Official Title: A Single Arm, Open Label Multicentre Extension Study of Bevacizumab in Patients With Solid Tumours on Study Treatment With Bevacizumab, at the End of A F. Hoffmann-La Roche and/or Genentech Sponsored Study

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MO25757

STATISTICAL ANALYSIS PLAN

Author:	[redacted]
Version:	**Final 3.0**
Date:	**18-FEB-2019**

1 Cover and signature pages

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We, the undersigned, confirm that we have read, understood and agree to the content of this document and hereby authorise its approval.

Name **Title, Organisation**	**Signature**	**Date**
[redacted]		
[redacted]		

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[redacted] [redacted] F.Hoffmann-La Roche Ltd		
[redacted], MD. [redacted] F.Hoffmann-La Roche Ltd		

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2 List of abbreviations

BC	Breast Cancer
OC	Ovarian Cancer
PC	Peritoneal Carcinoma
CRC	Colorectal Cancer
RCC	Renal Cell Carcinoma
NSCLC	Non-Squamous non-Small Cell Lung Cancer
GBM	Glioblastoma
SFU	Safety Follow-up
PFS	Progression free survival
OS	Overall survival
KM	Kaplan Meir
SOC	System Organ Class
PT	Preferred Term
Bev.	Bevacizumab
Treat.	Treatment
AE	Adverse Event
SAE	Serious Adverse Event
AESI	Adverse Event of Special Interest
MedDRA	Medical Dictionary for Regulatory Activities
NCI CTC-AE	National Cancer Institute Common Toxicity Criteria for Adverse Events
P-trial	Parent trial
E-trial	Extension trial
PTAP	Post-Trial Access Program
PDMS	Protocol Deviation Management System
RECIST	Response Evaluation Criteria in Solid Tumours
SAP	Statistical analysis plan

3 Introduction

The purpose of this document is to describe the statistical methods, data derivations and data summaries to be employed in this Single Arm, Open Label Multicentre Extension Study of Bevacizumab in Patients with Solid Tumours on Study Treatment with Bevacizumab, at the End of a F. Hoffmann-la Roche and/or Genentech Sponsored Study.

The preparation of this statistical analysis plan (SAP) has been based on International Conference on Harmonisation (ICH) E3 and E9 Guidelines and in reference to Protocol MO25757 (version 3.0, 08Nov2018).

4 Study Objectives

Primary objectives of this study are as follows:

- To provide continued Bevacizumab therapy as single agent or in combination with an anti-cancer drug to patients with cancer who were previously enrolled in a Roche/Genentech - sponsored Bevacizumab study (i.e. the Parent, P-trial) and who derived benefit from the therapy administered in the P-trial.
- To collect safety data with regard to long-term administration of Bevacizumab.

5 Study Design

5.1 STUDY DESIGN AND POPULATION

This study is a multicenter, open-label, single-arm phase IIIb/IV trial in patients with solid tumours. The primary aim is to provide continued Bevacizumab therapy to cancer patients who benefit from the therapy administered in the P-trial until progression of their disease, therefore this is an open labelled, single arm, non-comparative study. Patients on Bevacizumab at study end of the P-trial should be enrolled immediately thereafter into this E-trial. Patients will receive treatment with Bevacizumab as during their P-trial until progression of disease, unacceptable toxicity, withdrawal of consent, death or transition to another option for treatment with bevacizumab (e.g. licensed product or Post-Trial Access Program [PTAP]) (whichever occurs first).

This study is a multi-national trial and the number of countries and centers is open. The number of patients to be enrolled over the planned recruitment period of approximately 5 years is open. This E-trial will end after the last patient safety follow-up (SFU) visit (latest 30 days after last patient permanently discontinues bevacizumab treatment in this E-trial).

5.2 STUDY TREATMENTS AND ASSESSMENTS

All patients must provide written informed consent before any E-trial-specific assessments or procedures are performed. Patients must fulfil all of the inclusion and none of the exclusion criteria to be enrolled in the E-trial.

Patients in this study will receive Bevacizumab at doses of 2.5 or 5 mg/kg/week every 2 or 3 weeks in line with the treatment schedule and dose as mandated by the P-trial, i.e.:

- Bevacizumab 7.5 or 15 mg/kg IV on day 1 every 3 weeks or
- Bevacizumab 5 or 10 mg/kg IV on day 1 every 2 weeks

The dose and schedule of Bevacizumab will be the same as during treatment in the P-trial.

Treatment with Bevacizumab will be continued during the E-trial and will not be reduced for reasons other than a >10% change (loss or gain) in weight from baseline (at rollover assessment). Missed doses will not be administered subsequently. Treatment should not be omitted for more than 42 days unless because of planned surgery requiring bevacizumab interruption during P-trial. Bevacizumab can be restarted only after Sponsor's medical monitor approval.

At each cycle, Bevacizumab must be administered before concurrent anti-cancer therapy treatment at the same clinic visit, for oral agents the patients are allowed to follow their normal schedule.

Patients will receive treatment with Bevacizumab as during their P-trial until one of the following occurs:

- progression of disease;
- unacceptable Bevacizumab toxicity;
- withdrawal of consent;
- death;
- transition to another option for treatment with bevacizumab (e.g. licensed product).

The schedule of assessments is given in Table 1 below:

Table 1. Schedule of mandatory* assessments

	Roll over from P-trial into E-Trial (Day -14 to Day 1)	**Treatment period Per cycle**	**Safety FU§**
Informed Consent	X		
Confirmation of eligibility	X		
Patient characteristics (Gender, date of birth, tumour type)	X		
Pregnancy test for WOCP#	X		
Weight		X	
Bevacizumab Other P- trial anti-cancer IMP(s) if applicable**		X+	
Progression assessment		Per local standard°	

AE	X	X	X
Survival info		X	X

§ (1) for patients who withdraw from the trial for reasons other than transition to another option for treatment with bevacizumab, 30 (± 3) days after the last dose of bevacizumab (or other P-trial IMP(s), if applicable) and (2) for patients who withdraw from the trial to transition to another option for treatment with bevacizumab, before administration of non-trial bevacizumab outside of the study.
# Pregnancy test: WOCP will have a serum pregnancy test no more than 7 days prior to the first trial treatment or no more than 14 days (with a confirmatory urine pregnancy test within 7 days prior to the first trial treatment).
*Additional assessments (as per local standard and clinical judgement of the investigator) will only be documented in the patients' source documents
° The same method(s) as per P-trial are recommended
+ 1st Bevacizumab dose in MO25757 E-trial to be within 42 days of last dose in P-trial
** classified as non-IMP in the E-trial

5.3 RANDOMIZATION AND BLINDING

There will be no randomization or blinding to treatment as the study is a multicenter open label study. All patients in this study will receive Bevacizumab.

5.4 SAMPLE SIZE JUSTIFICATION

This is an E-trial. Patients will be enrolled from qualifying P-trials. The formal estimation of sample size is not possible.

Table 2 below presents a few possible scenarios for percentage of AEs grade ≥ 3 related to Bevacizumab with corresponding 95% Clopper-Pearson exact confidence intervals.

Table 2. Scenarios for Percentage and Number of Patients with AEs grade ≥ 3 related to Bevacizumab and corresponding Confidence Intervals

Sample Size	Percentage and Number of Patients with AEs grade ≥3 related to bevacizumab	95% Clopper Pearson exact confidence interval
50	10% (5 patients)	3% - 22%
50	20% (10 patients)	10% - 34%
100	10% (10 patients)	5% - 18%
100	20% (20 patients)	13% - 29%

It is difficult to estimate at this stage how many patients will be enrolled in this study. Assuming

a sample size of 100 patients then the percentage of patients with at least one AEs grade ≥ 3 related to Bevacizumab could be estimated to be within 5%-18% with a probability of 95% and assuming observed rate of patients with at least one AEs grade ≥ 3 of 10%.

The sample size was estimated using SAS Version 9.2 and nQuery Version 6.

6 Statistical Considerations

The following rules will be considered:

- **Post-text Tables, Figures and Listings:**
  - **Page Orientation**: Landscape
  - **Post-text outputs**, will be generated in .lst and converted to rtf.
  - **Font**: Courier New font with minimum of 9 point font size
  - **Margins**: top: 1", bottom: 0.8", left: 1.5" and right: 1.15" on A4 paper (i.e. line size of 120 and page size of 42)
- **In-text Tables, Figures and Listings:**
  - **Page Orientation**: Portrait where possible
  - **Post-text outputs**, Report outputs (i.e. in-text outputs) will be generated using SAS ODS RTF with no borders or framing around table elements
  - **Font**: Arial font with minimum of 9 point font size
- Columns header will be left aligned.
- **Treatment labels**: unless otherwise stated, all patients will be summarized under indication. Note a P-trial can be listed under more than one indication. The following labels will be used. Listing of P-trials with their indication can be found in section 12.2.
  - BC
  - OC or PC
  - CRC
  - RCC
  - NSCLC
  - GBM
  - Total
- **Visit labels**: the labels for the visits of the study are displayed in Table 3.
- **Continuous variables** (e.g., age) will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum.

- **Categorical variables** (e.g., sex, race) will be summarized using the number of observations (n) and percentage in each category.
    - The number of missing values will be presented as a separate category with no percentage, but only if 1 or more patients have missing data for the summary. Otherwise, all categories will be presented (even if no patients are counted in the category).
    - Counts of zero in any category will be presented without percentage. Precision for reporting derived endpoints will be determined by the statistician as appropriate for the study.
    - Except otherwise specified, percentages will be calculated based on the number of patients in the population
- **Precision of summary statistics:**
    - Integer – Sample size (n, N) and number of missing responses (if displayed)
    - One additional decimal place than reported/collected – mean, geometric mean, median, other percentile, confidence interval
    - Two additional decimal places than reported/collected – standard deviation
    - Same number of decimal places as reported/collected – minimum, maximum
    - Percentages –one decimal places
- All listings will be presented by Indication, P-trial, Non-IMP regimen, Country, Center/Patient and Age/Sex, and if applicable visit, assessment, assessment date/time and assessment (in order collected on CRF, unless specified otherwise).
- As Indication is not collected in the eCRF, for each P-trial the indication will be provided by Roche to be included in the analysis datasets.
- Summaries by P-trial should only be presented where there are at least 5 patients contributing from a P-trial.
- Study day calculations will be as follows. The calculation will result in dates prior to the date of first drug intake in the E-trial being presented as negative days, and those occurring on or after the date of first drug intake in the E-trial as Day 1 or later, i.e., there will be no Day 0.
    - [date of interest - date of first drug intake in the E-trial + 1] when the date of interest is on or after the date of first drug intake in the E-trial;
    - [date of interest - date of first drug intake in the E-trial] when the date of interest is prior to the date of first drug intake in the E-trial].
    - Missing if the patient was not treated in the E-trial.
- Days since last treatment (of Bevacizumab) in E-trial will be calculated to be presented in some TFLs, as mentioned in corresponding shells. The calculation is similar to the study day calculation:

- [date of interest - date of last drug intake in the E-trial+1] when the date of interest is on or after the date of last drug intake in the E-trial;
- [date of interest - date of last drug intake in the E-trial] when the date of interest is prior to the date of last drug intake in the E-trial;
- Missing if the patient was not treated in the E-trial.

- Days since initial treatment (of Bevacizumab) in P-trial will be calculated to be presented in some TFLs, as mentioned in corresponding shells. The calculation is similar to the study day calculation and will result in positive days:
  - [date of interest - date of first drug intake in the P-trial+1]
- Dates will be presented in format DDMMMYYYY.
- Dictionary names and versions will be included in the footnotes of the adverse events tables and listings.
- The following partial dates will be imputed following the standard document, "*Imputation Rules for Partial Dates*" (see Section 12.3):
  - Partial Adverse Event start and stop dates to determine the study days.

Table 3. Visit labels

Visit Name	**Visit Label for Tables**	**Visit Label for Listings/Figures**
Baseline (Day -14 to Day 1)	Baseline	BL
Treatment Period - Cycle x Day 1 to 14	Cycle X	Cycle x
Treatment Period - Cycle x Day 1 to 21	Cycle X	Cycle x
End of Treatment	End of Treatment	EoT
Safety Follow Up	Follow-Up	FU
End of Study	End of Study	EoS

7 Analysis Sets

The following populations will be considered in the data analysis:

All patients population:

All patients population consists of all patients who are enrolled regardless of whether they received study drug only in the P-trial or not. This population will be used to summarize patient disposition, and major protocol deviations.

Safety Population:

The Safety population will include all enrolled patients in the E-trial who received at least one dose of Bevacizumab during this study. All drug exposure, compliance, efficacy and safety summaries and analyses will be presented for the safety population.

8 Methods of Analyses and Presentations

8.1 SUBJECT DISPOSITION

The number and percentage of patients enrolled, in the safety population and discontinued from Bevacizumab with corresponding reason for discontinuation will be summarized and listed by indication and overall. The frequency and percentages of reasons for patients who discontinued from the study will be tabulated by indication and overall. The number of patients in each analysis population will also be summarized similarly.

In addition, the median observation time, its 95% confidence interval and standard error as well as the 25% and 75% estimate of the observation time, the number of patients censored and with event will be summarized by indication and overall, using a reverse Kaplan-Meier. The observation time will be derived as follows:

If the patient completed the safety follow-up (i.e. safety follow-up visit performed), the observation time is calculated as follows:

> Observation time (days) = (Date of safety follow-up visit - Date of first dose of Bevacizumab from E-trial) + 1.

If the patient has not completed the safety follow-up visit (for example the patient is lost-to follow-up, died or ongoing) then the patient will be censored at the last date of last known alive. Date of last known alive is the date of the last visit performed or if the patient died the day prior to the date of death.

> Observation time (days) = (Date of last known alive - Date of first dose of Bevacizumab from E-trial) + 1.

The number of patients in each center, each P-trial and each indication, will be summarized overall to show the contribution of each P-trial and center to the E-trial. Supportive listing of P-trial contribution and information will be provided.

8.2 PROTOCOL DEVIATIONS AND/OR VIOLATIONS

Non-compliance with the inclusion/exclusion criteria or major deviations from the protocol during the study conduct are considered protocol deviations. All protocol deviations will be recorded on the Roche Protocol Deviation Management System (PDMS) system and will be

reviewed on an ongoing basis by a Medical Monitor and assigned a severity. Pre-defined rules and categories for protocol deviations have been defined at the beginning of the trial and are included in the PDMS. At the time of database lock all protocol deviations will be extracted from the PDMS system and reviewed for final approval. There will be one record per subject per protocol deviation. All protocol deviations will be listed by P-trial, country, center and patient.

The following major protocol deviations will be summarized :

- Inclusion criteria 2 (Patient is treated with bevacizumab at the end of the Roche/Genentech sponsored P-trial and continues to have benefit as judged by the investigator) and inclusion criteria 3 (Eligible for continuation of bevacizumab treatment at the end of the P-trial, according to P-trial protocol)
- Exclusion criteria 8 (Evidence of any AE potentially attributable to bevacizumab, for which the local label recommends permanent discontinuation) and exclusion criteria 10 (Evidence of any other disease, neurological or metabolic dysfunction, physical examination finding or laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of the investigational drug(s) or puts the patient at high risk for treatment-related complications).
- Anything else that is a major protocol deviation potentially impacting the primary endpoint (AE grade >=3 rates) or put patient at risk

8.3 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

The following information will be collected at screening examination ("baseline") between 14 days and 1 day before the first dose of study drug in this E-trial:

- Demographics: date of birth, gender, age in years, tumour type;
- P-trial information: P-trial protocol, dates of first and last dose of Bevacizumab, dose regimen on P-trial, other IMP treatments from P-trial.

All data for baseline characteristics and demographics will be listed. Patient characteristics (including indication) as well as demographics, will be summarized for the safety population by indication and overall.

8.4 MEDICAL HISTORY

Medical History will not be coded. Only relevant medical history associated with a SAE is collected and will not be listed.

8.5 PRIOR AND CONCOMITANT MEDICATION

Medications other than the study treatment will be recorded in the CRF if they are associated with a SAE and will not be listed.

Concurrent P-trial anti-cancer IMP therapies will be referred as non-IMP treatment in this E-trial see section 8.6 for more details.

8.6 STUDY DRUG EXPOSURE AND/OR COMPLIANCE

8.6.1 Bevacizumab Exposure

Treatment duration for Bevacizumab from E-trial will be estimated as follows:

> Treatment Duration of Bevacizumab (E-trial) (months) = [(Date of last dose of Bevacizumab in E-trial – Date of first dose of Bevacizumab in E-trial) + 1] / 30.4375

Duration from first dose of Bevacizumab in P-trial to the last dose of Bevacizumab in the E-trial and derived approximate number of cycles of Bevacizumab will be also calculated. The derived approximate number of cycles of Bevacizumab will be calculated as the number of entire cycles, as follows:

> Approximate number of cycles (overall) = [(Date of last dose of Bevacizumab in E-trial – Date of first dose of Bevacizumab in P-trial + 1) / (number of days in a cycle)],
>
> where number of days in a cycle is the planned duration of cycle (14 or 21 days, depending of dose regimen).

Similarly, overall duration from first dose of Bevacizumab in P-trial to the last dose of Bevacizumab in the E-trial will be estimated as follows:

> Treatment Duration of Bevacizumab (overall) (months) = [(Date of last dose of Bevacizumab in E-trial - Date of first dose of Bevacizumab in P-trial + 1) / 30.4375]

Duration of treatment of Bevacizumab (during E-trial and overall) and the derived number of cycles will be summarized for the safety population by indication and overall.

The dose received (mg/kg) and compliance will also be summarized for the E-trial full study duration (cumulative dose received). The summary will be presented overall and for each indication. To derive the dose received at a specific visit in mg/kg the dose received will be divided by the patient's weight (kg) at that visit, if the weight is missing it will be derived for the previous non-missing weight reported (i.e. last observation carried forward principle will be applied).

> Cumulative dose of Bevacizumab = Sum (all doses of Bevacizumab within each cycle)
>
> Compliance (%) = Dose received (mg/kg) / Planned Dose (mg/kg) x 100.

The overall compliance will be derived using the cumulative dose received and the cumulative

planned dose. The cumulative planned dose will not be adjusted for dose reduction or interruption (i.e. dose not administered).

Bevacizumab administration details with corresponding exposure will be presented in a listing. A flag will be presented in case the amount of dose is reduced for reasons other than a >10% change (loss or gain) in corresponding weight from baseline.

8.6.2 Non-IMP Exposure

Non-IMP administration details will be presented in a listing.

8.7 EFFICACY DATA ENDPOINTS AND ANALYSES

The efficacy analysis will be performed on the safety population. No formal statistical testing is planned, so there will be no adjustment of the type I level for multiple endpoints.

All time to event efficacy endpoints defined in section 8.7.1 and section 8.7.2 will be calculated in days and converted to months considering the following conversion: 1 month = 30.4375 days.

8.7.1 Primary Efficacy Endpoint and Analyses

The primary variables will be based on the following safety endpoints: AE grade ≥ 3 related to Bevacizumab, SAEs and cause of death, Clopper-Pearson 95% CI will be derived for SAE incidence rates. Details on the summary of the primary endpoints are provided in section 8.10.1.

8.7.2 Secondary Efficacy Endpoints and Analysis

Assessments of efficacy will consist of assessments for progression of disease. Assessments for progression disease will be done as per the local standard, although it is recommended to continue using the same methods as in the P-trial. Results and dates of tumour assessments will be recorded. Assessment of progression of disease will be listed by indication, P-trial, country, center and patient.

8.7.2.1 Progression free survival

Progression free survival is defined as the time from first dose of Bevacizumab from E-trial to the time of first documented disease progression or death due to any cause, whichever occurs first. If a patient has not had an event, progression free survival is censored at the date of last tumour assessment. Time to event will be summarized in months (i.e. number of days/30.4375). The earliest date of disease progression will be used.

If a patient does not experience disease progression or did not die during the study then a censored progression free survival will be calculated as there will be no date of disease progression or date of death. This will be calculated as follows:

Progression free survival (days) = (Date of last tumour assessment - Date of first dose of Bevacizumab from E-trial) + 1

If no tumour assessment is done for the patient the censoring day will be set to 1.

Progression free survival will be summarised using the Kaplan-Meier approach. The number of patients included in the analysis, with the event and without events (censored) as well as the minimum and maximum time to progression (including censored valued) will be summarized. Kaplan Meier estimates will be presented for:

- Median time to progression free survival, including 95% confidence Interval;
- 25% and 75% quartile;

In addition, a description of the survival rates in tabular form with the Kaplan Meier estimate of cumulative survival at relevant time points (eg 6, 12, 18, 24, 30 and >36 months) will also be presented. The final choice of the time points presented in the summary table might be updated dependent upon the data at the time of the analysis.

Finally, a graph with lines by indication of the Kaplan Meier survival function showing the event free probability, number of patients still at risk and censored observations.

The 95% confidence interval of the median estimate will be derived for each indication via the Greenwood method. The cumulative Kaplan Meier estimate will be presented at each time point, where the estimate will be from the closest, prior event (real or censored).

An exploratory analysis for progression free survival will be considered. For the exploratory analysis, progression free survival will be defined with reference to first dose of Bevacizumab from P-trial. Similar definitions and analysis will be considered as stated above for the corresponding progression free survival with reference to first dose of Bevacizumab from P-trial.

All progression free survival summaries and graphical representation will be performed by indication, if there are more than 5 patients in the indication.

8.7.2.2 Overall survival time

Overall survival time is defined as the time from first dose of Bevacizumab from E-trial to death from any cause. Calculation is dependent on whether the patient dies or not and is measured in months i.e. (no. of days*12)/365.25.

If a patient dies then:

Overall Survival Time = (Date of death – Date of first dose of Bevacizumab from E-trial) + 1

If a patient does not die during the study then a censored overall survival time will be calculated as there will be no date of death. This will be calculated as follows:

> Overall Survival Time = (Date of last known to be alive – Date of first dose of Bevacizumab in E-trial) + 1

Date of last known alive will be derived as the date of last contact if the patient is lost to follow-up or date of last visit if no safety follow-up was performed.

The same summaries as the ones provided for the progression free survival (see section 8.7.2.1), will be presented for the overall survival.

An exploratory analysis for overall survival will be considered. For the exploratory analysis, overall survival will be defined with reference to first dose of Bevacizumab from P-trial. Similar definitions and analysis will be considered as stated above for the corresponding overall survival with reference to first dose of Bevacizumab from P-trial.

All overall survival summaries and graphical representation will be performed by indication, if there are more than 5patients in the indication.

8.8 PHARMACOKINETIC/ PHARMACODYNAMIC ENDPOINTS AND ANALYSES

Not applicable.

8.9 QUALITY OF LIFE OR PHARMACOECONOMIC ENDPOINTS AND ANALYSES

Not applicable.

8.10 SAFETY DATA ENDPOINTS AND ANALYSES

8.10.1 Adverse Events (AEs)

Adverse events recorded during the E-Trial (i.e. started after the first dose of Bevacizumab in the E-trial) will be summarized in frequency tables by primary system organ class and preferred term. All adverse events will be coded using the MedDRA dictionary. The version of the coding dictionary will be provided in the adverse events tables and listing footnote. Note: all AEs which started after the first dose of Bevacizumab in the E-trial are included in the AE summary and analyses tables.

The following adverse events are adverse events of special interest.

- Hypertension
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

- Proteinuria
- Haemorrhage, with a focus on haemoptysis and central nervous system (CNS) bleeding
- Arterial and venous thromboembolic events
- Wound healing complications
- Gastro-intestinal perforation
- Fistulae
- Congestive heart failure (CHF)

Roche will provide a complete list of preferred terms associated with each type of AE of special interest and [redacted] will use this list to programmatically identify the AE's of special interest.

The number of patients, associated percentage and number of events will be presented for each indication, System Organ Class, Preferred Term, and overall.

- All adverse events
- AEs leading to discontinuation of Bevacizumab
- AEs leading to discontinuation of Bevacizumab/non-IMP
- Adverse events of special interest
- Adverse events leading to death
- Serious adverse events[1]
- Severe AEs related to Bevacizumab (grade 3-5)[1]

[1]95% confidence intervals of the incidence rate of the number of patients with at least one such AE is presented. The 95% confidence intervals will be based on Clopper-Pearson method.

The incidence rate shown in the adverse event tables will only be based on adverse events that started on or after the first treatment date in this E-trial.

A patient who experienced the same event on more than one occasion are counted only once in the calculation of counts of adverse events. Overall number of events will be counted in the event frequency.

For the incidence tables of adverse events related to Bevacizumab, adverse events leading to discontinuation of Bevacizumab, adverse events leading to discontinuation of Bevacizumab/non-IMP, adverse events of special interest, the frequency and percentage will be presented by maximum severity. For patients with more than one adverse event during the study of the same type, the maximum severity will be tabulated.

All adverse events will be listed by indication, P-trial, country, center and patient with the start and end date of the adverse event and corresponding study day, days since initial treatment date in P-trial, the severity and its relationship to the study treatment/non-IMP, action taken concomitant drug given and corresponding outcome. In addition, AEs of Special Interest and AEs ongoing from P-trials will be flagged on the listing.

Separate listings will be provided for:

- All adverse events,
- Deaths

The number of patients who died, the cause of death, the relationship of death to Bevacizumab and relationship of death to non-IMP will be summarized overall and by P-trials.

Laboratory Assessments

The laboratory results collected as part of the SAE report will be listed as recorded in the CRF. The pregnancy test results will also be listed.

8.10.2 Vital signs

Weight as a vital signs measurement will be assessed at baseline and prior to each cycle of Bevacizumab (and it will be collected only if dose of Bevacizumab was administered). Baseline body weight is used to calculate the starting dose in this E-trial. Baseline, for vital signs will be considered as the value measured at the cycle for which the first dose of Bevacizumab is administered.

8.10.3 Other safety data

Not applicable.

9 Interim Analyses

No formal interim analyses for efficacy is planned for this E-trial.

A formal interim safety analysis was done and reviewed from Medical perspective. Outputs can be made available upon request and are listed in Table 4.

10 Document History

Date	Version	Modified by	Brief details of changes made to template
03-FEB-2015	1.0	[redacted]	Initial final version.
20-SEP-2015	2.0	[redacted]	• Added section after signature page (to match updated template) - The table of abbreviations for inclusion in the programmed outputs combined file. • Section 6: specify that date imputation is only performed for AE and reason why, update name

			of the appendix to match appendix title. • Section 8.1 – update definition of follow-up time to be based on follow-up visit not disease progression (added censoring rules). Also added requirement to display 25% and 75% estimate of the follow-up time and number of patients with event/censored. Renamed to observation time. • Section 8.2 – Updated to include definition of a major protocol violation. • Sections 8.6.1 and 8.6.3.1 – Clarified in the derivations of exposure that the last dose date of the non-IMP is not documented in the database and therefore this is assumed to be the same date as the last dose of Bevacizumab. • Section 8.10.1: clarify that only AE from the E-trial ((i.e. started after the first dose of Bevacizumab in the E-trial) are included in the summary tables. Added sentence to explain that all AE irrespective of start date compared to the last dose of treatment are included. Added that summary table of AEs ongoing from the P-trial, as well as a listing of AE related to non-IMP are required to interpret safety data. • Section 8.10.3 – updated the definition of baseline to match the first dose of Bevacizumab. • Section 13.1: o Minor cosmetic update to the TFLs o Footnote shortened to fit in one line. o Added Tables 1-1 to 3-1 for Roche publishing group (EudraCT format) o Post-text tables header added to all TFL to include date of data entry cut-off and date of data extraction o Post-text tables presenting data by indication and P-trial were split into 2 tables to help with the readability. o Tables 10-2 and 14.1.1-2 addition category for safety follow-up not performed added o Table 11-1 and 14.1.1-3 remove Tumor Type summary as included in the indication and remove the summary of duration of Bevacizumab in P trial and associated number of cycles are included in table 11-2 and 14.1.1-5.1.1. o Added tables 14.3.1-1.9.1 and 14.3.1-1.9.2 as per update to section 8.10.1. o Added Listing 16.2-7.3 and renumbered subsequent listing.

23-OCT-2015	2.1	[redacted]	• Section 13.1: Minor cosmetic updates to following TFLs (Tables 14.1.1-5.2.1.1, 14.1.1-5.2.1.2, 14.1.1-5.1.1.1, 14.1.1-5.1.1.2, 14.1.1-2.1, 14.1.1-2.2, 14.1.1-5.2.3.1; Listing 16.2.5-1.2)
21-JAN-2019	2.2	[redacted]	SAP text and TFL shells revised for upcoming final analysis.
18-FEB-2019	3.0	[redacted]	Finalized v3.0 of SAP.

11 References

None

12 Appendices

12.1 Tables, Figures and Listing shells

Table 4. List of Tables, Figures and Listings for the Clinical Study Report

Output Type	Number	Title	Included in IA?
IN-TEXT			
Table	10-1	P-trials Contribution to the E-trial	N
Table	10-2	Patient Disposition	N
Table	11-1	Demographics and Baseline Characteristics	N
Table	11-2	Duration and Exposure to Bevacizumab	Y*
Table	11-3	Bevacizumab Overall Compliance	N
Table	12-1	Number (%) of Patients with Adverse Events by System Organ Class and Preferred Term (Incidence ≥ 5% in any Indication)	N
Table	12-2	Number (%) of Patients with Adverse Events of Special Interest (AESI) by AESI Category and Preferred Term	N
Table	12-3	Cause of Death and Relationship of Death to Study Treatment	N
Table	1-1	Demographics by Indication (EudraCT Format)	N
Table	2-1	Serious Adverse Events by Indication (EudraCT Format)	N
Table	3-1	Non-Serious Adverse Events reported in >=5% of subjects in any indication by Indication (EudraCT Format)	N
POST-TEXT			
Section 14.1 Demographics and Baseline Characteristics			
Table	14.1.1-1	P-trials Contribution to the E-trial (All Patients Population)	Y
Table	14.1.1-2.1	Patient Disposition by Indication (All Patients Population)	Y
Table	14.1.1-3.1	Demographics and Baseline Characteristics by Indication (All Patients Population)	Y
Table	14.1.1-4.1	Major Protocol Deviations by Indication (All Patients Population)	N
Table	14.1.1-5.1.1.1	Duration and Exposure to Bevacizumab by Indication (Safety Population)	Y*
Table	14.1.1-5.1.2.1	Bevacizumab Compliance by Indication (Safety Population)	N
Section 14.2 Efficacy			
Table	14.2-1.1	Progression Free Survival (PFS) by Indication (Safety Population)	N

Output Type	Number	Title	Included in IA?
Table	14.2-1.2	Overall Survival (OS) by Indication (Safety Population)	N
Table	14.2-1.3	Progression Free Survival (PFS) by Indication - Exploratory analysis, PFS with reference to first dose of Bevacizumab from P-trial (Safety Population)	N
Table	14.2-1.4	Overall Survival (OS) by Indication - Exploratory analysis, OS with reference to first dose of Bevacizumab from P-trial (Safety Population)	N
Figure	14.2-1.1	Progression Free Survival (PFS) by Indication (Safety Population)	N
Figure	14.2-1.2	Overall Survival (OS) by Indication (Safety Population)	N
Figure	14.2-1.3	Progression Free Survival (PFS) by Indication - Exploratory analysis, PFS with reference to first dose of Bevacizumab from P-trial (Safety Population)	N
Figure	14.2-1.4	Overall Survival (OS) by Indication - Exploratory analysis, OS with reference to first dose of Bevacizumab from P-trial (Safety Population)	N
Section 14.3 Safety			
Section 14.3.1 Adverse Events			
Table	14.3.1-1.1.1	Number (%) of Patients with Adverse Events by Indication, System Organ Class and Preferred Term (Safety Population)	Y
Table	14.3.1-1.1.2	Number (%) of Patients with Severe (Grade 3-5) Adverse Events Related to Bevacizumab by Indication, System Organ Class and Preferred Term (Safety Population)	
Table	14.3.1-1.2.1	Number (%) of Patients with Adverse Events Related to Bevacizumab by Indication, System Organ Class, Preferred Term and Maximum Severity (Safety Population)	Y
Table	14.3.1-1.3.1	Number (%) of Patients with Adverse Events Leading to Discontinuation of Bevacizumab by Indication, System Organ Class and Preferred Term (Safety Population)	N
Table	14.3.1-1.3.2	Number (%) of Patients with Adverse Events Leading to Discontinuation of Bevacizumab/non-IMP by Indication, System Organ Class and Preferred Term (Safety Population)	N
Table	14.3.1-1.4.1	Number (%) of Patients with Adverse Events Leading to Discontinuation of Bevacizumab by Indication, System Organ Class, Preferred Term and Maximum Severity (Safety Population)	N
Table	14.3.1-1.4.2	Number (%) of Patients with Adverse Events Leading to Discontinuation of Bevacizumab/non-IMP by Indication, System Organ Class, Preferred Term and Maximum Severity (Safety Population)	N
Table	14.3.1-1.5.1	Number (%) of Patients with Adverse Events of Special Interest (AESI) by Indication, AESI Category and Preferred Term (Safety Population)	Y
Table	14.3.1-1.6.1	Number (%) of Patients with Adverse Events of Special Interest (AESI) by Indication, AESI Category, Preferred Term and Maximum Severity (Safety Population)	Y

Output Type	Number	Title	Included in IA?
Table	14.3.1-1.7.1	Number of Adverse Events Leading to Death by Indication, System Organ Class, Preferred Term and Outcome (Safety Population)	Y*
Table	14.3.1-1.8.1	Number (%) of Patients with Non-Serious Adverse Events by Indication, System Organ Class, Preferred Term (Incidence ≥ 5% in any Indication) (Safety Population)	N
Table	14.3.1-2.1	Number (%) of Patients with Serious Adverse Events by Indication, System Organ Class and Preferred Term (Safety Population)	Y
Table	14.3.1-2.2	Number (%) of Patients with Severe (Grade 3-5) Adverse Events Related to Bevacizumab by Indication, System Organ Class and Preferred Term (Safety Population)	Y*
Table	14.3.1-4.1	Cause of Death and Relationship of Death to Study Treatment by Indication (Safety Population)	Y
Section 16.2 Listings			
Section 16.2.1 End of Study			
Listing	16.2.1-1	End of Treatment/Study (All Patients Population)	Y*
Section 16.2.2 Protocol Deviations			
Listing	16.2.2-1	Protocol Deviations (All Patients Population)	N
Section 16.2.3 Analysis Populations			
Section 16.2.4 Demographics and Baseline Characteristics			
Listing	16.2.4-1.1	Demographics and Baseline Characteristics (All Patients Population)	Y
Listing	16.2.4-1.2	P-trial Information (All Patients Population)	Y*
Listing	16.2.4-2	Pregnancy Test (All Patients Population)	N
Section 16.2.5 Study Drug Administration			
Listing	16.2.5-1.1	Administration of Bevacizumab (Safety Population)	Y*
Listing	16.2.5-1.2	Administration of non-IMP Treatment (Safety Population)	Y
Listing	16.2.5-2	Duration of exposure to Bevacizumab (Safety Population)	N
Section 16.2.6 Efficacy			
Listing	16.2.6-1.1	Time to Event (Safety Population)	N
Listing	16.2.6-1.2	Progression Assessment (Safety Population)	N
Section 16.2.7 Adverse Events			

Output Type	Number	Title	Included in IA?
Listing	16.2.7-1	Adverse Events (Safety Population)	Y*
Listing	16.2.7-2	All Deaths (Safety Population)	Y*

Included in IA: N=No; Y=Yes; Y*=Yes, however shell was updated in version 3.0 of the SAP.
To note further TFLs were presented in the IA, as documented in version 2.0 of the SAP. For final analysis, all TFLs defined in final version 3.0 of the SAP will be presented.

12.1.1 In-text Tables, Figures and Listing shells

Table 10-1 P-trials Contribution to the E-trial

P-Trials	BC	OC or PC	CRC	RCC	NSCLC	GBM	Total
Any P-trials	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
XXXXXXX	XX (XX.X%)						XX (XX.X%)
XXXXXXX				XX (XX.X%)			XX (XX.X%)
XXXXXXX		XX (XX.X%)			XX (XX.X%)		XX (XX.X%)
XXXXXXX		XX (XX.X%)				XX (XX.X%)	XX (XX.X%)
XXXXXXX			XX (XX.X%)				XX (XX.X%)
XXXXXXX			XX (XX.X%)				XX (XX.X%)
XXXXXXX			XX (XX.X%)				XX (XX.X%)
XXXXXXX	XX (XX.X%)						XX (XX.X%)
(cont.)							XX (XX.X%)

Source: Table 14.1.1-1

Table 10-2 Patient Disposition

	BC (N=XX)	OC or PC (N=XX)	CRC (N=XX)	RCC (N=XX)	NSCLC (N=XX)	GBM (N=XX)	Total (N=XXX)
Enrolled	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Treated (Safety Population)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Ongoing	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Discontinued	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
SFU visit performed	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
SFU visit not perfromed	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Reason for discontinuation from Bevacizumab treatment:							
Adverse event	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Disease progression	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Withdrawal of consent	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Death	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Lack of compliance	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
(cont.)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Reason follow-up not completed:							
Withdrawal of consent	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Lost to follow-up	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Death	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
(cont.)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Observation Time (Months)*							
n	XX	XX	XX	XX	XX	XX	XX
Median	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
(95% CI)	(XX.X; XX.X)	(XX.X; XX.X)	(XX.X; XX.X)	(XX.X; XX.X)	(XX.X; XX.X)	(XX.X; XX.X)	(XX.X; XX.X)
(25% ; 75%)	(XX.X; XX.X)	(XX.X; XX.X)	(XX.X; XX.X)	(XX.X; XX.X)	(XX.X; XX.X)	(XX.X; XX.X)	(XX.X; XX.X)

* Onbervation time is defined as time to safety follow-up – first bev. admin in E-trial based on inverse KM.
Abbreviations: KM=Kaplan-Meier; SFU=Safety Follow-up; SE=Standard error.

Source: Table 14.1.1-2.1

Table 11-1 Demographics and Baseline Characteristics

	BC (N=XXX)	OC or PC (N=XXX)	CRC (N=XXX)	RCC (N=XXX)	NSCLC (N=XXX)	GBM (N=XXX)	Total (N=XXX)
Gender							
Female	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Male	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Age (years)							
n	XX	XX	XX	XX	XX	XX	XX
Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
Median	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
[Min; Max]	[XX; XX]	[XX; XX]	[XX; XX]	[XX; XX]	[XX; XX]	[XX; XX]	[XX; XX]
Weight at baseline (kg)							
n	XX	XX	XX	XX	XX	XX	XX
Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
Median	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
[Min; Max]	[XX; XX]	[XX; XX]	[XX; XX]	[XX; XX]	[XX; XX]	[XX; XX]	[XX; XX]

Source: Table 14.1.1-3.1

Table 11-2 Duration and Exposure to Bevacizumab

	BC (N=XXX)	OC or PC (N=XXX)	CRC (N=XXX)	RCC (N=XXX)	NSCLC (N=XXX)	GBM (N=XXX)	Total (N=XXX)
Treatment Duration of Bevacizumab (E-trial) * (Months)							
n	XX	XX	XX	XX	XX	XX	XX
Mean (SD)	XX.XX (XX.XXX)	XX.XX (XX.XXX)	XX.XX (XX.XXX)	XX.XX (XX.XXX)	XX.XX (XX.XXX)	XX.XX (XX.XXX)	XX.XX (XX.XXX)
Median	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X] XX	[XX.X; XX.X] XX	[XX.X; XX.X] XX	[XX.X; XX.X] XX	[XX.X; XX.X] XX	[XX.X; XX.X] XX
Treatment Duration of Bevacizumab (overall) ** (Months)							
n	XX	XX	XX	XX	XX	XX	XX
Mean (SD)	XX.XX (XX.XXX)	XX.XX (XX.XXX)	XX.XX (XX.XXX)	XX.XX (XX.XXX)	XX.XX (XX.XXX)	XX.XX (XX.XXX)	XX.XX (XX.XXX)
Median	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
Approximate number of cycles (overall) *** [n (%)]							
1-10	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
11-20	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
21-30	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
31-40	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
41-50	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
51-60	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
(cont.)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Note:
* Treatment Duration of Bev. (E-trial) = [(Date of last dose of Bev. in E-trial - Date of first dose of Bev. in E-trial) + 1]/30.4375.
** Treatment Duration of Bev. (overall) = [(Date of last dose of Bev. in E-trial – Date of first dose of Bev. in P-trial) + 1]/30.4375.
*** Approximate number of cycles (overall) = [(Date of last dose of Bev. in E-trial – Date of first dose of Bev. in P-trial) + 1] / (number of days in a cycle).

Source: Table 14.1.1-5.1.1.1

Table 11-3 Bevacizumab Overall Compliance

	BC (N=XXX)	OC or PC (N=XXX)	CRC (N=XXX)	RCC (N=XXX)	NSCLC (N=XXX)	GBM (N=XXX)	Total (N=XXX)
Dose Received (mg/kg)							
n	XX	XX	XX	XX	XX	XX	XX
Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
Median	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
[Min; Max]	[XX; XX]	[XX; XX]	[XX; XX]	[XX; XX]	[XX; XX]	[XX; XX]	[XX; XX]
Compliance (%)							
n	XX	XX	XX	XX	XX	XX	XX
Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
Median	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
[Min; Max]	[XX; XX]	[XX; XX]	[XX; XX]	[XX; XX]	[XX; XX]	[XX; XX]	[XX; XX]
Compliance [n (%)]							
< 80%	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
80 - 120%	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
> 120%	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Source: Table 14.1.1-5.1.2.1

Table 12-1 Number (%) of Patients with Adverse Events by System Organ Class and Preferred Term (Incidence ≥ 5% in any Indication)

System Organ Class/ Preferred Term	BC (N=XX) n (%) [Events]	OC or PC (N=XX) n (%) [Events]	CRC (N=XX) n (%) [Events]	RCC (N=XX) n (%) [Events]	NXCLC (N=XX) n (%) [Events]
Any System Organ Class	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]
System Organ Class 1	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]
Preferred Term 1	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]
Preferred Term 2	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]
Preferred Term 3	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]
(cont.)	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]
(cont.)	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]

Note:
MedDRA version <version number>.
A patient with multiple occurrences of an AE is counted only once in each SOC and/or PT.

Source: Table 14.3.1-1.1.1

Programming Note:
- Include all Indications (additional columns), including Total – If possible fit all in one page.

Table 12-2 Number (%) of Patients with Adverse Events of Special Interest (AESI) by AESI Category and Preferred Term

AESI Category/ Preferred Term	BC (N=XX) n (%) [Events]	OC or PC (N=XX) n (%) [Events]	CRC (N=XX) n (%) [Events]	RCC (N=XX) n (%) [Events]	NXCLC (N=XX) n (%) [Events]
Any AESI	XX (XXX.X) [XX]	XX (XXX.X) [XX]	XX (XXX.X) [XX]	XX (XXX.X) [XX]	XX (XXX.X) [XX]
Hypertension	XX (XXX.X) [XX]	XX (XXX.X) [XX]	XX (XXX.X) [XX]	XX (XXX.X) [XX]	XX (XXX.X) [XX]
Preferred Term 1	XX (XXX.X) [XX]	XX (XXX.X) [XX]	XX (XXX.X) [XX]	XX (XXX.X) [XX]	XX (XXX.X) [XX]
Preferred Term 2	XX (XXX.X) [XX]	XX (XXX.X) [XX]	XX (XXX.X) [XX]	XX (XXX.X) [XX]	XX (XXX.X) [XX]
Preferred Term 3	XX (XXX.X) [XX]	XX (XXX.X) [XX]	XX (XXX.X) [XX]	XX (XXX.X) [XX]	XX (XXX.X) [XX]
(cont.)	XX (XXX.X) [XX]	XX (XXX.X) [XX]	XX (XXX.X) [XX]	XX (XXX.X) [XX]	XX (XXX.X) [XX]
(cont.)	XX (XXX.X) [XX]	XX (XXX.X) [XX]	XX (XXX.X) [XX]	XX (XXX.X) [XX]	XX (XXX.X) [XX]

Note:
MedDRA version <version number>.
A patient with multiple occurrences of an AE is counted only once in each AESI category and/or PT. A PT can contribute to more than one AESI category.

Source : Table 14.3.1-1.5.1

Programming Note:
- Include all Indications (additional columns), including Total

Table 12-3 Cause of Death and Relationship of Death to Study Treatment

	BC (N=XXX)	OC or PC (N=XXX)	CRC (N=XXX)	RCC (N=XXX)	NSCLC (N=XXX)	GBM (N=XXX)	Total (N=XXX)
No of patients who died	XXX (XX.X%)	XXX (XX.X%)	XXX (XX.X%)	XXX (XX.X%)	XXX (XX.X%)	XXX (XX.X%)	XXX (XX.X%)
Cause of death*							
Progressive disease	XXX (XX.X%)	XXX (XX.X%)	XXX (XX.X%)	XXX (XX.X%)	XXX (XX.X%)	XXX (XX.X%)	XXX (XX.X%)
Adverse event	XXX (XX.X%)	XXX (XX.X%)	XXX (XX.X%)	XXX (XX.X%)	XXX (XX.X%)	XXX (XX.X%)	XXX (XX.X%)
Other	XXX (XX.X%)	XXX (XX.X%)	XXX (XX.X%)	XXX (XX.X%)	XXX (XX.X%)	XXX (XX.X%)	XXX (XX.X%)
Relationship of death to Bevacizumab*							
Related	XXX (XX.X%)	XXX (XX.X%)	XXX (XX.X%)	XXX (XX.X%)	XXX (XX.X%)	XXX (XX.X%)	XXX (XX.X%)
Unrelated	XXX (XX.X%)	XXX (XX.X%)	XXX (XX.X%)	XXX (XX.X%)	XXX (XX.X%)	XXX (XX.X%)	XXX (XX.X%)
Relationship of death to Other Non-IMP*							
Related	XXX (XX.X%)	XXX (XX.X%)	XXX (XX.X%)	XXX (XX.X%)	XXX (XX.X%)	XXX (XX.X%)	XXX (XX.X%)
Unrelated	XXX (XX.X%)	XXX (XX.X%)	XXX (XX.X%)	XXX (XX.X%)	XXX (XX.X%)	XXX (XX.X%)	XXX (XX.X%)

* Percentages are calculated from the number of patients who died within the indication considered.

Source: Table 14.3.1-4.1

12.1.2 EudraCT Tables

Table 1-1 Demographics by Indication (EudraCT Format) (All Patients population)

	BC (N=XXX) n (%)	OC or PC (N=XXX) n (%)	CRC (N=XXX) n (%)	RCC (N=XXX) n (%)	NSCLC (N=XXX) n (%)	GBM (N=XXX) n (%)	Total (N=XXX) n (%)
Age							
18-64	XXX (XX.X)	XXX (XX.X)	XXX (XX.X)	XXX (XX.X)	XXX (XX.X)	XXX (XX.X)	XXX (XX.X)
65-84	XXX (XX.X)	XXX (XX.X)	XXX (XX.X)	XXX (XX.X)	XXX (XX.X)	XXX (XX.X)	XXX (XX.X)
85+	XXX (XX.X)	XXX (XX.X)	XXX (XX.X)	XXX (XX.X)	XXX (XX.X)	XXX (XX.X)	XXX (XX.X)
Total	XXX (XX.X)	XXX (XX.X)	XXX (XX.X)	XXX (XX.X)	XXX (XX.X)	XXX (XX.X)	XXX (XX.X)
Country							
Country #1	XXX (XX.X)	XXX (XX.X)	XXX (XX.X)	XXX (XX.X)	XXX (XX.X)	XXX (XX.X)	XXX (XX.X)
Country #2	XXX (XX.X)	XXX (XX.X)	XXX (XX.X)	XXX (XX.X)	XXX (XX.X)	XXX (XX.X)	XXX (XX.X)
Country #3	XXX (XX.X)	XXX (XX.X)	XXX (XX.X)	XXX (XX.X)	XXX (XX.X)	XXX (XX.X)	XXX (XX.X)
(cont.)	XXX (XX.X)	XXX (XX.X)	XXX (XX.X)	XXX (XX.X)	XXX (XX.X)	XXX (XX.X)	XXX (XX.X)
Total	XXX (XX.X)	XXX (XX.X)	XXX (XX.X)	XXX (XX.X)	XXX (XX.X)	XXX (XX.X)	XXX (XX.X)

Source: Listing 16.2.4-1.1

Program Name: xxxxxxx Date generated: xxxxxxxx Page X of Y

Table 2-1 Serious Adverse Events by Indication (EudraCT Format) (Safety Population)

System Organ Class Preferred Term	BC (N=XXX)					OC or PC (N=XXX)					CRC (N=XXX)				
	NSUB	NEVS	NTRE	NERD	NTRD	NSUB	NEVS	NTRE	NERD	NTRD	NSUB	NEVS	NTRE	NERD	NTRD
Number of subjects with at least one serious adverse event	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SOC 1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PT 1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PT 2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
...															
SOC 2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PT 1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PT 2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
...															

NSUB=Number of Subjects with Event, NEVS=Number of Events, NTRE=Number of Treatment Related Events, NERD=Number of Events Resulting in Death, NTRD=Number of Treatment Related Events Resulting in Death

Source: Listing XXXX
Program Name: xxxxxxx Date generated: xxxxxxxx Page X of Y

Programming Note:
- Repeat for all indication + total
- Sort by decreasing frequency for SOC and PT.

Table 3-1 Non-Serious Adverse Events reported in >=5% of subjects in any indication by Indication (EudraCT Format) (Safety population)

System Organ Class Preferred Term	BC (N=XXX)		OC or PC (N=XXX)		CRC (N=XXX)	
	Number (%) of Subjects	Number of events	Number (%) of Subjects	Number of events	Number (%) of Subjects	Number of events
Number of subjects with at least one non-serious adverse events reported in >=5% of subjects	XXX (XX.X)	XXX	XXX (XX.X)	XXX	XXX (XX.X)	XXX
SOC 1	XXX (XX.X)	XXX	XXX (XX.X)	XXX	XXX (XX.X)	XXX
PT 1	XXX (XX.X)	XXX	XXX (XX.X)	XXX	XXX (XX.X)	XXX
PT 2	XXX (XX.X)	XXX	XXX (XX.X)	XXX	XXX (XX.X)	XXX
…	XXX (XX.X)	XXX	XXX (XX.X)	XXX	XXX (XX.X)	XXX
SOC 2	XXX (XX.X)	XXX	XXX (XX.X)	XXX	XXX (XX.X)	XXX
PT 1	XXX (XX.X)	XXX	XXX (XX.X)	XXX	XXX (XX.X)	XXX
PT 2	XXX (XX.X)	XXX	XXX (XX.X)	XXX	XXX (XX.X)	XXX
…	XXX (XX.X)	XXX	XXX (XX.X)	XXX	XXX (XX.X)	XXX

Source: Listing XXXXX

Program Name: xxxxxxx Date generated: xxxxxxxx Page X of Y

Programming Note:

- Repeat for all indications + total
- Sort by decreasing frequency for SOC and PT.
- MUST EXCLUDE any SAEs
- Organized by SOC, then preferred term that occurred at a frequency of >= 5% for the indication considered. The table should also include the following:
  - Total number of patients with at least 1 non-serious AE (per indication applying the >= 5% threshold; i.e., reflective of ONLY the terms included in the table)
  - Number of patients with each non-serious AE (at the >= 5% threshold) by treatment group
- Number of EVENTS for each preferred term by treatment group

12.1.3 Post-text Tables, Figures and Listing shells

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Table 14.1.1-1
P-trials Contribution to the E-trial
(All Patients Population)

P-Trial/ Center	BC (N=XX) n (%)	OC or PC (N=XX) n (%)	CRC (N=XX) n (%)	RCC (N=XX) n (%)	NSCLC (N=XX) n (%)	GBM (N=XX) n (%)	Total (N=XX) n (%)
Any P-trial	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)
AVF3694g	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)
XXXXX	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)
XXXXX	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)
XXXXX	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)
(cont.)							
XXXXXX	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)
XXXXX	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)
XXXXX	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)
XXXXX	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)
(cont.)							

Note : Percentages at a center level are based on the number of patients enrolled from the corresponding P-trial.

Source : Listing XXXXXX
<Program Path\Program name.sas> <run on: datetime>

Programming Note:
- Include all P-trials.

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Table 14.1.1-2.1
Patient Disposition by Indication
(All Patients Population)

	BC (N=XX)	OC or PC (N=XX)	CRC (N=XX)	RCC (N=XX)	NSCLC (N=XX)
Enrolled [n (%)]	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)
Treated (Safety Population) [n (%)]	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)
Ongoing [n(%)]	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)
Discontinued [n(%)]	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)
SFU visit performed [n(%)]	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)
SFU visit not performed [n(%)]					
Reason for discontinuation from Bevacizumab treatment: [n(%)]					
Adverse event	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)
(cont.)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)
Reason follow-up not completed: [n(%)]					
Withdrawal of consent	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)
Death	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)
(cont.)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)
Other					
Observation Time (Months)*					
n	XX	XX	XX	XX	XX
Median	XX.X	XX.X	XX.X	XX.X	XX.X
(95% CI)	(XX.X; XX.X)	(XX.X; XX.X)	(XX.X; XX.X)	(XX.X; XX.X)	(XX.X; XX.X)
(25%; 75%) quartiles	(XX.X; XX.X)	(XX.X; XX.X)	(XX.X; XX.X)	(XX.X; XX.X)	(XX.X; XX.X)

Note: * Observation time is defined as time to safety follow-up - first bev. admin in E-trial based on inverse KM.
Abbreviations: KM=Kaplan-Meier; SFU=Safety Follow-up; SE=Standard error.

Source : Listing XXXXXX
<Program Path\Program name.sas> <run on: datetime>

Programming Note:
- Include all Indications (additional columns), including Total, if possible try to fit all column in 1 page
- List only the reasons for discontinuation that are populated.

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Table 14.1.1-3.1
Demographics and Baseline Characteristics by Indication
(All Patients Population)

	BC (N=XX)	OC or PC (N=XX)	CRC (N=XX)	RCC (N=XX)	NSCLC (N=XX)
Gender [n (%)]					
Female	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)
Male	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)
Age (years)					
n	XX	XX	XX	XX	XX
Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
Median	XX.X	XX.X	XX.X	XX.X	XX.X
[Min; Max]	[XX; XX]	[XX; XX]	[XX; XX]	[XX; XX]	[XX; XX]
Weight at baseline (kg)					
n	XX	XX	XX	XX	XX
Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
Median	XX.X	XX.X	XX.X	XX.X	XX.X
[Min; Max]	[XX; XX]	[XX; XX]	[XX; XX]	[XX; XX]	[XX; XX]

Source : Listing XXXXXX
<Program Path\Program name.sas> <run on: datetime>

Programming Note:
- Include all Indications (additional columns), including Total, if possible try to fit all column in 1 page
- Display summary statistics with 0 dp for weight and 0 dp for age.

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Table 14.1.1-4.1
Major Protocol Deviations by Indication
(All Patients Population)

	BC (N=XX) n (%)	OC or PC (N=XX) n (%)	CRC (N=XX) n (%)	RCC (N=XX) n (%)	NSCLC (N=XX) n (%)
Any major protocol deviations	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)
Inclusion criteria	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)
Protocol Deviation 2	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)
Protocol Deviation 3	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)
Exclusion Criteria	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)
Protocol Deviation 8	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)
Protocol Deviation 10	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)
Not compliant to Bevacizumab treatment	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)
Not allowed medications	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)
(cont.)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)

Source : Listing XXXXXX
<Program Path\Program name.sas> <run on: datetime>

Programming Note:
- Include all Indications (additional columns), including Total, if possible try to fit all column in 1 page
- Included in summary major protocol deviations from :
  - inclusion criteria 2 (Patient is treated with bevacizumab at the end of the Roche/Genentech sponsored P-trial and continues to have benefit as judged by the investigator) and inclusion criteria 3 (Eligible for continuation of bevacizumab treatment at the end of the P-trial, according to P-trial protocol);
  - exclusion criteria 8 (Evidence of any AE potentially attributable to bevacizumab, for which the local label recommends permanent discontinuation) and exclusion criteria 10 (Evidence of any other disease, neurological or metabolic dysfunction, physical examination finding or laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of the investigational drug(s) or puts the patient at high risk for treatment-related complications)

- anything else that is a major protocol deviation potentially impacting the primary endpoint (AE grade >=3 rates) or put patient at risk.

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Table 14.1.1-5.1.1.1
Duration and Exposure to Bevacizumab by Indication
(Safety Population)

	BC (N=XX)	OC or PC (N=XX)	CRC (N=XX)	RCC (N=XX)	NSCLC (N=XX)
Treatment Duration of Bevacizumab (E-trial) * (Months)					
n	XX.X	XX.X	XX.X	XX.X	XX.X
Mean (SD)	XX.XX (XX.XXX)	XX.XX (XX.XXX)	XX.XX (XX.XXX)	XX.XX (XX.XXX)	XX.XX (XX.XXX)
Median	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
Treatment Duration of Bevacizumab (overall) ** (Months)					
n	XX.X	XX.X	XX.X	XX.X	XX.X
Mean (SD)	XX.XX (XX.XXX)	XX.XX (XX.XXX)	XX.XX (XX.XXX)	XX.XX (XX.XXX)	XX.XX (XX.XXX)
Median	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
Approximate number of cycles (overall) *** [n (%)]					
1-10	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)
11-20	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)
21-30	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)
31-40	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)
41-50	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)
51-60	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)
(cont.)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)

Note: * Treatment Duration of Bev. (E-trial) = [(Date of last dose of Bev. in E-trial - Date of first dose of Bev. in E-trial) + 1]/30.4375.
** Treatment Duration of Bev. (overall) = [(Date of last dose of Bev. in E-trial – Date of first dose of Bev. in P-trial) + 1]/30.4375.
*** Approximate number of cycles (overall) = [(Date of last dose of Bev. in E-trial – Date of first dose of Bev. in P-trial) + 1] / (number of days in a cycle).

Source : Listing XXXXXX
<Program Path\Program name.sas> <run on: datetime>

Programming Note:

- Include all Indications (additional columns), including Total, if possible try to fit all column in 1 page.
- Display treatment duration with 1dp.

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Table 14.1.1-5.1.2.1
Bevacizumab Compliance by Indication
(Safety Population)

	BC (N=XX)	OC or PC (N=XX)	CRC (N=XX)	RCC (N=XX)	NSCLC (N=XX)
Dose Received (mg/kg)					
n	XX	XX	XX	XX	XX
Mean (SD)	XX.XX (XX.XXX)	XX.XX (XX.XXX)	XX.XX (XX.XXX)	XX.XX (XX.XXX)	XX.XX (XX.XXX)
Median	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
Compliance (%)					
n	XX	XX	XX	XX	XX
Mean (SD)	XX.XX (XX.XXX)	XX.XX (XX.XXX)	XX.XX (XX.XXX)	XX.XX (XX.XXX)	XX.XX (XX.XXX)
Median	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
[Min; Max]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]	[XX.X; XX.X]
Compliance [n (%)]					
< 80%	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)
80 - 120%	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)
> 120%	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)

Source : Listing XXXXXX
<Program Path\Program name.sas> <run on: datetime>

Programming Note:

- Include all Indications (additional columns), including Total, if possible try to fit all column in 1 page
- Repeat for all cycles.

Table 14.2-1.1
Progression Free Survival (PFS) by Indication
(Safety Population)

Indication: XXXXX

	Bevacizumab Total (N=XX)
Number of patients [n (%)] [a]	
who were censored	XXX (XXX.X)
who did have disease progression or died	XXX (XXX.X)
Time to disease progression (months) [b]	
Mean (SD)	XX.XX (XX.XXX)
Q1	XX.X
Median (95% CI)	XX.X (XX.X, XX.X)
Q3	XX.X
[Min; Max]	[XX.X; XX.X]
Estimated probabilities of progression (95% CI) [c]	
6 months	XX (XX.X, XX.X)
12 months	XX (XX.X, XX.X)
(cont.)	

[a] Percentages are based on the number of patients in the Safety population.
[b] Estimates are from a Kaplan-Meier analysis.
[c] 95% CI (confidence interval) for the estimated probability are derived using Greenwood method.
PFS calculated with reference to first dose of Bevacizumab from E-trial.

Source : Listing XXXXXX
<Program Path\Program name.sas> <run on: datetime>

Programming Note:
- Repeat for all indications, if > 5 patients are included in the considered indication.

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Table 14.2-1.2
Overall Survival (OS) by Indication
(Safety Population)

Indication: XXXXX

	Bevacizumab Total (N=XX)
Number of patients [n (%)] [a]	
who were censored	XXX (XXX.X)
who died	XXX (XXX.X)
Time to death (months) [b]	
Mean (SD)	XX.XX (XX.XXX)
Q1	XX.X
Median (95% CI)	XX.X (XX.X, XX.X)
Q3	XX.X
[Min; Max]	[XX.X; XX.X]
Estimated probabilities of death (95% CI) [c]	
6 months	XX (XX.X, XX.X)
12 months	XX (XX.X, XX.X)
(cont.)	

[a] Percentages are based on the number of patients in the Safety population.
[b] Estimates are from a Kaplan-Meier analysis.
[c] 95% CI (confidence interval) for the estimated probability are derived using Greenwood method.
OS calculated with reference to first dose of Bevacizumab from E-trial.

Source : Listing XXXXXX
<Program Path\Program name.sas> <run on: datetime>

Programming Note:
- Repeat for all indications, if > 5 patients are included in the considered indication.

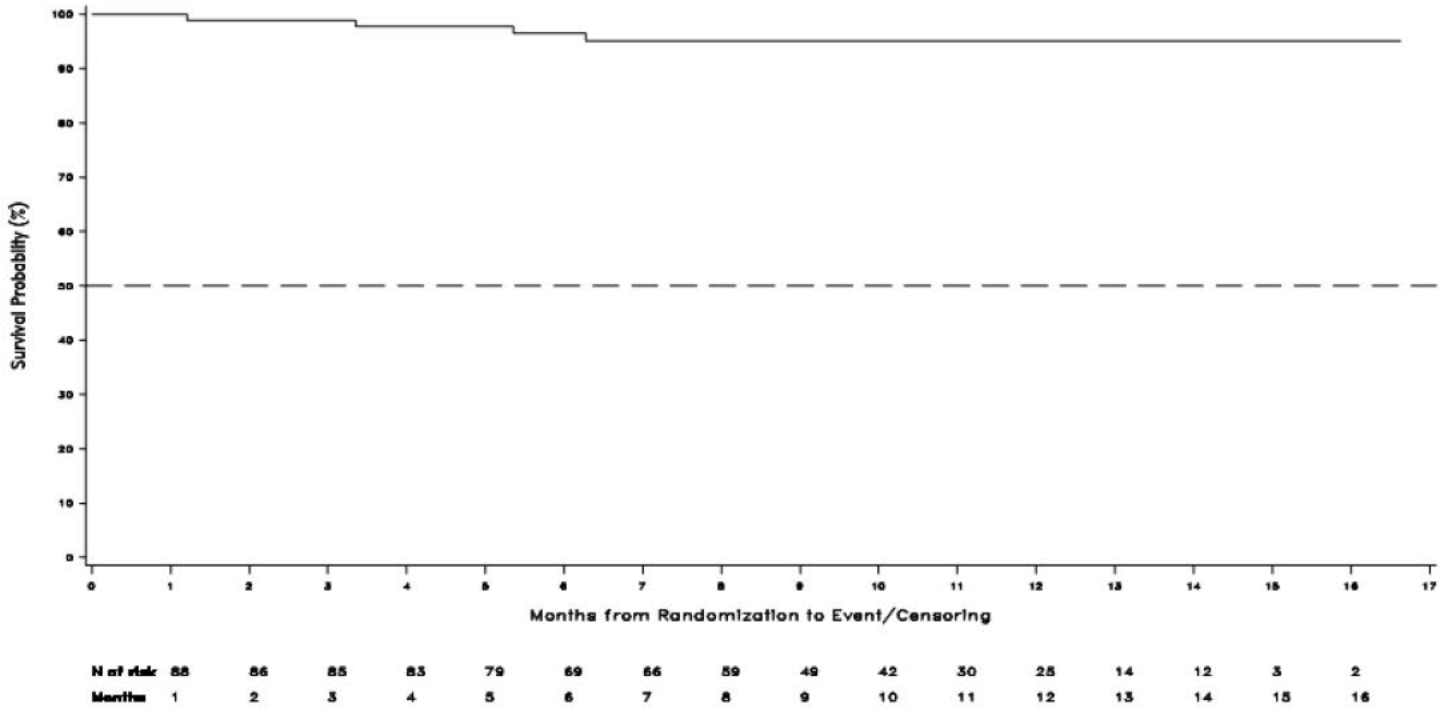
Table 14.2-1.3
Progression Free Survival (PFS) by Indication – Exploratory analysis, PFS with reference to first dose of Bevacizumab from P-trial
(Safety Population)

Programming Note:
- Replicate of Table 14.2-1.1.
- Updated last footnote to the following: PFS calculated with reference to first dose of Bevacizumab from P-trial.

Table 14.2-1.4
Overall Survival (OS) by Indication – Exploratory analysis, OS with reference to first dose of Bevacizumab from P-trial
(Safety Population)

Programming Note:
- Replicate of Table 14.2-1.2.
- Updated last footnote to the following: OS calculated with reference to first dose of Bevacizumab from P-trial.

Figure 14.2-1.1
Progression Free Survival (PFS) by Indication
(Safety Population)



PFS calculated with reference to first dose of Bevacizumab from E-trial.
Source : Listing XXXXXX
<Program Path\Program name.sas> <run on: datetime>

Programming Note:

- X-axis – Label "Progression free survival (Months)"
- Y-axix – Label "Survival probability (%).
- Present "Median PFS" and 95% CI.
- Present a line for each indication (if > 5 patients). Do not display number of patients at risk.

Figure 14.2-1.2
Overall Survival (OS) by Indication
(Safety Population)

Programming Note:
- Replicate of Figure 14.2-1.1.
- X-axis – Label "Overall survival (Months)"
- Y-axix – Label "Survival probability (%).
- Present "Median OS" and 95% CI.
- Updated footnote to the following: OS calculated with reference to first dose of Bevacizumab from E-trial.

Figure 14.2-1.3
Progression Free Survival (PFS) by Indication – Exploratory analysis, PFS with reference to first dose of Bevacizumab from P-trial
(Safety Population)

Programming Note:
- Replicate of Figure 14.2-1.1.
- Updated footnote to the following: PFS calculated with reference to first dose of Bevacizumab from P-trial.

Figure 14.2-1.4
Overall Survival (OS) by Indication – Exploratory analysis, OS with reference to first dose of Bevacizumab from P-trial
(Safety Population)

Programming Note:
- Replicate of Figure 14.2-1.1.
- Updated footnote to the following: OS calculated with reference to first dose of Bevacizumab from P-trial.

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Table 14.3.1-1.1.1
Number (%) of Patients with Adverse Events by Indication, System Organ Class and Preferred Term
(Safety Population)

System Organ Class/ Preferred Term	BC (N=XX) n (%) [Events]	OC or PC (N=XX) n (%) [Events]	CRC (N=XX) n (%) [Events]	RCC (N=XX) n (%) [Events]	NSCLC (N=XX) n (%) [Events]
Any System Organ Class	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]
System Organ Class 1	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]
Preferred Term 1	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]
Preferred Term 2	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]
Preferred Term 3	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]
(cont.)	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]
(cont.)	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]	XX (XXX.X) [XXX]

Note: MedDRA version <version number>.
A patient with multiple occurrences of an AE is counted only once in each SOC and/or PT.

Source : Listing XXXXXX
<Program Path\Program name.sas> <run on: datetime>

Programming Note:
- Include all Indications (additional columns), including Total, if possible try to fit all column in 1 page.
- Order the SOC and PT by decreasing frequency.

Table 14.3.1-1.1.2
Number (%) of Patients with Severe (Grade 3-5) Adverse Events Related to Bevacizumab by Indication, System Organ Class and Preferred Term
(Safety Population)

Programming Note:
- Replicate of Table 14.3.1-1.1.1.

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Table 14.3.1-1.2.1
Number (%) of Patients with Adverse Events Related to Bevacizumab
by Indication, System Organ Class, Preferred Term and Maximum Severity
(Safety Population)

Indication: <indication>

System Organ Class/ Preferred Term	Grade 1 (N=XX) n (%)	Grade 2 (N=XX) n (%)	Grade 3 (N=XX) n (%)	Grade 4 (N=XX) n (%)	Grade 5 (N=XX) n (%)	Any Grade (N=XX) n (%)
Any System Organ Class	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)
System Organ Class 1	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)
Preferred Term 1	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)
Preferred Term 2	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)
Preferred Term 3	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)
System Organ Class 2	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)
Preferred Term 1	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)
Preferred Term 2	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)
System Organ Class 3	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)
Preferred Term 1	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)	XX (XXX.X)
(cont.)						

Note: MedDRA version <version number>.
A patient with multiple occurrences of an AE is counted only once in each SOC, PT and/or maximum severity.

Source : Listing XXXXXX
<Program Path\Program name.sas> <run on: datetime>

Programming Note:
- Repeat for each Indication.
- Order the SOC and PT by decreasing frequency.

Table 14.3.1-1.3.1
Number (%) of Patients with Adverse Events Leading to Discontinuation of Bevacizumab by Indication, System Organ Class and Preferred Term
(Safety Population)

Programming Note:
- Replicate of Table 14.3.1-1.1.1.

Table 14.3.1-1.3.2
Number (%) of Patients with Adverse Events Leading to Discontinuation of Bevacizumab/non-IMP by Indication, System Organ Class and Preferred Term
(Safety Population)

Programming Note:
- Replicate of Table 14.3.1-1.1.1.

Table 14.3.1-1.4.1
Number (%) of Patients with Adverse Events Leading to Discontinuation of Bevacizumab
by Indication, System Organ Class, Preferred Term and Maximum Severity
(Safety Population)

Programming Note:
- Replicate of Table 14.3.1-1.2.1.

Table 14.3.1-1.4.2
Number (%) of Patients with Adverse Events Leading to Discontinuation of Bevacizumab/non-IMP
by Indication, System Organ Class, Preferred Term and Maximum Severity
(Safety Population)

Programming Note:
- Replicate of Table 14.3.1-1.2.1.

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Table 14.3.1-1.5.1
Number (%) of Patients with Adverse Events of Special Interest (AESI)
by Indication, AESI Category and Preferred Term
(Safety Population)

AESI Category/ Preferred Term	BC (N=XX) n (%) [Events]	OC or PC (N=XX) n (%) [Events]	CRC (N=XX) n (%) [Events]	RCC (N=XX) n (%) [Events]	NSCLC (N=XX) n (%) [Events]
Any AESI	XX (XXX.X) [XX]	XX (XXX.X) [XX]	XX (XXX.X) [XX]	XX (XXX.X) [XX]	XX (XXX.X) [XX]
Hypertension	XX (XXX.X) [XX]	XX (XXX.X) [XX]	XX (XXX.X) [XX]	XX (XXX.X) [XX]	XX (XXX.X) [XX]
Preferred Term 1	XX (XXX.X) [XX]	XX (XXX.X) [XX]	XX (XXX.X) [XX]	XX (XXX.X) [XX]	XX (XXX.X) [XX]
Preferred Term 2	XX (XXX.X) [XX]	XX (XXX.X) [XX]	XX (XXX.X) [XX]	XX (XXX.X) [XX]	XX (XXX.X) [XX]
Preferred Term 3	XX (XXX.X) [XX]	XX (XXX.X) [XX]	XX (XXX.X) [XX]	XX (XXX.X) [XX]	XX (XXX.X) [XX]
(cont.)	XX (XXX.X) [XX]	XX (XXX.X) [XX]	XX (XXX.X) [XX]	XX (XXX.X) [XX]	XX (XXX.X) [XX]
(cont.)	XX (XXX.X) [XX]	XX (XXX.X) [XX]	XX (XXX.X) [XX]	XX (XXX.X) [XX]	XX (XXX.X) [XX]

Note: MedDRA version <version number>.
A patient with multiple occurrences of an AE is counted only once in each AESI category and/or PT.
A PT can contribute to more than one AESI category.

Source : Listing XXXXXX
<Program Path\Program name.sas> <run on: datetime>

Programming Note:

- Include all Indications (additional columns), including Total, if possible try to fit all column in 1 page.
- List all the AESI categories as presented in the SAP, if there is zero case, please display the AESI with 0 patients.
- AESI category and PT are sorted by decreasing frequency
- SOC will be updated by AESI and PT will be the preferred terms that fall under the AESI category
- A PT can be contributing to more than one AESI category.

Table 14.3.1-1.6.1
Number (%) of Patients with Adverse Events of Special Interest (AESI)
by Indication, AESI Category, Preferred Term and
Maximum Severity
(Safety Population)

Programming Note:
- Replicate of Table 14.3.1-1.2.1.
- Repeat for each Indication and P-trial.
- List all the AESI categories as presented in the SAP, if there is zero case, please display the AESI with 0 patients.
- AESI category and PT are sorted by decreasing frequency
- SOC will be updated by AESI and PT will be the preferred terms that fall under the AESI category
- A PT can be contributing to more than one AESI category.

Table 14.3.1-1.7.1
Number (%) of Patients with Adverse Events Leading to Death by Indication, System Organ Class and Preferred Term
(Safety Population)

Programming Note:
- Replicate of Table 14.3.1-1.1.1.

Table 14.3.1-1.8.1
Number (%) of Patients with Non-Serious Adverse Events by Indication, System Organ Class and Preferred Term
(Incidence ≥ 5% in any Indication)
(Safety Population)

Programming Note:
- Replicate of Table 14.3.1-1.1.1.

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Table 14.3.1-2.1
Number (%) of Patients with Serious Adverse Events by Indication, System Organ Class and Preferred Term
(Safety Population)

Indication: BC

System Organ Class/ Preferred Term	Bevacizumab Total (N=XX) n (%)	Clopper-Pearson (95% CI)
Any System Organ Class	XX (XXX.X)	(XXX.X; XXX.X)
System Organ Class 1	XX (XXX.X)	(XXX.X; XXX.X)
Preferred Term 1	XX (XXX.X)	(XXX.X; XXX.X)
Preferred Term 2	XX (XXX.X)	(XXX.X; XXX.X)
Preferred Term 3	XX (XXX.X)	(XXX.X; XXX.X)
(cont.)	XX (XXX.X)	(XXX.X; XXX.X)
(cont.)	XX (XXX.X)	(XXX.X; XXX.X)

Note: MedDRA version <version number>.
A patient with multiple occurrences of an AE is counted only once in each SOC and/or PT.

Source : Listing XXXXXX
<Program Path\Program name.sas> <run on: datetime>

Programming Note:
- Repeat for each Indication including Total.
- SOC category and PT are sorted by decreasing frequency

Table 14.3.1-2.2
Number (%) of Patients with Severe (Grade 3-5) Adverse Events Related to Bevacizumab by Indication, System Organ Class and Preferred Term
(Safety Population)

Programming Note:
- Replicate of Table 14.3.1-2.1.

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Table 14.3.1-4.1
Cause of Death and Relationship of Death to Study Treatment by Indication
(Safety Population)

P-trial: Overall

	BC (N=XX) n (%)	OC or PC (N=XX) n (%)	CRC (N=XX) n (%)	RCC (N=XX) n (%)	NSCLC (N=XX) n (%)	GBM (N=XX) n (%)
No of patients who died	XXX (XXX.X)	XXX (XXX.X)	XXX (XXX.X)	XXX (XXX.X)	XXX (XXX.X)	XXX (XXX.X)
Cause of death*						
Progressive disease	XXX (XXX.X)	XXX (XXX.X)	XXX (XXX.X)	XXX (XXX.X)	XXX (XXX.X)	XXX (XXX.X)
Adverse event	XXX (XXX.X)	XXX (XXX.X)	XXX (XXX.X)	XXX (XXX.X)	XXX (XXX.X)	XXX (XXX.X)
Other	XXX (XXX.X)	XXX (XXX.X)	XXX (XXX.X)	XXX (XXX.X)	XXX (XXX.X)	XXX (XXX.X)
Relationship of death to Bevacizumab*						
Related	XXX (XXX.X)	XXX (XXX.X)	XXX (XXX.X)	XXX (XXX.X)	XXX (XXX.X)	XXX (XXX.X)
Unrelated	XXX (XXX.X)	XXX (XXX.X)	XXX (XXX.X)	XXX (XXX.X)	XXX (XXX.X)	XXX (XXX.X)
Relationship of death to Other Non-IMP*						
Related	XXX (XXX.X)	XXX (XXX.X)	XXX (XXX.X)	XXX (XXX.X)	XXX (XXX.X)	XXX (XXX.X)
Unrelated	XXX (XXX.X)	XXX (XXX.X)	XXX (XXX.X)	XXX (XXX.X)	XXX (XXX.X)	XXX (XXX.X)

Note: * Percentages are calculated from the number of patients who died within the indication considered.

Source : Listing XXXXXX
<Program Path\Program name.sas> <run on: datetime>

Programming Note:
- Include all Indications (additional columns), including Total, if possible, fit all column in the same page.

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Listing 16.2.1-1
End of Treatment/Study
(All Patients Population)

Indication: XXXX P-trial: XXXXX
Non-IMP: XXXXXXX

Country/ Center/ Patient	Age/ Sex	Safety Pop.?	First dose date/ Last dose date (day) [a]	Visit	Days since initial treat. in P-trial [c]	Completed FU?	Reason for discontinuation, specify	Date consent withdrawn	Observation time (months)[b]
XXXX/XXXX/XXXX	XX/X	Yes	DDMMMYYYY/ DDMMMMYYYY (XXX)	EoT	X		Adverse Event		
				EoS	XX	No	Other, XXXXX		XX.X*
XXXX/XXXX/XXXX	XX/X	Yes	DDMMMYYYY/ DDMMMMYYYY (XXX)	EoT	XX		Withdrawal of consent	DDMMMYYYY	
				EoS	XX	Yes			XX.X
XXXX/XXXX/XXXX	XX/X	No		EoS		No	XXXXX	DDMMMYYYY	

[a] First and last dose date of Bevacizumab treatment. Day is relative to the first dose date of treatment in the E-trial.
[b] Observation time is calculated as the time to safety follow-up visit from first bev. admin in E-trial.
[c] Days since initial treatment in P-trial is relative to the first dose date of treatment (Bevacizumab) in the P-trial.
* censored.

<Program Path\Program name.sas> <run on: datetime>

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Listing 16.2.2-1
Protocol Deviations
(All Patients Population)

Indication: XXXX; P-trial: XXXXX
Non-IMP: XXXXXXX

Country/ Center/ Patient	Age/ Sex	Date of Protocol Deviation (day) [a]	Protocol Deviation Category	Protocol Deviation Description	Included in summary? [b]
XXXX/XXXX/XXXX	XX/X	DDMMMMYYYY (XXX)	XXXXXXX	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	XXXXXXX
		DDMMMMYYYY (XXX)	XXXXXXX	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	XXXXXXX
XXXX/XXXX/XXXX	XX/X	DDMMMMYYYY (XXX)	XXXXXXX	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	

[a] Day is relative to the first dose date of treatment in the E-trial.
[b] Major protocol deviations from inclusion criteria 2 and 3, exclusion criteria 8 and 10 or anything else that is a major protocol deviation potentially impacting the primary endpoint (AE grade >=3 rates) or put patient at risk.

<Program Path\Program name.sas> <run on: datetime>

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Listing 16.2.4-1.1
Demographics and Baseline Characteristics
(All Patients Population)

Indication: XXXX P-trial: XXXXX
Non-IMP: XXXXXXX

Country/ Center/ Patient	Age/ Sex	Date of birth	Tumour Type	Indication	Baseline Weight (kg)
XXXX/XXXX/XXXX	XX/X	DDMMMYYYY	XXXXX	XXXXXXX	XX.X
XXXX/XXXX/XXXX	XX/X				

Note: Baseline is defined as the Cycle for which the first dose of Bevacizumab was administered.

<Program Path\Program name.sas> <run on: datetime>

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Listing 16.2.4-1.2
P-trial Information
(All Patients Population)

Indication: XXXXX P-trial: XXXXX

Country/ Center/ Patient	Age/ Sex	Site Nb.	Bevacizumab: Date of first dose	Bevacizumab: Date of last dose (day) [a]	Dose Regimen on P-trial	Continued with other P-trial IMP?	Other IMPs from P-trial
XXXX/XXXX/XXXX	XX/X	XXXX	DDMMMYYYY	DDMMMYYYY (XXX)	7.5 mg/kg IV every 21 days	Yes	Interferon alpha-2a
XXXX/XXXX/XXXX	XX/X	XXXX					

[a] Day is relative to the first dose date of Bevacizumab in the P-trial.

<Program Path\Program name.sas> <run on: datetime>

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Listing 16.2.4-2
Pregnancy Test
(All Patients Population)

Indication: XXXX; P-trial: XXXXX
Non-IMP: XXXXXXX

Country/ Center/ Patient	Age/ Sex	Visit	Pregnancy test done?	Reason not done	Date (day) of sample	Result
XXXX/XXXX/XXXX	XX/X	Screening	Yes		DDMMMYYYY (-XX)	Negative
XXXX/XXXX/XXXX	XX/X	Screening	No	Other, XXXXXX		

Note: Day is relative to the first dose of treatment in the E-trial.

<Program Path\Program name.sas> <run on: datetime>

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Listing 16.2.5-1.1
Administration of Bevacizumab
(Safety Population)

Indication: XXXX P-trial: XXXXX
Non-IMP: XXXXXXX

Country/ Center/ Patient	Age/ Sex	Baseline weight (kg)	Cycle	Date (day) dose administered	Dose (mg) administered	Weight (kg)	Dose (mg/kg)	Compliance (%)	Reason dose not given, specify	Flag*
XXXX/XXXX/XXXX	XX/X	XX.X	Cycle 1	DDMMMYYYY (1)	XXX.X	XX.X	XX.X	XX.X		
		XX.X	Cycle 2	DDMMMYYYY (XX)	XXX.X	XX.X	XX.X	XX.X		*
			Cycle 3	DDMMMYYYY (XX)			XX.X	XX.X	Other, XXXXX	
			Overall				XX.X	XX.X		
XXXX/XXXX/XXXX	XX/X		Cycle 1							

Note: Day is relative to the first dose of treatment in the E-trial.
* Dose is reduced for reasons other than a >10% change (loss or gain) in weight from baseline.

<Program Path\Program name.sas> <run on: datetime>

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Listing 16.2.5-1.2
Administration of non-IMP Treatment
(Safety Population)

Indication: XXXX P-trial: XXXXX
Non-IMP: XXXXXXX

Country/ Center/ Patient	Age/ Sex	Cycle	Drug name	Date (day) dose administered/ Last dose date (day) in cycle [a]	Dose (unit) admin./ No. of Dose per Cycle	Was NIMP admin. as planned?	Percentage dose given	Reason dose modified/ not given, specify [b]
XXXX/XXXX/XXXX	XX/X	Cyc1e 1	XXXXXXXXXX	DDMMMYYYY (1)/ DDMMMYYYY (XX)	XXX.X (XX)/ 2 dose	No	85%	XXXXXXXXX
			XXXXXXXXXX	DDMMMYYYY (1)/ DDMMMYYYY (XX)	XXX.X (XX)/ 1 dose	Yes		
		Cycle 2		DDMMMYYYY (XX) / DDMMMYYYY (XX)	XXX.X (XX)/ 2 dose	XXX		
		Cycle 3		DDMMMYYYY (XX) / DDMMMYYYY (XX)		No	0%	Other, XXXXX
		Cycle 4	XXXXXXXXX	DDMMMYYYY (XX)				Adverse Event
XXXX/XXXX/XXXX	XX/X	Cycle 1						

Note: Day is relative to the first dose of treatment in the E-trial.
[a] If the non-IMP administration was discontinued, the date (day) of last dose is presented
[b] If the non-IMP administration was discontinued, the reason the non-IMP were discontinued is displayed.

<Program Path\Program name.sas> <run on: datetime>

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Listing 16.2.5-2
Duration of exposure to Bevacizumab
(Safety Population)

Indication: XXXX P-trial: XXXXX
Non-IMP: XXXXXXX

Country/ Center/ Patient	Age/ Sex	Treatment duration of Bev.(E-trial) (months) [a]	Treatment duration of Bev. (overall) (months) [b]	Approximate number of cycles (overall) [c]
XXXX/XXXX/XXXX	XX/X	XX.X	XX.X	XX.X
XXXX/XXXX/XXXX	XX/X	XX.X	XX.X	XX.X
XXXX/XXXX/XXXX	XX/X	XX.X	XX.X	XX.X

Note: Day is relative to the first dose of treatment in the E-trial.
[a] Treatment Duration of Bev. (E-trial) = [(Date of last dose of Bev. in E-trial - Date of first dose of Bev. in E-trial) + 1]/ 30.4375.
[b] Treatment Duration of Bev. (overall) = [(Date of last dose of Bev. in E-trial – Date of first dose of Bev. in P-trial) + 1]/30.4375.
[c] Approximate number of Cycles (overall) = [(Date of last dose of Bev. in E-trial – Date of first dose of Bev. in P-trial) + 1] / (number of days in a cycle).

<Program Path\Program name.sas> <run on: datetime>

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Listing 16.2.6-1.1
Time to Event
(Safety Population)

Indication: XXXX; P-trial: XXXXX
Non-IMP: XXXXXXX

Country/ Center/ Patient	Age/ Sex	Progression Free Survival (mths.) [1]	Overall Survival (mths.) [1]	Progression Free Survival (mths.) - Exploratory analysis [2]	Overall Survival (mths.) - Exploratory analysis [2]
XXXX/XXXX/XXXX	XX/X	XXX	XXX	XXX	XXX
XXXX/XXXX/XXXX	XX/X	XXX	XXX*	XXX	XXX*
XXXX/XXXX/XXXX	XX/X	XXX	XXX	XXX	XXX
XXXX/XXXX/XXXX	XX/X	XXX	XXX	XXX	XXX
XXXX/XXXX/XXXX	XX/X	XXX*	XXX	XXX*	XXX
XXXX/XXXX/XXXX	XX/X	XXX	XXX*	XXX	XXX

(cont.)

Note: Time to event is relative to the first dose of treatment in the E-trial (or in the P-trial for the exploratory analysis).
[1] Progression Free Survival/Overall Survival calculated with reference to first dose of Bevacizumab from E-trial.
[2] Progression Free Survival/Overall Survival calculated with reference to first dose of Bevacizumab from P-trial.
1 month=30.4375 days.
* censored.

<Program Path\Program name.sas> <run on: datetime>

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Listing 16.2.6-1.2
Progression Assessment
(Safety Population)

Indication: XXXX; P-trial: XXXXX
Non-IMP: XXXXXXX

Country/ Center/ Patient	Age/ Sex	Cycle	Date (day) of assessment	Disease progression?	Date (day) of progression	How progression was assessed?	RECIST version
XXXX/XXXX/XXXX	XX/X	Cycle 1	DDMMMYYYY (XXX)	No		Clinical Assessment	
		Cycle 2	DDMMMYYYY (XXX)	No		Clinical Assessment	
		Cycle 3	DDMMMYYYY (XXX)	ND			
		Cycle 4	DDMMMYYYY (XXX)	Yes	DDMMMYYYY (XXX)	Radiological Assessment	V1.0
XXXX/XXXX/XXXX	XX/X						

Note: Day is relative to the first dose of treatment in the E-trial.
RECIST=Response Evaluation Criteria in Solid Tumours; ND=Not Done; NE=Assessment not scheduled at this visit.
Assessments for progression disease done as per the local standard, although it is recommended to continue using the same methods as in the P-trial.

<Program Path\Program name.sas> <run on: datetime>

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Listing 16.2.7-1
Adverse Events
(Safety Population)

Indication: XXXX P-trial: XXXXX
Non-IMP: XXXXXXX

Country/ Center/ Patient	Age/ Sex	Adverse Event (REPORTED)/ Preferred Term/ System Organ Class	Start date (day)/ Stop date (day)	Days since last treat. in E-trial [a]	Duration (days)/ Severity*/ SAE?/AESI?	Related to Bevacizumab/ Non-IMP	Action Taken/ Concomitant med non drug?/ Outcome	Action Taken with Bevacizumab /Non-IMP
XXXX/XXXX/XXXX	XX/X	$ XXXXXXXXXXX/ XXXXXXXX/ XXXXXXXX	DDMMMYYYY (XXX)/ --MMMYYYY (XXX)	-XXX	XXX/ Grade 1 (4.0)/ No/No	Rel./ Not Rel.	Yes/ No/ Resolved	Inter./ Disc.
		XXXXXXXXXXX/ XXXXXXXX/ XXXXXXXX	DDMMMYYYY (XXX)/ -----YYYY (XXX)		XXX/ Grade 5 (4.1)/ Yes/Yes	Not Rel./ Not Rel.	None/ Yes/ Death	None/ Adjusted
				-XX				
XXXX/XXXX/XXXX	XX/X	$ XXXXXXXXXXX/ XXXXXXXX/ XXXXXXXX	DDMMMYYYY (XXX)/ DDMMMYYYY (XXX)		XXX/ Grade 1 (4.0)/ No/Yes	Rel./ Not Rel.	Yes/ No/ Unres.	Disc./ Non

Note: Day is relative to the first dose of treatment in the E-trial. Study day will be derived based on imputed dates.
* version of the NCI-CTCAE used is displayed in parenthesis. $ Ongoing from P-trial.
MedDRA version <x.x>.
[a] Days since last treatment in E-trial is relative to the last dose date of treatment (Bevacizumab) in the E-trial.
Abbreviations: Disc=Discontinued; Inter=Interrupted; Rel=Related; Unres=Unresolved/Ongoing (at Safety Follow Up).

<Program Path\Program name.sas> <run on: datetime>

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Listing 16.2.7-2
All Deaths
(Safety Population)

Indication: XXXX P-trial: XXXXX
Non-IMP: XXXXXXX

Country/ Center/ Patient	Age/ Sex	Cause of death	Adverse event or prefered term (if other)	Date (day) of death	Days since last treat. in E-trial [a]	Related to Bevacizumab	Related to non-IMP	AE/SAE reported?
XXXX/XXXX/XXXX	XX/X	Adverse Event	XXXXXXXXXXX	DDMMMYYYY (XXX)	-XXX	Related	Not related	Yes
XXXX/XXXX/XXXX	XX/X	Other	XXXXXXXXXXX	DDMMMYYYY (XXX)	-XXXX	Not related	Not related	No
XXXX/XXXX/XXXX	XX/X	Progressive disease		DDMMMYYYY (XXX)	-XXX	Not related	Not related	No

Note: Day is relative to the first dose of treatment in the E-trial.
[a] Days since last treatment in E-trial is relative to the last dose date of treatment (Bevacizumab) in the E-trial.

<Program Path\Program name.sas> <run on: datetime>

12.2 Imputation of partial dates

With regards to missing start and stop date for AEs the following imputation rules will be followed.

- Stop dates:
    - If the AE is not ongoing and the stop date is partial (day or day/month missing), the stop date will be imputed by the last day of the month if the day is missing, the 31st of December if the day and month is missing or the date of death (if occurred on the same year or same month and year as the stop date), whichever date occurred first.
    - If the AE is not ongoing and the stop date is missing, the stop date will be imputed by the start date (if complete), by the last day of the month the AE started (if only day is missing), by the 31st of December of the year the AE started (if the day and month are missing) and by the first dose of treatment (if the start date is missing)
- Start dates: once the stop dates have been imputed as above the following rules will be used:
    - If the start date is missing it will be imputed by the date of the first dose of treatment
    - If the day is missing it will be imputed by the last day of the month
    - If the day and month are missing they will be imputed by the 31st of December
    - If the start date once imputed is after the stop date, the start date will be imputed with the stop date.
    - If the start date once imputed is after the date of death, the start date will be imputed with date of death.