMCR to the Head of IDMC Support Unit .

- The final version is jointly signed by the (unblinded) statistician and the (unblinded) CRP and approved by the Head of IDMC Support Unit (ST-004-AF-01).
- Once approved by the Head of IDMC Support Unit, the (unblinded) statistician sends the final version of the IDMCR to the IDMC Support Unit Officer.
- The (unblinded) statistician prepares slides and presents the IDMCR to the IDMC according to ST-004-SOP.
- The IDMCR shall not be distributed to anybody else than the IDMC, the IDMC Support Unit and the (unblinded) statistician and (unblind) CRP/PvP.

5.4 Final analysis report (FAR)

Database lock is required to produce a FAR (DM-005-SOP).

For blind studies, CM-011-SOP applies: the EORTC HQ study team is unblinded once the clinical database for the final analysis of the primary endpoint is locked and the Head of Statistics Department, or delegate approves the request for unblinding. The subsequent steps are the same for open or blind studies:

- The contents and format of the report are described in the WINs associated to the present SOP (ST-006-WIN-01, ST-006-WIN-02 and ST-006-WIN-03). The PVM prepares SAE cumulative tables for inclusion in the FAR according to timelines discussed during the pre-analysis meeting.
- The Statistician sends the draft FAR to the HQ study team for comments and additions (including case narratives….).
- After incorporation of the comments of the HQ study team, the Statistician sends the draft FAR to the Study Coordinator, to members of the Group steering committee (if specified in the Group's statutes), to collaborating group representatives (if intergroup study) and to third party (according to the contract, for fully supported studies) for review and comments.
- The Statistician, with the help of the study team, addresses all comments raised during the review and includes additional results as required.
- The study report must be signed off by the CRP and the statistician and approved by the Head of Statistics Department (or delegate) using ST-006-AF-02.
- The Statistician sends the final version of the FAR to the Study Coordinator, the CRP, the PM and the DM(s), the PVM of the study, as well as members of the Group steering committee, according to Group's statutes. The PM informs RAU on the availability of the FAR. The PM sends the final version of the FAR to external partners (other participating groups, representatives of the sponsors…) according to collaboration agreements.
- If feasible, the Study Coordinator or the Statistician presents the data at a Group meeting before the publication; the Statistician prepares the PowerPoint presentation.

5.5 Publication

Abstracts for congresses and other publications are prepared and submitted under the conditions described in the study protocol, the EORTC publication policy (POL009), related SOP (ST-007-SOP) and Disease/Treatment Oriented Groups statutes.

5.6 Posting of result-related information to EudraCT

According to Commission Guideline (2012/C 302/03) result-related information should be posted for all interventional clinical studies regulated by Directive 2001/20/EC with EudraCT number.

- The information to be provided is based on the final analysis of the study. For clinical studies with end of trial date after 21 July 2014, it is required to post all information required by EMA (summary attachement is optional) within 12 months (and within 6 months for paediatric studies) after the end of trial.
- For old studies with end of trial prior to 21 July 2014, the following rules apply:
  - For clinical studies with end of trial date between 21 July 2013 and 21 July 2014, but also all paediatric studies with final database before 21 July 2014 it is required to post all information required by EMA (summary attachment is optional) before 21/07/2015.
  - For clinical studies with end of trial date before 21 July 2013 (non-paediatric studies), it is required to post all information required by EMA and/or a summary attachment before 21 July 2016.

A 3-month delay is tolerated for all the above timelines after which the clinical study will be flagged if no information has been posted.

The information required by EMA (i.e. the "full data set" according to the terminology used in EMA guidance) and/or the summary attachment are based on the FAR, using the locked database.

The content of the information required by EMA (i.e. the "full data set" according to the terminology used in EMA guidance) is given in the technical guidance:

- http://ec.europa.eu/health/files/eudralex/vol-10/2013_01_22_tg_en.pdf

The study team posts the full data set to EudraCT by entering the information via the web interface, or by uploading an XML file using the web interface:

- https://eudract.ema.europa.eu/results-web/

In case only a summary attachment is provided, it will follow the format recommended by ICH E3 Annex 1 “Short Synopsis”, available in ST-006-AF-01. The Statistician will post the summary attachments to EudraCT by uploading one or more files (e.g. PDF) using the web interface:

- https://eudract.ema.europa.eu/results-web/

5.7 Other statistical reports

Additional statistical analyses may be needed after the publication of the primary study results (i.e. secondary end-points, long term follow-up, translational research projects, quality-of-life analyses, other research projects).

Unless the analysis is already foreseen in the protocol, permission to perform these analyses should be obtained from from the Study Coordinator and EORTC HQ (Director General and/or Methodology Director) according to CM-013-AF-01 .

Formal statistical analysis reports are always prepared by the Statistician using a procedure similar to the FAR described in section 5.4 (including a database lock).

5.8 Development safety update reports (DSUR)

Those reports are described in the SOP on Safety Reporting (CM-009-SOP) and the WIN on Safety Development Safety Update Report (CM-009-WIN-02).

The content of the DSUR is based on the ICH Topic E2F: Development Safety Update Report, issued as EMEA/CHMP/ICH/309348/2008, with the intention to be a common standard for annual clinical trial safety reporting among the ICH regions.

A single DSUR per trial is prepared instead of per drug unless otherwise agreed upon between EORTC, company and other participating groups.

5.9 Administrative reports

Administrative reports may be requested by external partners, according to the contract(s) in place. These reports are generally prepared by DMs. Their contents must be checked by the statistician and the CRP and must comply with the rules of disclosure as per POL009. Other members of the study team may need to review these reports (to be decided by the team on a case by case basis). The PM is informed in all cases.

6 FILING AND ARCHIVING

DMs keep filing of their programs, reports and associated documents in the appropriate section of the Trial Master File as described per EORTC procedure.

All statistical analysis reports are filed electronically in the appropriate statistical study folder (or in the corresponding blinded trial folder, for an interim unblind report of a blind study). Once approved, final analysis reports and other statistical reports (analysis of secondary end-points, long term follow-up, translational research projects, quality-of-life analyses, other research projects) and the corresponding approval forms are stored in the appropriate section of the Trial Master File, **except IARs and IDMCRs which are NOT ALLOWED to be stored in the Trial Master File**.

The mandatory documents of the Trial Master File are filed according to EORTC procedure.

7 RACI MATRIX

Functions / Activities	CRP	Stat	DM	PM	PVM	Head PVU	PVP	PVS	SC[2]	Head Stat	Head IDMC Support Unit
TSR, other administrative reports											
Development	C	C/R[3]	A	C	C/R[3]		C		C		
Distribution within EORTC			A								
Distribution to external partners				A							
FAR, IAR[1], other statistical reports (not for IDMC)											
Development	R	R	C	C	C/R[3]				C	A	
Distribution within EORTC		A									
Distribution to external partners				A							
Posting to EudraCT *(for FAR only)*	C	A		C	C						
IDMC report											
Development	R[4]	R[5]			C/R[3]		R[4]				A
Distribution to IDMC Support Unit		A									
DSUR											
Development	R		R		R	C	A	R			
Distribution *(internal/external)*					A			R			

R: responsible; A: accountable; C: consulted; I: informed.
Use 'A' when 'A' and 'R' are assigned to the same person.

[1]: in case of unblind reporting of a blind study is required for IAR, the process for IDMCR needs to be followed

[2]: and also, as appropriate: members of the Group steering committee (if specified in the Group's statutes), collaborating group representatives (if intergroup study), third party (according to the contract, for fully supported studies).

[3]: as appropriate, depending on the contents f the report

[4]: The CRP is replaced by the PVP in case of unblind reporting of a blind study

[5]: by the Unblind Statistician in case of unblind reporting of a blind study

8 REFERENCES

- ICH Topic E3 (1995): Structure and Content of Clinical Study Reports
- Commission Guidelines 2012/c 302/03– Guidance on posting and publication of result-related information on clinical trials in relation to the implementation of Article 57(2) of Regulation (EC) No 726/2004 and Article 41(2) of Regulation (EC) No 1901/2006.
- Technical guidance on the format of the data fields of result-related information on clinical trials submitted in accordance with article 57(2) of Regulation (EC) No 726/2004 and Article 41(2) of Regulation (EC) No 1901/2006
- ICH Topic E2F: Development Safety Update Report, issued as EMEA/CHMP/ICH/309348/2008

9 ASSOCIATED DOCUMENTS

Document title	Reference (file name or path)
Statistical Analysis Reports of Phase I Trials	ST-006-WIN-01
Analysis Report Template for Phase I Trials	ST-006-AF-03
Statistical Analysis Reports of Phase II Trials	ST-006-WIN-02
Analysis Report Template for Phase II Trials	ST-006-AF-04
Statistical Analysis Reports of Phase III Trials	ST-006-WIN-03
Analysis Report Template for Phase III Trials	ST-006-AF-05
Trial Status Report (TSR)	ST-006-WIN-04
DSUR - Development Safety Update Report	CM-009-WIN-02
DSUR template	CM-009-AF-04
Statistical Analysis Report Approval Form	ST-006-AF-02
Summary attachment for EudraCT	ST-006-AF-01
Internal Research Project Form	CM-013-AF-01

10 DOCUMENT HISTORY

Version N°	Brief description of change	Author	Effective Date
1.00	Initial release	Martine Van Glabbeke	02 Dec 2009
1.01	Redundancies with SOPs ST-004 and DM-005 and ST-007-WIN-01 are removed from the responsibilities, IARS and FARs sections.	Catherine Fortpied	15 Dec 2011
1.01	No change	Catherine Fortpied	15 Dec 2014
2.0	Clarification of scope / purpose Distinction between interim analysis reports: IAR (any interim analysis, not for IDMC) and IDMCR (for IDMC). Reference to CM-011-SOP for blind studies. Approval of FAR (and other statistical reports) by Head of Stats. Updated process for reporting to Health Authorities according to 2012 EMA guidelines. RACI matrix included.	Catherine Fortpied	25 Apr 2016