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The future of cancer therapy

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Statistical Analysis Reports of Phase II Trials

ST-006-WIN-02

Version 3

ALWAYS REFER TO THE INTRANET TO CHECK THE VALIDITY OF THIS DOCUMENT

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1 PURPOSE

To describe the contents of the non-inferential parts of statistical analysis reports (interim analysis reports or final analysis reports) for phase II clinical trials.

2 INSTRUCTION

2.1 Before starting the analysis report

Make sure that the study analysis plan is absolutely clear in respect of the following points:

- How endpoints are calculated (For time to event endpoints, this includes specification of the starting date, end date, what events are considered to be part of the endpoint, and what constitutes censoring and/or competing risks)
- Define the analysis populations
- For the primary analysis of each endpoint, the analysis population to use for the analysis and the inference method (exact versus asymptotic confidence intervals) and confidence level and, for comparative phase II studies, the statistical test to be used (for example Cox or Logrank), whether it is one sided or two sided, the significance level to be used, and whether or not it is adjusted or stratified for factors used at the time of the randomization (or for other prognostic factors).
- In case of central review of pathology or response, specify how these data will be taken into account in the analysis

If not sufficiently detailed in protocol and/or Statistical Analysis Plan (SAP), please refer to ST-005-SOP.

2.2 Standard table of contents of Phase II Analysis Reports

The analysis report is to be structured according to the form ST-006-AF-04.

	Chapter	**Interim Analysis Report***	**Stage I Report (multi-stage designs)****	**Final Analysis Report**
1	Summary of the trial	X	X	X
2	Statistical considerations and study history *(includes summary of major amendments affecting the statistics and of past interim analyses, if any)*	X	X (statistical considerations only)	X
3	Objectives of the present analysis and data selection for this report *(includes statement about cut-off data and database lock date)*	X	X	X
4	Patient availability (recruitment, follow-up, eligibility, patient populations used in the analysis)	X	X	X
5	Baseline characteristics	X		X
6	Compliance to protocol	X		X
7	Exposure to treatment	X		X
8	Safety evaluations	X		X

9	Reasons for stopping treatment	X		X
10	Treatment activity (*as appropriate, usually response to treatment, surgery and pathology …)*	X (if appropriate)	X	X
11	Decision rule		X	X
12	Summary of the results	X		X
13	CONSORT flow chart			X

Supplementary chapters or sections within chapters may be added as necessary.
* Interim analyses of phase II studies are uncommon and are generally requested for emerging safety concerns. Before preparing an interim analysis report for a phase II study, **the Statistician must consult the Clinical Research Physician (CRP) (and possibly the secretary of the IDMC) to decide on the exact contents of the report**.
** The results for intermediate stage analysis of multi-stage phase II studies, based on all available information, are summarized by the Statistician for discussion with the Medical Review Team. The decision to continue or stop the study is documented in the minutes of the Medical Review meeting. Results are not distributed outside the EORTC Headquarters

2.3 Automatic reporting

A SAS program has been developed to automatically insert SAS output at pre-specified locations in the report. These locations are identified by bookmarks. Standard bookmarks have been inserted in the template report form ST-006-AF-05 and can be modified/extended as necessary. For more information, see the EORTC SAS Macro Guide.

2.4 Patient selection

All patients are accounted for in the reports except those who never signed an informed consent or who withdrew consent and asked that none of their data be used. Such patients, if any have been identified, are reported separately in the publication and in all reports: the total number of such patients and the fact that they are excluded is mentioned at the beginning of the report, no other data is reported.
It may occur that some centers were "quality excluded" due to poor data documentation. Patients from these centers are reported in the recruitment figures but their exclusion from analysis is documented in the chapter "data selection for the present analysis".
The patient population (subset) used must be clearly stated at the beginning of each chapter.

2.4.1 General guidelines for data display

- Frequency tables are tabulated for all categorical variables, by level of the variable.
- Whenever categories prompt for a specification, a listing details for the patients fulfilling the condition the patient id, institution, (eligibility) treatment, value of the item and text field contents.
- Time delays are calculated as delays in days between the past event and the date of entry (date of entry – date of past event + 1), and expressed in a suitable time unit. They are presented using median and range, and/or categorized into appropriate intervals.
- Continuous variables such as laboratory data, for which a grading system exists and is specified in the protocol are recoded into the corresponding categories. Whenever no grading exists, lab data is categorized in function of the normal range as below the lower normal limit, within the normal range, above the upper normal limit. For

laboratory data, the nadir may be displayed. The nadir in a given cycle is the lowest laboratory value in that cycle; the overall nadir for a patient is the lowest laboratory value among all cycles.

- Other continuous variables (eg. Age, doses …) are presented using median and range (minimum, maximum). If appropriate, the data may additionally be presented in categories (eg. Age may be grouped in decades in addition to the median and range being reported).
- **Dose intensity:** The dose intensity of a drug is calculated on actual treatment duration (in appropriate units of time, weeks, cycles, or days) and actual treatment dose received (total dose received expressed in appropriate units (kg, m².).
  - Whenever the treatment is given in cycles and the last planned day of treatment is not the last day of the cycle, the total duration of the treatment must account for this by adding the appropriate number of days to complete the last cycle (e.g. if treatment is given on days 1-5 of a 21-day cycle, the total treatment duration in days is [date of last injection]-[date of first injection]+1+(21-5).
  - The dose intensity (expressed in units of dose / unit of time) (e.g. mg/m² x week) is the ratio of the total dose received to the total treatment duration, for example, for a dose in mg/m² and a duration in weeks

$$DI_{observed}\ (mg/m^2 \times week) = \frac{Total\ dose\ (mg/m^2)}{Actual\ total\ treatment\ duration\ (weeks)}$$

  - The relative dose intensity is calculated as the ratio of the dose intensity as calculated above to the dose intensity indicated in the protocol, expressed in percent (%). Note that to obtain a correct ratio, the theoretical dose intensity must be expressed in the same units of dose and time as those used for the actual dose intensity. For example

$$DI_{protocol}\ (mg/m^2 \times week) = \frac{Dose\ \ per\ cycle\ (mg/m^2)}{Theoretical\ \ duration\ of\ \ one\ cycle\ (weeks)}$$

  - The relative dose intensity is usually presented using median and ranges, accompanied or not by a distribution into categories (e.g. ≤70%, >70-90%, >90-110%, >110-120%, >120%).

2.5 Contents of the chapters

In all following sections: "by treatment arm" means "by combination stratum and treatment" in case of trials with multiple strata for which separate statistical objectives are set in the protocol.

The populations used to display the various tables and analyses should be clear from the SAP/protocol.

In general,

- Patient availability is displayed for all patients
- Baseline characteristics and endpoint tables are displayed for the population of patients used for the primary analysis of the primary endpoint (typically all eligible patients for a phase II).
- Treatment exposure, safety and reasons to stop treatment are displayed for the safety population. Patients excluded from that population (those who did not start the allocated treatment) are displayed separately (in general in a listing in appendix)
- Treatment activity tables are displayed for all populations used for the analysis of the endpoints (primary or sensitivity)

2.5.1 Summary of the trial

This chapter is a one-page summary of the study.

2.5.2 Statistical considerations and study history

This chapter consists of several sections detailing respectively:

- a summary of any recent or important amendments to the trial;
- the sample size and objectives of the trial (those stated in the current version of the protocol);
- a summary of any interim or other past analyses, with their conclusions, and any modifications to the trial design or analysis plan they triggered. For multi-stage studies, the results of the former stage (e.g. phase I results for a phase I/II trial, statement about decision taken at intermediate steps of multi-stage phase II trials) must also be reported;
- A description of trial-specific quality control procedures, if any, and an explanation of how these affected the trial and/or analysis. (Do not describe the standard EORTC Quality Assurance procedures, as those are detailed in the study protocol).

2.5.3 Objectives of the present analysis and data selection for this report

This section must clearly state the nature and the objectives of the analysis that is being reported (interim, intermediate stage, final, translational research.)
For IAR, this section must also clearly state the precise questions that the Independent Data Monitoring Committee or Data Safety Monitoring Board is asked to answer.
This section also reports any remarks of the Headquarters team regarding the study conduct and any problems related to data collection or data management.
The cut-off date and data selection (database cut-off date, exclusion of patients for quality reasons…),
The total number of patients randomized versus planned number.

2.5.4 Patient availability

2.5.4.1 Accrual

This chapter provides information regarding the recruitment rate both over time and by institution and with some information regarding the compliance to the entry rate foreseen in the protocol.
The sections in this chapter include:

- For interim analyses only, a graph of the actual and expected accrual over the time since the trial was open to patient entry.
- A table of the number of patients entered by institution, optionally split further by time period and/or treatment arm and/or step (in case it is a multi step trial). In this table, the institutions are referred to by the institution short name rather than by institution number. The tables are sorted by descending order of total accrual.
  For intergroup trials, the accrual by group is displayed in a 2-way table cross tabulating the primary group affiliation (variable “group1” as columns) versus the affiliation of the center to the EORTC (an indicator variable that takes value 1 if “EORTC” was reported in either “Group1” or “Group2”, and 0 otherwise, as rows). If the report is intended for use by EORTC only, the accrual by institution is displayed only for the centers that belong to

EORTC (ie. The patients and institutions for whom “EORTC” is reported in the variables “Group1” or “Group2”); otherwise, the table is given for all centers.

- A table of the number of patients by country (required for EUDRACT reporting).

2.5.4.2 Follow-up

This section is needed only if one of the activity endpoints is a time to event endpoint.

The follow-up data in the trial is documented by treatment arm and overall. The follow-up duration is estimated by the inverse Kaplan-Meier method (1) (i.e. doing a curve with event in curve=censored data and censored in curve=event reached in the database).

The Kaplan-Meier figure is also provided in the report (by treatment arm, in general).

If the trial uses a fixed time-anchor (example: progression-free survival at 1 year) then a table is also displayed by treatment arm, the number of patients with complete follow-up for the endpoint of interest (patients with event or with follow-up until the time of interest) and the number of patients with incomplete follow-up.

Whenever different endpoints are followed-up differently (e.g. overall survival takes all observations, but PFS would need the time until last measurements) then several durations of follow-up ("follow-up for survival", "follow-up for progression" may need to be documented).

2.5.4.3 Eligibility

This information is summarized in a table eligibility status by treatment arm or by stratum, as appropriate, supplemented by a listing of ineligible patients (with institution number, seqid, date of entry, treatment arm/stratum, and details of the reasons of ineligibility).

Patients who have been entered in the study with a waiver on some eligibility criteria (ref. CM-010-WIN-01: Management of Eligibility Compliance) must be identified clearly in the table and are considered as eligible when defining the populations used in the analysis.

2.5.4.4 Patient populations used in the analysis

This section shows in a tabular format the number of patients included (by treatment arm/stratum and in total) in all the "patient populations" defined in the SAP. In general, for phase II trials, there is always the "per protocol" population for the analysis of the activity endpoints, and the "safety population" for the reporting of the safety endpoints. In the rare cases where intent to treat (ITT) population is used instead of 'per protocol' population for the activity endpoint analysis, reasons for the use of ITT should be included.

The total number entered must always appear in this table.

2.5.5 Baseline characteristics

This chapter describes the distribution of all baseline characteristics for all patients collected on the set of baseline case report forms and is presented by treatment/stratum. It is best organized in meaningful sections, for example:

- Demographics: age, sex (if applicable)

- Of note, to facilitate EUDRACT reporting, make sure to include a table according to the following categories: Newborns (0-27 days) / Infants and toddlers (28 days – 23 months) / Children (2-11 years) / Adolescents (12-17 years) / Adults (18-64 years) / From 65 to 84 years / 85 years and over.

- Medical history: Concomitant illnesses, relevant previous illnesses, previous treatments for protocol disease, if appropriate
- Disease characteristics: TNM or other relevant classification, baseline measurements
- Baseline values of other known prognostic factors such as markers used as stratification factors.
- Baseline hematology
- Baseline biochemistry
- Baseline signs and symptoms

For multi-step trials, this section may need to be duplicated to report the status of the patients at entry in each step of the study.
It is common that the same information is available from the randomization questions and from the eligibility checklist. If stratification factors were defined for the study (for randomized trials), these are described according to the values declared at the time of randomization. Tables describe the frequency of inconsistencies between the values of stratification factors declared during the randomization versus those updated later on (from baseline forms).

2.5.6 Compliance to the protocol

2.5.6.1 Central medical review of compliance to protocol

This section presents in tabular format, supplemented by listings as appropriate, the central assessment (by study coordinator or according to Medical Review Plan) of the "deviations from protocol treatment".
The table is provided by treatment arm.

2.5.6.2 Compliance to treatment allocation

This table shows the treatment actually received versus the assigned treatment. For single-arm phase II trials, it thus contains only one column.
It shows, by treatment arm/stratum: the number of patients who started the allocated treatment, the number of patients who did not start the allocated treatment with details on the reasons for not adhering to the protocol and the number of patients for whom no information is available, if any.

Whenever the treatment is complex, the table may need a number of entries to represent the possible combinations of treatments received.

2.5.6.3 Other compliance measures

This section, when relevant, describes other aspects of the compliance to the protocol, for example, compliance to the schedule of assessment for the endpoint of PFS or response.
This includes but is not limited to: tables displaying the number of patients with missed assessment for the fixed timepoint of interest (when the endpoint is PFS rate at xx months), frequency of missed visits (&/or of inadequate

visits – if the concept of "adequate visit" is defined in Medical Review Plan), frequency of patients lost to follow-up for survival (by > x years), deviations from scheduled visit time by arm by visit…

2.5.7 Exposure to treatment

This chapter describes the adherence to the theoretical main protocol treatment and the reasons for non-adherence by treatment arm. It should be organized to be concise, yet meaningful.
In most EORTC protocols, the treatment consists in a succession of different therapeutic modalities (e.g. radiotherapy/surgery/chemotherapy/others) some of which may be standard or under investigation. **When one of these therapeutic modalities is either standard or considered as a secondary question in a protocol, it is usually less detailed than the part of the treatment that is the main trial investigation.**
For each part of the treatment, a section typically describes, for all patients who started that treatment

- The summary of the total duration of exposure to the treatment (total duration of treatment, total number of cycles)
- For all patients who did not receive the full treatment, a table and/or a listing detailing the number of such patients, when they stopped the treatment and for which reason.
- A summary table of the total dose received (relative dose intensity and/or total dose (as appropriate)
- Tables of modifications of the treatment (dose reduction, dose delays, treatment interruptions).

In general the report of the exposure to treatment is heavily driven by the information that was collected on the case report form and by medical considerations. In case of doubts on the best format to report these data, it is strongly suggested to agree on the contents and format of this chapter with the CRP before drafting the report.

2.5.8 Safety evaluations

2.5.8.1 Toxicity

In all reports, the toxicities are grouped logically according to the type of toxicity: hematological toxicity (WBC, neutrophils, platelets, hemoglobin), non hematological toxicity and by organ class (gastro-intestinal, genito-urinary, skin, neurological, and pulmonary). Of note, febrile neutropenia is an hematological adverse event.
Safety is a major objective of phase II trials, especially phase IIa (or "early" phase II) trials. Therefore, the adverse event tables are described in more details than for phase III trials.
It is strongly advised to discuss the format and contents of this section of the report with the CRP, before preparing the draft report.
The chapter on adverse event/adverse events contains the following sections:

- The worst grade of adverse event observed over a specified time period is displayed. The frequency of number of patients and % with a given grade of adverse event is presented by treatment arm/stratum. Extra columns may also report the total % with grade>0 and/or grade>2.
- For most studies, there is only one time period that consists in the complete follow-up time from start of treatment, however, some SAPs may specify different time periods (e.g. during treatment versus during follow-up after treatment, or acute versus late adverse event or even by cycle for early phase II studies).
- When relationship is collected, tables of non hematological adverse events may need to be repeated, taking only the "related" adverse events into account.

In case an adverse event was already present at entry on study ('pre-existing adverse event'), the patients for whom the grade decreased or remain stable is presented in a separate column labeled 'Pre-existing/unrelated', the patients for whom the grade increased are displayed with the patients who had no adverse event at entry, according to the observed grade, as described above.
As an option in phase II trials where it is relevant, Kaplan-Meier estimates of 'dose to adverse event' or 'time to adverse event' may be provided for specific items. The choice of these items is discussed with the CRP and the investigators.
To prepare these tables, one first reclassifies the "other adverse events" (from the non preprinted items) inside the appropriate organ class. In displaying the tables, listings are provided to describe all the adverse events that are either of particular interest to the medical reader, or for which a specification ("text field") was collected on the case report form.

2.5.8.2 Serious Adverse Events

This section contains the **standard tables provided by the Pharmacovigilance Unit.**
Further descriptions of the serious adverse events and toxic deaths events are added by the CRP.
The format of the presentation is the same as that used in the Development Safety Update Report which is, for example:

2.5.8.2.1 Study safety overview per treatment arm

Trt/stratum	SAE	SAR	SUSAR	Deaths	Toxic Deaths
Stratum 1: stage III	139	78	5	12	5
Arm 2: Doxorubicin + Ifosf.	354	312	4	5	2
Grand Total	493	390	9	17	7

2.5.8.2.2 SUSARs by SOC and PT

Case ID	Trt	SOC	PT
62012-270-2	Arm 1: Doxorubicin	Gastrointestinal disorders	Intestinal perforation
62012-6-3	Arm 1: Doxorubicin	Gastrointestinal disorders	Steatorrhea

2.5.8.2.3 Toxic deaths by SOC and PT

Case ID	Trt	SOC	PT
62012-105-1	Arm 1: Doxorubicin	Respiratory, thoracic and mediastinal disorders	Respiratory failure
62012-143-1	Arm 1: Doxorubicin	Infections and infestations	Pneumonia

2.5.8.2.4 Line Listings of Serious Adverse Reactions (SAR)

Provided in a pdf table that is placed in appendix and referred to in this chapter

2.5.8.2.5 Cumulative Summary Tabulation of Serious Adverse Events (SAE).

PRIMARY SOC	PT	Arm 1: Doxorubicin	Arm 2: Doxorubicin + Ifosf.	Grand Total
Blood and lymphatic system disorders	Anaemia	3	23	26
	Febrile bone marrow aplasia		5	5
	Febrile neutropenia	19	87	106
	Leukopenia		4	4
	Neutropenia	6	35	41
	Pancytopenia		7	7
	Thrombocytopenia		27	27
Blood and lymphatic system disorders Total		28	188	216
Cardiac disorders	Cardiac arrest	1	1	2
	Cardiac failure		1	1
	Congestive cardiomyopathy	1		1
	Tachycardia		1	1

2.5.8.2.6 Cumulative Summary Tabulations of Serious Adverse Reactions (SAR)

PRIMARY SOC	PT	Arm 1: Doxorubicin	Arm 2: Doxorubicin + Ifosf.	Grand Total
Blood and lymphatic system disorders	Anaemia	2	22	24
	Febrile bone marrow aplasia		5	5
	Febrile neutropenia	19	87	106
	Leukopenia		4	4
	Neutropenia	6	34	40
	Pancytopenia		7	7
	Thrombocytopenia		27	27
Blood and lymphatic system disorders Total		27	186	213

2.5.9 Reasons for stopping treatment

This table describes by stratum/treatment arm, the current status of all patients who started protocol treatment (on treatment versus off treatment) with the reasons for stopping the treatment. Listings must be added whenever further details were collected in text fields.

2.5.10 Treatment activity

This section is very specific to each trial and reports all activity endpoint (short or long term) that were collected in the trial, with a special emphasis on the primary endpoint of activity, if there is one.
This section is usually subdivided in several sections according to the endpoint that is considered

- In case response to treatment is an endpoint, a section tabulates the response to the treatment in the patient population(s) defined in the SAP/protocol for this endpoint, by treatment arm/stratum. Patients who cannot be evaluated are included in the denominator and reported as "non evaluable".
- For long term endpoints (progression, survival), the section displays the frequency of all events and combinations of events of interest by treatment arm/stratum in the primary analysis set. If sensitivity analyses are conducted in alternative patient populations, separate tables tabulate the events in the various analysis. For survival, the cause of death is also tabulated (with listings describing the "other" and "toxic" deaths and any other cause of death for which further details were collected in text fields). For composite endpoints such as progression-free survival, it is recommended to also tabulate the type of first event that was considered in the endpoint.
- Time to event-analyses may be needed for some long term endpoints. This is performed according to the SAP using the methods described in ST-005-SOP. Confidence intervals for the estimated event-free rate at a fixed time point are often needed. The time of interest is obtained from the protocol and/or SAP.
- A paragraph at the end of the section pertaining to the primary trial endpoint (if it is an activity endpoint).

2.5.11 Decision rules

This chapter presents the statistical analysis of the study results with reference to the planned trial design. It presents in tabular format, for the primary analysis set, the number of patients who achieved a "success" of the treatment and the number and frequency of "failures". Confidence intervals around the success rates is provided, and for comparative trials only, the P-values for the comparative test (according to ST-005-SOP).

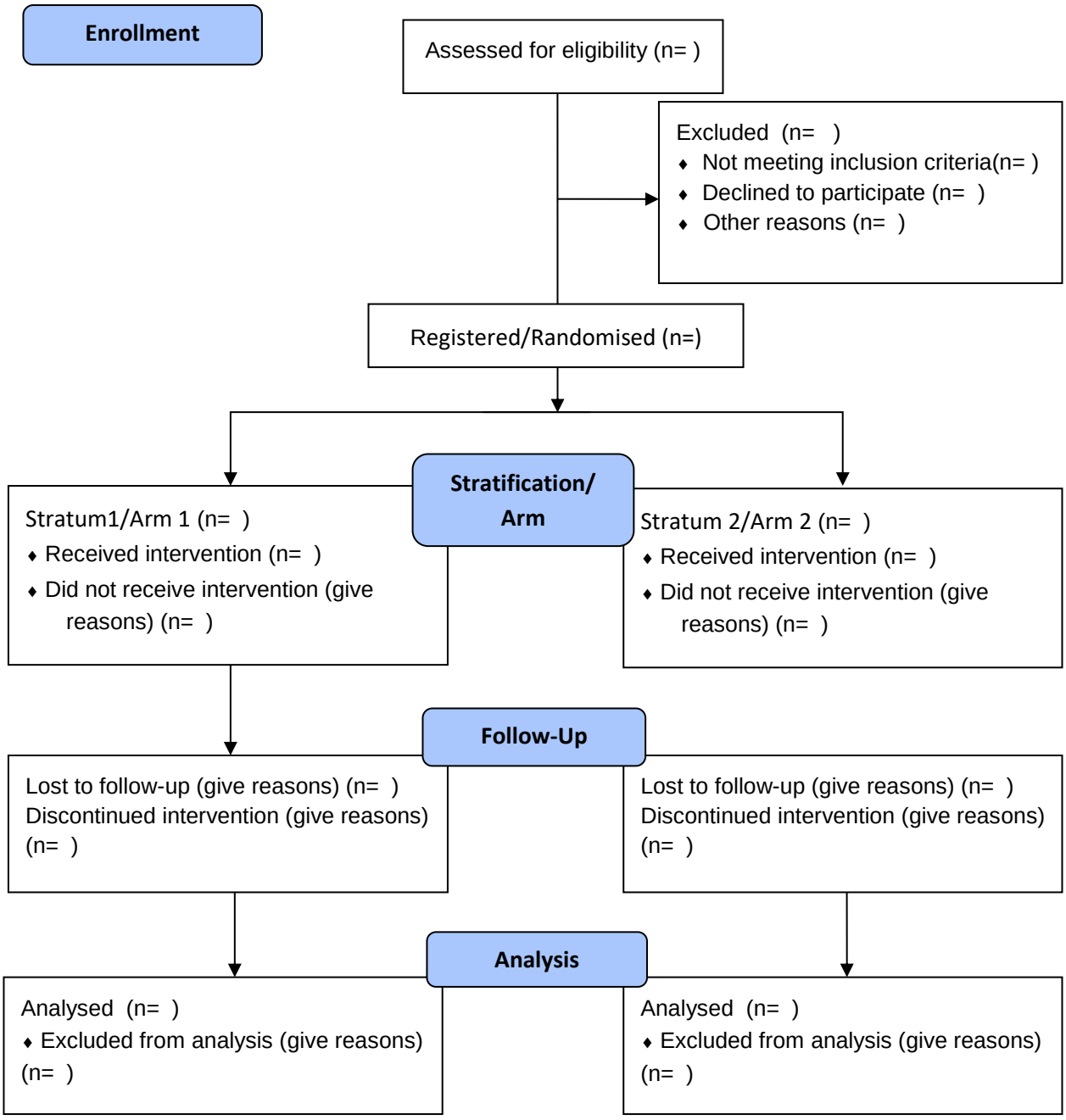
2.5.12 Summary of the results

This chapter consists of a short text summarizing the main features (recruitment, safety, activity) and statistical and medical conclusions of the trial, to help the reader to appreciate the study results. It is written by the Statistician (activity) and the CRP (safety).

2.5.13 CONSORT Flow Chart

For Final Analysis Reports, a CONSORT Flow Chart must be prepared according to the current recommendations (http://www.consort-statement.org/consort-statement/). It may alternatively be placed in appendix. The CONSORT diagram may need to be adapted to non randomized phase II trials.

The 2010 Consort Flow Chart looks as follows



2.5.13.1 EudraCT reporting

Since the July 21, 2014, it is mandatory for sponsors to post of clinical trials with a European Clinical trials Database (EudraCT) identifier in the database managed by the European Medicines Agency (EMA).

Most of the information required to complete EudraCT website is readily available from

- The protocol "summary" section
- The accrual tables
- The section in the FAR of efficacy results (and quality of life);

- For Adverse event reporting on EudraCT website, an xml file should be uploaded. This is derived from the adverse events analysis in the FAR and the Serious Adverse Events recorded by the pharmacovigilance unit (PVU). The macro program %AE_table2 creates an excel file containing all information requested by EudraCT and a converter from xlsx to xml is available from the EORTC intranet.

3 REFERENCES

(1) Korn E.L. Censoring distributions as a measure of follow-up in survival analysis. Statistics in Medicine 1986; 5: 225-260.

4 ASSOCIATED DOCUMENTS

Document title	Reference (file name or path)
CONSORT guidelines	(http://www.consort-statement.org/consort-statement/).
Analysis report template	ST-006-AF-04

5 DOCUMENT HISTORY

Version N°	Brief description of change	Author	Effective date
1.00	Initial release; supersedes WP1302 version 4.1 for phase II trials	Laurence Collette	25 Feb 2011
1.00	No change	Laurence Collette	25 Feb 2014
2	Short Study Report for Health Authorities optional for Interventional Clinical Trials that ended on or after 21 July 2014 (EudraCT) + Minor edits	Baktiar Hasan	19 Jan 2015
3	Removal references to TSRs + Instructions for automatic reporting + clarifications concerning EudraCT reporting	Saskia Litière	03 Jul 2018