NIS PROTOCOL

TITLE:	**AN INDIAN MULTICENTRIC OPEN LABEL PROSPECTIVE POST MARKETING SURVEILLANCE STUDY OF BEVACIZUMAB IN THE FRONT LINE MANAGEMENT OF ADVANCED/METASTATIC EPITHELIAL OVARIAN CANCER, FALLOPIAN TUBE CANCER OR PRIMARY PERITONEAL CANCER IN REAL-LIFE CLINICAL PRACTICE**
PROTOCOL NUMBER:	ML28446
VERSION NUMBER:	2.0
DATE OF LAST VERSION:	26 Nov 2012
MEDICINAL PRODUCT:	Bevacizumab
SPONSOR:	Roche Products (India) Pvt. Ltd.
DATE AMENDED:	Version 2.0, 13 July 2015

FINAL PROTOCOL APPROVAL

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PROTOCOL AMENDMENT, VERSION 2.0
RATIONALE

Protocol ML28446 has been amended to update the safety reporting requirements according to Roche policies and updated Non-Interventional Study (NIS) protocol template.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

PROTOCOL AMENDMENT, VERSION 2.0
SUMMARY OF CHANGES

GLOBAL CHANGES

The amendment includes global changes in the document and in particular the safety reporting section in order to align with the latest NIS protocol template.

CHANGES IN SECTIONS

Synopsis and Section 8.3.3: Grades have been added to the list of adverse events of special interest (AESI) and Non-GI fistula or abscess ≥ grade 2 has been added to this list. A list of guided questionnaires to be completed for certain conditions has also been added.

Section 10.1.2 and 10.1.3: These sections state that all SAEs and AESIs should be immediately reported by the physician to the Sponsor (i.e., no more than 24 hours after occurrence of the event.

Section 10.1.4: This section clarifies that all non-serious adverse events (AEs) other than AESIs will be reported by the physician to the Sponsor within 30 calendar days.

Section 10.2.1: Information regarding the collection of AEs after the end of the observation period has been added here.

Section 10.2.4: Subsections have been added to this section on Procedures for Recording Adverse Events to provide further guidance on recording different types of AEs.

Section 10.3.3: This section describes the process of reporting requirements for non-serious related AEs.

PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**AN INDIAN MULTICENTRIC OPEN LABEL PROSPECTIVE POST MARKETING SURVEILLANCE STUDY OF BEVACIZUMAB IN THE FRONT LINE MANAGEMENT OF ADVANCED/METASTATIC EPITHELIAL OVARIAN CANCER, FALLOPIAN TUBE CANCER OR PRIMARY PERITONEAL CANCER IN REAL-LIFE CLINICAL PRACTICE**
PROTOCOL NUMBER:	ML28446
VERSION NUMBER:	2.0
MEDICINAL PRODUCT:	Bevacizumab
SPONSOR:	Roche Products (India) Pvt. Ltd.

I agree to conduct the study in accordance with the current protocol.

_____
Principal Investigator's Name (print)

_____ _____
Principal Investigator's Signature Date

Please return the signed original of this form as instructed by your local study monitor to Roche Products (India) Pvt. Ltd. Please retain a copy for your study files.

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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AESI	Adverse Event Of Special Interest
ALT	Alanine Aminotransferase
ASR	Annual Status Report
AST	Aspartate Aminotransferase
CI	Confidence Interval
CR	Complete Response
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DCGI	Drugs Controller General of India
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic Data Capture
FIGO	International Federation of Gynecology and Obstetrics
GI	Gastrointestinal
GPP	Good Pharmacoepidemiological Practice
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ISPE	International Society of Pharmacoepidemiology
LPLV	Last Subject, Last Visit
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NIS	Non-interventional Study
PI	Prescribing Information
PFS	Progression Free Survival
PRES	Posterior Reversible Encephalopathy Syndrome
PR	Partial Response
PS	Performance Status
RBC	Red Blood Cell
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event

Abbreviation	Definition
SD	Stable Disease
SDV	Source Data Verification
SPC	Summary of Product Characteristics
ULN	Upper Limit Of Normal
VEGF	Vascular Endothelial Growth Factor
WBC	White Blood Cell

2. RESPONSIBLE PARTIES

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3. SYNOPSIS

TITLE:	**AN INDIAN MULTICENTRIC OPEN LABEL PROSPECTIVE POST MARKETING SURVEILLANCE STUDY OF BEVACIZUMAB IN THE FRONT LINE MANAGEMENT OF ADVANCED/METASTATIC EPITHELIAL OVARIAN CANCER, FALLOPIAN TUBE CANCER OR PRIMARY PERITONEAL CANCER IN REAL-LIFE CLINICAL PRACTICE**
PROTOCOL NUMBER:	ML28446
VERSION NUMBER:	2.0
DATE OF PROTOCOL:	13 Jul 2015
MEDICINAL PRODUCT:	Bevacizumab
INTERNATIONAL MEDICAL LEADER:	Dr. [redacted]
MAIN AUTHOR:	[redacted]
PHASE:	IV, non-interventional study
INDICATION:	Advanced/metastatic epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer
SPONSOR:	Roche Products (India) Pvt. Ltd.

Rationale and Background

Ovarian cancer is the fourth most common cause of cancer-related deaths in women, with an estimated 200,000 cases and 125,000 deaths occurring annually worldwide. In India, ovarian cancer is the fourth most common cancer with 26,834 new cases and 19,549 deaths per year [Globocan 2012]. The standard treatment for women with advanced ovarian cancer has been surgery and platinum-based chemotherapy [Perren TJ, NEJM 2011]. Ovarian cancer is associated with high concentrations of vascular endothelial growth factor (VEGF), a protein associated with tumor growth and spread. Studies have shown a correlation between a high concentration of VEGF and ascites development (excess fluid in the body cavity), disease worsening, and a poorer prognosis in women with ovarian cancer [Yamamoto S, 1997; Trinh XB, 2009]

Bevacizumab (Avastin®) is a recombinant humanized monoclonal Immunoglobulin G1 antibody that binds to and inhibits the biologic activity of human VEGF in *in vitro* and *in vivo* assay systems.

The efficacy and safety of bevacizumab in the front-line treatment of patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer were studied in two phase III trials (GOG-0218 and BO17707). The trials have demonstrated the efficacy and safety of the addition of bevacizumab to carboplatin and paclitaxel when compared to the chemotherapy regimen alone [Avastin® (Bevacizumab) Prescribing information].

Based on these pivotal trials, bevacizumab in combination with carboplatin and paclitaxel has been approved recently for the front-line treatment of advanced (International Federation of Gynecology and Obstetrics [FIGO] stages III B, III C and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer in European Union as well as in India.

The aim of this non-interventional post-marketing surveillance study is to characterize the safety profile of bevacizumab in Indian patients in real life practice.

Research Question and Objectives

Safety Objective

The primary objective for this study is as follows:

- To determine the safety profile (all grade 3 and above) of bevacizumab when added to standard chemotherapy (carboplatin and paclitaxel) in front line advanced/metastatic epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer (FIGO Stage IIIb, IIIc, and IV) in Indian population

Effectiveness Objectives

The effectiveness secondary objectives for this study are as follows:

- Progression free survival (PFS)
- Overall survival (OS)
- Overall response rates (Complete response [CR]+ Partial response [PR])
- Clinical benefit response rates (CR+PR+ Stable disease [SD])

Study Design

Description of Study

This is a single arm, open label, non-interventional, post marketing surveillance study in real-life clinical setting.

Patients with advanced/metastatic epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer (FIGO Stage IIIb, IIIc, and IV) will provide audio-visual and written informed consent for their data. The patients' medical records will be the source of all data that would be captured in the electronic case report form (eCRF). Patients that are already prescribed or are ongoing on bevacizumab in front line therapy, can be enrolled after providing an informed consent and all the data from their medical records available or known, would be entered into the eCRF.

Subjects will be followed up till disease progression, death, treatment discontinuation, consent withdrawal or lost to follow up for a maximum of 15 months or until unacceptable toxicity, whichever occurs earlier. Subjects will visit the study center as per routine clinical practice and not as per a required schedule. No additional tests/investigations/scans would be conducted.

Adverse Events (AEs) will be followed up for up to 30 days after last dose of bevacizumab. Adverse event data including grading of AEs at screening and subsequent evaluation will be entered into the eCRF

Subjects who complete the study or pre-maturely discontinue from the study will be followed up for survival till the end of study. Follow up information will be collected via telephone calls and/or clinic visits (only if they happen during the normal course of treatment) until death, loss to follow-up, or study termination by the Sponsor.

Start Date of Study

The study start date will be the date of the first data collection: the date from which information on the first study subject is recorded in the study database**.**

End of Study

The end of the study will be the date on which the last information of the last subject is recorded in the study database.

Population

In this study, documentation of patients who are treated according to India specific Prescribing Information (PI) will be collected.

Subjects must meet the following criteria for study entry:

- Subjects willing and able to give informed consent for data collection
- Subjects who are prescribed to receive bevacizumab and/or are already ongoing on treatment with bevacizumab for advanced/metastatic epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer (FIGO Stage lllb, lllc and lV) according to the routine clinical practice are eligible to enter this non-interventional study (NIS).

Subjects who meet any of the following criteria will be excluded from study entry:

- There is no specific exclusion criteria for this NIS and subjects who are considered not eligible to receive bevacizumab for advanced/metastatic epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer (FIGO Stage IIIb, IIIc and IV) according to the local prescribing information will not be enrolled in the study

Variables

Only variables, obtained according to routine clinical practice can and should be documented in this study.

Primary Safety Variable

The primary safety variable for this study is as follows:

- Incidence, nature, and severity of adverse events

Safety Variables

The other safety variables for this study are as follows:

The following adverse events of special interest (AESI), will be captured:

- Gastrointestinal (GI) perforation, *abscesses* and fistulae *(any grade)*
- Hypertension ≥ *grade 3*
- Proteinuria ≥ *grade 3*
- Wound healing complications ≥ *grade 3*
- Hemorrhage ≥ *grade 3 (any grade CNS bleeding;* ≥ *grade 2 haemoptysis)*
- Venous thromboembolic events ≥ *grade 3*
- Arterial thromboembolic events *(any grade)*
- Congestive heart failure ≥ *grade 3*
- Posterior Reversible Encephalopathy Syndrome (PRES) *(any grade)*
- *Non-GI fistula or abscess*≥ *grade 2*

Secondary Effectiveness Variable

The effectiveness variables for this study are as follows:

- PFS
- OS
- Overall response rates (CR+ PR)
- Clinical benefit response rates (CR+PR+ SD)

Data Sources

The data sources will include but not limited to source notes, laboratory records, and patient files etc.

Study Size

Approximately 100 patients will be enrolled across 20 study centers in India.

Statistical Considerations

Descriptive statistics will be provided for all safety, efficacy and laboratory endpoints at each specified visit of the study. All enrolled patients who have received minimum of one dose would be evaluated in safety analysis, and patients with at least one follow-up evaluation would be evaluated in efficacy analysis.

Analysis Methods

Safety Analysis

AEs and Serious Adverse Events (SAE) will be summarized by using number and percentage (incidence of AEs and SAEs). AEs and SAEs related to bevacizumab will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) classification of the International Conference on Harmonisation (ICH). AEs and SAEs also will be summarized using number and percentage by system organ class and preferred term. Summaries will be presented for all SAEs and related AEs.

All AEs/SAEs will be captured in the eCRF. All SAEs and AESIs would be reportable to sponsor immediately and latest within 24 hours of the occurrence of the event. Enrolled subjects who have received minimum one dose would be evaluated in safety analysis.

Effectiveness Analysis

Based on the observation during real-life clinical practice, all efforts would be made to regularly follow up patients to calculate Progression Free survival (PFS) and Overall Survival (OS). Kaplan-Meier method will be used to estimate the median PFS and OS for total as well as Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 and ECOG PS 1-2 at baseline. Log rank test will be used to compare the median survival time between subjects with ECOG PS 0 and ECOG PS 1-2 at baseline. The ORR (CR + PR) will be summarized using number and percentage along with two-sided 95% Pearson-Clopper confidence interval (CI). Similarly, the Clinical Benefit Response rate (CR + PR + SD) will be summarized using number and percentage along with the two-sided 95% Pearson-Clopper CI.

All statistical tests will be done at 5% level of significance. All patients with at least one follow up evaluation available would be evaluated for effectiveness.

Interim Analyses

In addition to the final analysis, there will an interim analysis for safety reporting that will be conducted when approximately 50% of the planned population has had any of the following: disease progression, death, treatment discontinuation, consent withdrawal, or is lost to follow up.

Sample Size Justification

This study will enroll approximately 100 patients at 20 sites across India.

The sample size was calculated using the formula:

$$n = \frac{Z^2 \times p \times (1 - p)}{d^2}$$

Where,

p :Incidence of any adverse events (All grade 3 and above) related to bevacizumab in Ovarian cancer

d : Precision

Z: Z value (1.96 for 95% confidence level)

In order to estimate the incidence of any AEs (All grade 3 and above) related to bevacizumab in ovarian cancer by assuming level of significance 5%, incidence of any AEs (All grade 3 and above) 66% [Perren TJ, 2011], precision 10% and dropout rate 10%, a total of 97 patients are required. Hence, it is proposed to enroll 100 patients for the present study.

Milestones

Study milestones are given in the following table.

Milestone	***Planned Date***
Protocol approval by an IRB/EC	*Q4, 2015*
Start of data collection	*Q1, 2016*
End of data collection	*Q4, 2018*
Study progress report 1 (ASR to be submitted annually to DCGI)	*Q4, 2016*
Study progress report 2 (ASR to be submitted annually to DCGI)	*Q4, 2017*
Study progress report 3 (ASR to be submitted annually to DCGI)	*Q4, 2018*
Interim report	*Q1, 2018*
Final report of study results	*Q4, 2019*

Medicine

Bevacizumab (Avastin) will be administered in accordance to local prescribing information. It is administered in addition to carboplatin and paclitaxel for up to 6 cycles of treatment followed by

continued use of bevacizumab as single agent until disease progression or for a maximum of 15 months or until unacceptable toxicity, whichever occurs earlier.

The recommended dose of bevacizumab is 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion.

4. PROTOCOL AMENDMENTS AND UPDATES

Any protocol amendments will be prepared by the Sponsor or designee.

Protocol amendments will be submitted to the Institutional Review Board (IRB)/Ethics Committee (EC) and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes that involve logistical or administrative aspects only (e.g., change in Study Monitor or contact information).

5. MILESTONES

Milestone	***Planned Date***
Protocol approval by an IRB/EC	*Q4, 2015*
Start of data collection	*Q1, 2016*
End of data collection	*Q4, 2018*
Study progress report 1 (ASR to be submitted annually to DCGI)	*Q4, 2016*
Study progress report 2 (ASR to be submitted annually to DCGI)	*Q4, 2017*
Study progress report 3	*Q4, 2017*
Interim report	*Q1, 2018*
Final report of study results	*Q4, 2019*

6. RATIONALE AND BACKGROUND

6.1 BACKGROUND ON OVARIAN CANCER

Ovarian cancer is the fourth most common cause of cancer-related deaths in women, with an estimated 200,000 cases and 125,000 deaths occurring annually worldwide. In India, ovarian cancer is the fourth most common cancer with 26,834 new cases and 19,549 deaths per year [Globocan 2012]. For the past decade, the standard treatment for women with advanced ovarian cancer has been surgery and platinum-based chemotherapy [Perren TJ et al, 2011]. Surgery to remove as much of the tumor as possible is a mainstay of treatment but unfortunately, the majority of patients are diagnosed with late stage disease (when the cancer has grown or spread) and they require further treatment [Hennessy B et al, 2009]. Attempts to improve the standard two-drug chemotherapy by adding a third cytotoxic drug failed to affect either progression free survival (PFS) or Overall Survival (OS) and resulted in an increase in

toxic effects. Although intraperitoneal chemotherapy has extended OS by 12 to 17 months, it is an option only for women with advanced ovarian cancer who have a small amount of residual disease after surgery and is not widely used [Perren TJ et al, 2011]. Intraperitoneal chemotherapy has its own drawbacks in terms of increased toxicity and infections.

6.2 BACKGROUND ON BEVACIZUMAB

Bevacizumab (Avastin®, Roche) is a recombinant humanized monoclonal Immunoglobulin G1 (IgG1) antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF) in *in vitro* and *in vivo* assay systems.

Administration of bevacizumab to xenotransplant models of colon cancer in nude (athymic) mice caused reduction of microvascular growth and inhibition of metastatic disease progression [Avastin® Local prescribing information; Burger RA et al. 2010].

The efficacy and safety of bevacizumab in the front-line treatment of patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer were studied in two phase III trials (GOG-0218 and BO17707). These trials have demonstrated the efficacy and safety of the addition of bevacizumab to carboplatin and paclitaxel when compared to the chemotherapy regimen alone [Avastin® Local prescribing information; Burger RA et al. 2010].

The GOG-0218 study was a Phase III multicenter, randomized, double-blind, placebo-controlled, three arm study evaluating the effect of adding bevacizumab to an approved chemotherapy regimen (carboplatin and paclitaxel) in patients with advanced (FIGO [International Federation of Gynecology and Obstetrics] stages III(Incompletely resectable) and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer [Burger RA et al 2010].

The trial met its primary objective of improvement in PFS. In comparison to patients treated with chemotherapy (carboplatin and paclitaxel) alone in the front-line setting (median PFS of 10.6 months), patients who received bevacizumab at a dose of 15 mg/kg q3w in combination with chemotherapy and continued to receive bevacizumab alone for up to 22 cycles (CPB15+), had a clinically meaningful and statistically significant improvement in PFS (median PFS of 14.7 months) [Burger RA et al 2010].

BO17707 (ICON 7) was a Phase III, two arm, multicenter, randomized, controlled, open-label study comparing the effects of adding bevacizumab to carboplatin plus paclitaxel in patients with FIGO Stage I or IIA (Grade 3 or clear cell histology only, n = 142), or FIGO Stage IIB - IV (all grades and all histological types, n = 1386) epithelial ovarian, fallopian tube, or primary peritoneal cancer following surgery [Yamamoto S et al. 1997].

The trial met its primary objective of PFS improvement. In comparison to patients treated with chemotherapy (carboplatin and paclitaxel) alone in the front-line setting (median PFS of 16.9 months), patients who received bevacizumab at a dose of 7.5 mg/kg q3w in combination with chemotherapy and continued to receive bevacizumab for up to 18

cycles had a statistically significant improvement in PFS (median PFS of 19.3 months) [Avastin® Local prescribing information; Yamamoto S et al. 1997].

6.3 STUDY RATIONALE

Ovarian cancer is associated with high concentrations of VEGF, a protein associated with tumor growth and spread. Studies have shown a correlation between a high concentration of VEGF and ascites development (excess fluid in the body cavity), disease worsening, and a poorer prognosis in women with ovarian cancer [Yamamoto S et al. 1997; Trinh XB et al. 2009].

Bevacizumab is designed to specifically target VEGF. Bevacizumab is a monoclonal antibody that binds to all isoforms of the VEGF-receptor ligand VEGF-A, with evidence of efficacy in metastatic colorectal and lung cancers, as well as activity in renal, and brain cancers [Avastin® Local prescribing information].The safety and efficacy of bevacizumab in the front-line treatment of patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer were studied in two phase III trials (GOG-0218 and BO17707) that evaluated the effect of the addition of bevacizumab to carboplatin and paclitaxel compared to the chemotherapy regimen alone [Local prescribing information; Burger RA et al 2010; Yamamoto S et al. 1997]. Based on these pivotal trials, bevacizumab in combination with carboplatin and paclitaxel has been approved for the front-line treatment of advanced (FIGO stages III B, III C and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer in the European Union as well as in India.

The aim of this non-interventional study (NIS) is to fulfill regulatory requirements by characterizing the safety profile of bevacizumab in Indian patients in real life practice.

7. RESEARCH QUESTION AND OBJECTIVES

7.1 RESEARCH QUESTION

This NIS is being conducted to characterize safety of bevacizumab in Indian patients.

7.2 OBJECTIVES

Safety Objectives

The primary objective of this study is as follows:

- To determine the safety profile (all grade 3 and above) of bevacizumab when added to standard chemotherapy (carboplatin and paclitaxel) in front line advanced/metastatic epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer (FIGO Stage IIIb, IIIc, and IV) in Indian population

Effectiveness Objectives

The effectiveness secondary objectives of this study are as follows:

- Progression free survival (PFS)
- Overall survival (OS)

- Overall Response rates (Complete response (CR)+ Partial response (PR))
- Clinical Benefit Response rates (CR+PR+ Stable disease(SD))

8. RESEARCH METHODS

8.1 STUDY DESIGN

This is a single arm, open label, prospective, non-interventional, post marketing surveillance study in real-life clinical setting.

8.1.1 Overview of Study Design

Patients with advanced/metastatic epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer (FIGO Stage IIIb, IIIc, and IV) will provide audio-visual and written informed consent for their data. The patients' medical records will be the source of all data that would be captured in the eCRF. Patients that are already prescribed or are ongoing on bevacizumab in front line therapy, can be enrolled after providing an informed consent and all the data from their medical records available or known, would be entered into the eCRF. The enrollment period will be 24 months.

Patients will visit the study center as per routine clinical practice and not as per a required schedule. No additional tests/investigations/scans would be conducted.

Patients will be followed-up till disease progression, death, treatment discontinuation, consent withdrawal or lost to follow up. Adverse Events (AEs) will be followed up for up to 30 days after last dose of bevacizumab. Adverse event data including grading of AEs at screening and subsequent evaluation will be entered into the eCRF

Patients who complete the study or pre-maturely discontinue from the study due to disease progression or withdrawal of consent, will be followed up for survival till the end of study. Follow-up information will be collected via telephone calls and/or clinic visits (only if they happen during the normal course of treatment) until death, loss to follow-up, or study termination by the Sponsor.

A data collection overview is provided in Appendix 2.

8.1.2 Number of Patients Observed in the Study

A total of 100 patients will be enrolled in the study across India.

8.1.3 Centers

This study will be conducted at approximately 20 centers in India.

8.1.4 Rationale for Study Design

This post-marketing study has been designed as a NIS in order to evaluate safety of bevacizumab in Indian population in real life clinical settings. Therefore the primary objective is safety and secondary objectives include effectiveness evaluation routinely used in oncology studies.

As data is to be primarily collected from the patient files, patients that have already been prescribed and commenced treatment with bevacizumab can be also enrolled in the study.

An interim analysis has been planned to analyze new safety concerns, if any.

8.2 POPULATION

All patients who are considered candidates to receive bevacizumab or are already prescribed and receiving bevacizumab for advanced/metastatic epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer (FIGO Stage IIIb, IIIc and IV) according to the local prescribing information and willing to provide voluntary audio-visual and written informed consent, are eligible to enter this NIS.

8.2.1 Concomitant Medication and Treatment

Concomitant medication prescribed for concomitant diseases at the beginning of the observation period or introduced during the observation period will be documented in the eCRF from start of therapy with bevacizumab until disease progression, lost to follow up, withdrawal of consent, or discontinuation of treatment, if applicable.

8.2.2 Dosage, Administration, and Compliance

Dosing and treatment duration of bevacizumab are at the discretion of the physician in accordance with local clinical practice and local labeling.

8.3 VARIABLES

8.3.1 Primary Safety Variable

The primary safety variable for this study is as follows:

- The incidence, nature, and severity of AEs observed will be evaluated.

8.3.2 Secondary Effectiveness Variables

- PFS
- OS
- Overall response rates (CR + PR)
- Clinical benefit response rates (CR+PR+SD)**Other Variables of Interest**

The following adverse events of special interest (AESI), will be captured :

- Gastrointestinal (GI) perforation, *abscesses* and fistulae *(any grade)*
- Hypertension ≥ *grade 3*
- Proteinuria ≥ *grade 3*
- Wound healing complication ≥ *grade 3*
- Hemorrhage ≥ *grade 3* (any grade CNS bleeding; ≥ grade 2 haemoptysis)
- Venous thromboembolic events ≥ *grade 3*
- Arterial thromboembolic events *(any grade)*

- Congestive heart failure ≥ *grade 3*
- Posterior Reversible Encephalopathy Syndrome *(any grade)*
- Non-GI fistula or abscess ≥ *grade 2*

In addition to the primary safety variable, guided questionnaires will be completed for the following:

Bevacizumab specific
- *Arterial Thromboembolic Events*
- *Congestive Heart Failure*
- *Interstitial Lung Disease*
- *Osteonecrosis of Jaw*

Non-product specific
- *Drug Induced Liver Injury*
- *Progressive Multifocal Leukoencephalitis*
- *Suspected Transmission of Infectious Agent by Medicinal Product*

8.4 DATA COLLECTION

8.4.1 Collection of Data on the eCRF

Patients' medical records will be the source of all data that will be recorded in the eCRFs. Therefore, only data available and already existing in patient's files will be recorded in eCRFs. The degree of detail and completeness of data collected is dependent on what is recorded in the patient charts. Data from patient notes should be entered in the eCRF as soon as they become available.

8.4.2 Data Collected during the Observation Period

During therapy with bevacizumab laboratory assessments are routinely performed in accordance with current guidelines and local standard of care. When performed during the observational period, available results from the range of assessments described below will be documented on the eCRF. Most data will be documented when subject visits the study center as per routine clinical practiceThe proposed assessments and suggested timings for assessments in the protocol/observational plan are not mandatory. It is up to the treating physician to perform and document the assessments as performed in the real clinical setting.

In the routine care setting, patients are seen regularly by their treating physicians either for treatment or for regular assessment after treatment. Thus, no study-specific visits or evaluations are required by this protocol.

Please see Appendix 2 for the data collection overview (as per standard of care).

8.4.2.1 Medical History and Demographic Data

Available medical history which may include but not restricted to clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, use of alcohol and drugs of abuse, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient will be recorded on the eCRF

Demographic data will include age, sex, and self-reported race/ethnicity.

8.4.2.2 Physical examination

As per routine clinical practice, available physical examination data of relevant body systems will be recorded on the eCRF.

The medical history of the subject and the AEs will be captured in the eCRF, only if available in the medical records. New or worsened clinically significant abnormalities should be recorded as AEs on the Adverse Event Form.

8.4.2.3 Vital Signs

As per routine clinical practice, available vital signs including measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature will be recorded on the eCRF. New or worsened clinically significant abnormalities should be recorded as AEs on the Adverse Event Form.

8.4.2.4 Tumor and Response Evaluations

Available data on tumor and treatment outcome from the medical records and a patient interview on medical history and disease characteristics (which are routinely performed in accordance with current guidelines and local clinical practice) will be documented in the eCRF. The data available according to the response assessment will be captured in the eCRF.

The investigator will continue to assess patients according to routine clinical practice at their discretion. Additional treatment outcome data may be collected for patients who continue to visit the doctor as per local standard of care till the end of study.

8.4.2.5 Laboratory Assessments

Laboratory assessments available from the records at baseline, subsequent visits to the clinic (only if they happen during the normal course of treatment) and on completion of treatment period will be collected.

New or worsened clinically significant abnormalities should be recorded as AEs on the Adverse Event Form.

Available laboratory assessment data on following parameters will be recorded on the eCRF

- Hematology (WBC count, red blood cell (RBC count, hemoglobin, hematocrit, platelet count, differential count [neutrophils, eosinophils, basophils, monocytes, lymphocytes]).

Serum chemistry (sodium, potassium, chloride, bicarbonate, fasting glucose, blood, urea nitrogen creatinine, total protein, albumin, phosphorus, calcium, magnesium, total and direct bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), Asparate aminotransferase (AST), uric acid, LDH, creatine phosphokinase).

8.4.3 Data Collected at Study Completion/Early Termination Visit

For patients who complete the study, including early termination, the study completion visit should be documented.

Please see Appendix 2 for the data collection overview at the treatment completion visit if available.

8.4.4 Data Collected during Follow-Up

After the study completion/early termination visit, AEs should be followed as outlined in Section 10.5.

Please see Appendix 2 for the data collection overview during follow-up.

8.4.5 Safety Data Collection

Clinical AEs, serious and non-serious, will be recorded in the eCRF during the total observation period, with physician's assessment of severity (mild, moderate, severe or in oncology studies using the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] v 4.03) and relationship to therapy (i.e., related or unrelated) as described in Section 10.

8.4.6 Retrospective Data Collection

For patients already on treatment with bevacizumab, if data collected as per routine clinical practice is available from patient files, then those patients will be considered for participation in this study.

8.5 PATIENT, STUDY, AND SITE DISCONTINUATION

8.5.1 Patient Discontinuation

As the decision for treatment lies with the treating physician and is not bound to the participation of a patient in the study, the investigator has the right to withdraw a patient from the study at any time. In addition, patients have the right to voluntarily withdraw from the study at any time for any reason. Reasons for discontinuation of treatment with the medicinal product or withdrawal from the study may include, but are not limited to, the following*:*

- Patient withdrawal of consent at any time

- Physician or Sponsor judges discontinuation is in the patient's best interest
- Patient is lost to follow-up

8.5.2 Discontinuation from Treatment with Medicinal Product

The decision for discontinuation from treatment lies with the treating physician in agreement with the patient's decision and is not regulated by this protocol. In accordance with the local PI, the following situations might require treatment discontinuation:

- GI perforation
- Tracheoesophageal fistula or any Grade 4 fistula
- Medically significant hypertension which cannot be adequately controlled with antihypertensive therapy, or if, the patient develops hypertensive crisis or hypertensive encephalopathy
- Arterial thromboembolic events
- Grade 4 proteinuria
- Any other condition as deemed appropriate by the treating physician

The early termination visit should be completed by patients who discontinue treatment with bevacizumab earlier than planned according to labeling. The primary reason for early treatment discontinuation should be documented on the appropriate eCRF page. Every effort should be made to obtain information on patients who discontinue treatment.

8.5.3 Withdrawal from Study

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF page. Patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

8.5.4 Study and Site Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- Patient enrollment is unsatisfactory

The Sponsor will notify the physician if the study is placed on hold, or if the Sponsor decides to discontinue the study.

The Sponsor has the right to replace a site at any time. Reasons for replacing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording

· Non-compliance with the Guidelines for Good Pharmacoepidemiological Practices (GPP) or any other pertinent local law or guideline

8.6 STATISTICAL CONSIDERATIONS

8.6.1 General Considerations

Descriptive statistics will be provided for all safety, efficacy and laboratory endpoints at each specified visit of the study

8.6.2 Analysis Populations

Safety analyses will include all patients who received at least one dose of bevacizumab. Effectiveness analyses will be based on all enrolled patients.

8.6.3 Analysis Methods

8.6.3.1 Primary Safety Analysis

Adverse and Serious adverse events

All Adverse Event (AE) and Serious Adverse Event (SAE) data will be summarized by using number and percentage (Incidence of AEs and SAEs). AEs and SAEs will be coded using the applicable version of the Medical Dictionary for Regulatory Activities (MedDRA) classification of the International Conference on Harmonisation (ICH), AEs and SAEs also will be summarized using number and percentage by System Organ Class and Preferred Term. Summaries will be presented for all adverse events and adverse events related to bevacizumab.

8.6.3.2 Secondary Safety Analysis

Physical Examinations

Descriptive statistics for all the physical examination parameters will be computed for baseline and at end of the treatment period. A listing will also be prepared for all the patients.

Vital signs:

Descriptive statistics for all the vital sign parameters will be computed for baseline and at end of the treatment period. A listing will also be provided as per the parameters available for all patients.

Clinical Laboratory evaluation:

For hematology and biochemistry parameters, descriptive statistics will be reported at screening, all cycles and end of treatment period. Change from baseline will also be reported from all the available clinic visits. Individual patient laboratory results will be provided in listing with abnormalities. Clinical laboratory shift tables will also be presented using CTCAE criteria (version 4.03) with counts and percentages.

8.6.3.3 Effectiveness Analysis

Based on the observation during real-life clinical practice, all efforts will be made to regularly follow up patients to ensure that Progression Free survival (PFS) (using Response Evaluation Criteria In Solid Tumors [RECIST] v 1.1) and Overall Survival (OS) data are reported. The log rank test will be used to compare the median survival time between subjects with ECOG PS 0 and ECOG PS 1-2 at baseline. The overall response rate (CR + PR) will be summarized using number and percentage along with two-sided 95% Pearson-Clopper confidence interval (CI). Similarly, the Clinical Benefit Response rate (CR + PR + SD) will be summarized using number and percentage along with the two-sided 95% Pearson-Clopper CI.

All statistical tests will be done at 5% level of significance. All patients with at least one follow up evaluation available would be evaluated for efficacy.

8.6.4 Interim Analyses

In addition to the final analysis, there will an interim analysis for safety reporting that will be conducted when approximately 50% of the planned population has had any of the following: disease progression, death, treatment discontinuation, consent withdrawal, or is lost to follow up.

8.6.5 Sample Size Justification

The sample size was calculated using the formula:

$$n = \frac{Z^2 \times p \times (1 - p)}{d^2}$$

Where,

p :Incidence of any AE (All grade 3 and above) related to bevacizumab in ovarian cancer

d : Precision

Z: Z value (1.96 for 95% confidence level)

In order to estimate the incidence of any AEs (All grade 3 and above) related to bevacizumab in ovarian cancer by assuming level of significance 5%, incidence of any AEs (All grade 3 and above) 66% [Perren TJ et al, 2011], precision 10% and dropout rate 10%, a total of 97 patients are required. Hence, it is proposed to recruit 100 patients for the present study.

8.7 DATA MANAGEMENT

The Sponsor will supply electronic eCRF specifications for this study. A contract research organization (CRO) will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via electronic data capture (EDC) using eCRFs. Sites will be responsible for data entry into

the EDC system. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will perform oversight of the data management of this study, including approval of the CRO's data management plans and specifications. Data will be periodically transferred electronically from the CRO to the Sponsor, and the Sponsor/CRO standard procedures will be used to handle and process the electronic transfer of these data.

All changes in the eCRF will be recorded in the EDC systems audit trial. Data backup and records retention for the study data will be done according to the CRO's standard procedures.

8.7.1 Data Quality Assurance

A CRO will be responsible for the data management of this study, including quality checking of the data. Data entered manually will be collected via EDC using eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will perform oversight of the data management of this study. The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data.

Electronic CRFs and correction documentation will be maintained in the EDC system audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

8.7.2 Electronic Case Report Forms

Electronic CRFs are to be completed using a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. Electronic CRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated trained site staff. Electronic CRFs should be reviewed and electronically signed and dated by the physician or a designee.

At the end of the study, the physician will receive the data related to patients from her site in an electronically readable format (e.g., on a compact disc) as per Roche standard operating procedures. Data must be kept with the study records. Acknowledgement of receipt of the data is required.

8.7.3 Source Data Documentation

Study monitors will perform ongoing source data verification as defined in the Trial Monitoring Plan to confirm that critical protocol data (i.e., source data) entered in the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, PROs, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that contain study-relevant information will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRF (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered in the eCRF must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 8.7.5.

To facilitate source data verification (SDV), the physicians and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The participating sites must also allow inspection by applicable health authorities.

8.7.4 Use of Computerized Systems

When clinical observations are entered directly into a participating site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

8.7.5 Retention of Records

Records and documents pertaining to the conduct of this study, including eCRFs and Informed Consent Forms, must be retained by the Physician for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8.8 STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

8.8.1 Study Documentation

The physician must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and applicable health authorities notification. In addition, at the end of the study, the physician will receive the patient data, which include an audit trail containing a complete record of all changes to data.

8.8.2 Site Audits and Inspections

Site visits will be conducted by the Sponsor or an authorized representative for audit of study data, patients' medical records, and eCRFs.

The physician will also permit national and local health authorities to inspect facilities and records relevant to this study.

8.8.3 Administrative Structure

Sponsor	Roche Products (India) Pvt. Ltd.
Clinical Supplies	Not applicable
Clinical Laboratory	Institutional laboratories and/or external laboratories
Study Monitoring	Roche Products (India) Pvt. Ltd, designated CRO, as applicable
Project Management	Roche Products (India) Pvt. Ltd.
Data Management	Designated CRO
List of Investigators	List will be included in the clinical trial application dossier to local health authorities

8.9 LIMITATIONS OF THE RESEARCH METHOD

One of the limitations of this study is the heterogeneity of data. In this multi-center observational study, the data will be obtained from the patient files. Due to diverse local clinical and laboratories' documentation styles the available patient information may vary from center to center. In order to minimize this effect, along with on-going patients those patients who are initiating treatment with bevacizumab will also be enrolled for follow up in this study.

9. PROTECTION OF HUMAN SUBJECTS/ETHICAL CONSIDERATIONS

This study will be conducted in compliance with ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

9.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the Guidelines for GPP published by the International Society of Pharmacoepidemiology (ISPE) and the laws and regulations of the country in which the research is conducted.

9.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate Consent Forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final Consent Forms approved by the IRB/EC must be provided to the Sponsor for health authority submission purposes according to local requirements.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

By signing the form, the patient confirms that he/she has been informed about the study and agrees to pseudonymous data collection, pooling of data with similar scientific data (if applicable), and the possibility of monitoring activities. It is the responsibility of the physician to obtain written informed consent from each patient participating in the study, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. The physician must also explain that the patient is completely free to refuse to enter the study or to withdraw from it at any time, for any reason and without losing the benefit of any medical care to which the patient is entitled or is presently receiving.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

9.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Lead Scientific Responsible and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Lead Scientific Responsible is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Physicians are also responsible for promptly informing the IRB/EC of any protocol amendments.

In addition to the requirements for collecting all AEs in the eCRF and reporting all suspected ns ADRs (including causality unknown or not provided), AESI, and SAEs to the Sponsor, physicians must comply with requirements for AE reporting to the local health authority and IRB/EC.

9.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in datasets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other national and local health authorities, Sponsor

monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ ADVERSE REACTIONS

10.1 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording SAEs and non-serious AEs (including AESIs), performing safety laboratory assessments, measuring vital signs, and conducting other tests that are deemed critical to the safety evaluation of the study as per standard medical practice. For details of the monitoring and recording of AEs, please see Sections 10.2 and 10.3. Situations requiring safety reporting possibly without an associated AE are outlined in Section 10.3.4.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 10.3.

10.1.1 Adverse Events

According to the International Conference of Harmonisation (ICH), an AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An AE can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 10.2.4.10.
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., electrocardiogram [ECG], X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study medicine.

10.1.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

An SAE is any AE that meets any of the following criteria:

- Is fatal (i.e., the AE actually causes or leads to death)
- Is life-threatening (NOTE: The term “life-threatening” refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires or prolongs inpatient hospitalization (see Section 10.2.4.11)

- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study medicine
- Is a significant medical event in the physician's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE criteria; see Section 10.2.2); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each AE recorded on the eCRF.

SAEs are required to be reported by the physician to the Sponsor immediately (i.e., no more than 24 hours after occurrence of the event; see Section 10.3.1 and Section 10.3.2 for reporting instructions).

10.1.3 Non-Serious Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Non-serious AEs of special interest are required to be reported by the physician to the Sponsor immediately (i.e., no more than 24 hours after occurrence of the event; see Section 10.3.1 and Section 10.3.2 for reporting instructions). AEs of special interest for this study include the following:

- Gastrointestinal (GI) perforation, *abscesses* and fistulae *(any grade)*
- Hypertension ≥ *grade 3*
- Proteinuria ≥ *grade 3*
- Wound healing complication ≥ *grade 3*
- Hemorrhage ≥ *grade 3* (any grade CNS bleeding; ≥ grade 2 haemoptysis)
- Venous thromboembolic events ≥ grade 3
- Arterial thromboembolic events *(any grade)*
- Congestive heart failure ≥ *grade 3*
- Posterior Reversible Encephalopathy Syndrome *(any grade)*
- *Non-GI fistula or abscess* ≥ *grade 2*

In addition to the primary safety variable, guided questionnaires will be completed for the following:

Bevacizumab specific

- *Arterial Thromboembolic Events*

- *Congestive Heart Failure*
- *Interstitial Lung Disease*
- *Osteonecrosis of Jaw*

Non-product specific

- *Drug Induced Liver Injury*
- *Progressive Multifocal Leukoencephalitis*
- *Suspected Transmission of Infectious Agent by Medicinal Product*

10.1.4 Non-Serious Adverse Events other than Adverse Events of Special Interest

All non-serious AEs (in addition to AEs of special interest) will be collected for this study.

Non-serious AEs are required to be reported by the physician to the Sponsor within 30 calendar days (see section 10.3.3 for reporting instructions).

10.2 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The physician is responsible for ensuring that all AEs (see Section 10.1.1 for definition) are recorded on the AE eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 10.3- Section 10.5.

For each AE recorded on the AE eCRF, the physician will make an assessment of seriousness (see Section 10.1.2 for seriousness criteria), severity (see Section 10.2.2), and causality (see Section 10.2.3).

10.2.1 Adverse Event Reporting Period

Adverse Events will be reported for up to 30 days after last dose of bevacizumab. Physicians will seek information on AEs at each patient contact. All AEs subject to the collecting and reporting requirements outlined in this protocol, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the AE eCRF.

Once the patient is enrolled in the study, AEs will be collected until the end of his or her observation period. After this period, the physician is not required to actively monitor patients for AEs but if the treating physician becomes aware of any related AEs to the medicinal product they should be notified to the competent authority in India where the reactions occurred and to the marketing authorization holder of the suspected medicinal product.

10.2.2 Assessment of Severity of Adverse Events

The AE severity grading scale for the NCI CTCAE (v 4.03) will be used for assessing AE severity. The table below will be used for assessing severity for AEs that are not specifically listed in the NCI CTCAE (v 4.03).

Table 1 Adverse Event Severity Grading Scale

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living a
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living b, c
4	Life-threatening consequences or urgent intervention indicated d
5	Death related to AE d

Note: Based on the NCI CTCAE (v 4.03), which can be found at:
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

a Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

b Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

c If an event is assessed as a "significant medical event," it must be reported as an SAE (see Section 10.3.2 for reporting instructions), per the definition of SAE in Section 10.1.2.

d Grade 4 and 5 events must be reported as SAEs (see Section 10.3.2 for reporting instructions), per the definition of SAE in Section 10.1.2.

10.2.3 Assessment of Causality of Adverse Events

Physicians should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to the study medicine, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study medicine
- Course of the event, considering especially the effects of dose reduction, discontinuation of study medicine, or reintroduction of study medicine (when applicable)
- Known association of the event with the study medicine or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

For patients receiving combination therapy, causality will be assessed individually for each of the medicinal product.

10.2.4 Procedures for Recording Adverse Events

Physicians should use correct medical terminology/concepts when recording AEs in the AE section of the eCRF. Colloquialisms and abbreviations should be avoided.

Only one AE term should be recorded in the event field of the eCRF.

10.2.4.1 Infusion-Related Reactions

AEs that occur during or within 24 hours after study medicine administration should be captured as individual signs and symptoms in the AE section of the eCRF rather than an overall diagnosis (e.g., record dyspnea and hypotension as separate events rather than a diagnosis of infusion-related reaction.

10.2.4.2 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded in the AE section of the eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded in the AE section of the eCRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by one AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

10.2.4.3 Adverse Events Occurring Secondary to Other Events

In general, AEs that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary AE that is separated in time from the initiating event should be recorded as an independent event in the AE section of the eCRF. For example:

- *If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.*
- *If vomiting results in severe dehydration, both events should be reported separately on the eCRF.*
- *If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.*
- *If dizziness leads to a fall and subsequent fracture, all three events should be reported separately on the eCRF.*
- *If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.*

All AEs should be recorded separately in the AE section of the eCRF if it is unclear as to whether the events are associated.

10.2.4.4 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once in the AE section of the eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent AE becomes more severe, the most extreme severity should also be recorded in the AE section of the eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after that event became serious; see Section 10.3.1 and Section 10.3.2 for reporting instructions). The AE section of the eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to SAEs.

A recurrent AE is one that resolves between patient evaluations timepoints and subsequently recurs. Each recurrence of an AE should be recorded separately in the AE section of the eCRF.

10.2.4.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an AE. A laboratory test result must be reported as an AE if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the physician's judgment

It is the physician's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5´ the upper limit of normal [ULN] associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded in the AE section of the CRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded in the AE section of the CRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the AE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once in the AE section of the eCRF (see Section 10.2.4.4 for details on recording persistent AEs).

10.2.4.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an AE. A vital sign result must be reported as an AE if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the physician's judgment

It is the physician's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an AE.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded in the AE section of the eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once in the AE section of the eCRF (see Section 10.2.4.4 for details on recording persistent AEs).

10.2.4.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST (>3 ´ the ULN) in combination with either an elevated total bilirubin (>2 ´ the ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, physicians must report as an AE the occurrence of either of the following:

- *Treatment-emergent ALT or AST >3 ´ ULN in combination with total bilirubin >2 ´ the ULN*
- *Treatment-emergent ALT or AST >3 ´ ULN in combination with clinical jaundice*

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded in the AE section of the eCRF (see Section 10.2.4.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after occurrence of the event) either as an SAE or a non-serious AE of special interest (see Section 10.3.1 and Section 10.3.2).

10.2.4.8 Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 10.2.1), regardless of relationship to study medicine, should be classified as serious adverse events (SAEs) must be recorded in the Adverse Events section of the

eCRF and immediately reported to the Sponsor and IEC (see Section 10.3.1 and Section 10.3.2).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Events section of the eCRF. Generally, only one such event should be reported. The term **"sudden death"** should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the AE section of the eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

10.2.4.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions section of the eCRF.

A preexisting medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens during the study. When recording such events in the AE section of the eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

10.2.4.10 Lack of Therapeutic Efficacy or Worsening of Ovarian Cancer

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as AEs. These data will be captured as effectiveness assessment data only. In most cases, the expected pattern of progression will be based on RECIST criteria v1.1. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an AE. This exception from reporting includes events of disease progression with a fatal outcome which are clearly attributable to disease progression.

10.2.4.11 Hospitalization or Prolonged Hospitalization

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE (per the definition of SAE in Section 10.1.2), except as outlined below.

The following hospitalization scenarios are not considered to be SAEs:

- Hospitalization for respite care

- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.
  - The patient has not suffered an AE.
  - Hospitalization solely due to the progression of underlying malignancy should NOT be reported as an SAE.

The following hospitalization scenarios are not considered to be SAEs but should be reported as AEs instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

10.2.4.12 Overdoses, Misuses, Abuses, Off-Label Use, Occupational Exposure, or Medication Error

Any overdose, misuse, abuse, off-label use, occupational exposure, medication error, or any other incorrect administration of medicine under observation should be noted on the Drug Administration section of the eCRF. Any overdose, abuse, misuse, inadvertent/erroneous administration, medication error, or occupational exposure reports must be forwarded to the sponsor with or without an AE.

Reports with or without an AE should be forwarded to the Sponsor as per non-serious timelines. If the associated AE fulfills the seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after the occurrence of the event, see Section 10.3.1 and Section 10.3.2).

For the purpose of reporting cases of suspected adverse reactions, an occupational exposure to a medicine means an exposure to a medicine as a result of one's professional or non-professional occupation.

10.3 REPORTING REQUIREMENTS FROM PHYSICIAN TO SPONSOR

10.3.1 Immediate Reporting Requirements from Physician to Sponsor

Certain events require immediate reporting to allow the Sponsor/Marketing Authorization Holder (MAH) and the regulatory authorities to take appropriate measures to address potential new risks associated with the use of the medicine. The physician must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the occurrence of the event. The following is a list of events that the physician must report to the Sponsor within 24 hours after occurrence or learning of the event, regardless of relationship to study medicine, as per local regulatory requirements:

- SAEs

- Non-serious AEs of special interest Pregnancies

The physician must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Physicians must also comply with local requirements for reporting SAEs to the local health authority and IRB/EC.

10.3.2 Reporting Requirements for Serious Adverse Events and Non-Serious Adverse Events of Special Interest

For reports of SAEs and non-serious AEs of special interest, physicians should record all case details that can be gathered immediately (i.e., within 24 hours) in the AE page of the eCRF and Appendix XI form and submit the report via the EDC system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is temporarily unavailable, please refer to Section 10.6.

10.3.3 Reporting Requirements for Non-Serious Adverse Events

For all non-serious AEs physicians must record all case details that can be gathered within 30 calendar days of learning of the event on the AE section of the eCRF and submit the report via the EDC system. A report will be generated and sent to Roche Safety Risk Management or the relevant MAH (for non-Roche studied products) to allow appropriate reporting to relevant competent authorities.

In the event that the EDC system is temporarily unavailable, please refer to Section 10.6.

Non-serious AEs that are suspected to be related only to medicinal products other than the studied medicine should be reported by the physician/consumer to the marketing authorization holder of the suspected medicinal product, or to the concerned competent authorities via the national spontaneous reporting system.

10.3.4 Reporting Requirements for Pregnancies/Breastfeeding

10.3.4.1 Pregnancies/Breastfeeding in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the physician if they become pregnant during the study or within 3 months after the last dose of medicine. A Pregnancy Report eCRF (if available) should be completed by the physician immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. A pregnancy report will automatically be generated and

sent to Roche Safety Risk Management. Pregnancy should not be recorded on the AE eCRF. The physician should discontinue the medicine andcounsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any SAEs associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the AE section of the eCRF.

In the event that the EDC system is temporarily unavailable, please refer to Section 10.6.

Suspected adverse reactions that occur in infants following exposure to a medicinal product from breast milk should be reported to Roche Safety Risk Management.

10.3.4.2 Abortions

Any abortion should be classified as an SAE (as the Sponsor considers abortions to be medically significant), recorded in the AE section of the eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after occurrence of the event; see Section 10.3.1 and Section 10.3.2).

10.3.4.3 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a patient exposed to the medicine should be classified as an SAE, recorded in the AE section of the CRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after occurrence of the event; see Section 10.3.1 and Section 10.3.2).

10.4 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

10.4.1 Physician Follow-Up

The physician should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the physician, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all SAEs considered to be related to study medicine or trial-related procedures until a final outcome can be reported.

During the study period, resolution of AEs (with dates) should be documented in the AE section of the eCRF and in the patient's medical record to facilitate SDV.

All pregnancies reported during the study should be followed until pregnancy outcome. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section 10.6.

10.4.2 Sponsor Follow-Up

For SAEs, non-serious AESIs, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant

reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

10.5 EXPEDITED REPORTING TO HEALTH AUTHORITIES, PHYSICIANS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all SAEs and non-serious AESIs against cumulative product experience to identify and expeditiously communicate possible new safety findings to physicians, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single AE cases, the Sponsor will assess the expectedness of these events using the following reference document:

- Local prescribing information for bevacizumab

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the physician's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

Certain AEs are anticipated to occur in the study population at some frequency independent of exposure to the drug under observation and will be excluded from expedited reporting.

10.6 IF EDC SYSTEM IS TEMPORARILY UNAVAILABLE OR NOT USED

In the event that the EDC system is temporarily unavailable, a completed paper reporting form Appendix XI format, and fax coversheet should be faxed/scanned to Roche Safety Risk Management or its designee immediately (i.e., no more than 24 hours after the occurrence of the event) or within 30 days for non-serious AEs if not AESIs, using the fax number or email address provided to physicians.

In the event that the EDC system is temporarily unavailable the Clinical Trial Pregnancy Reporting Form provided to physicians should be completed and submitted to Roche or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy). The contact information for submission is as follows:

Drug Safety

Telephone No.: [redacted]

Direct: [redacted]

Fax: [redacted]

E-mail: [redacted]

Once the system is available again, all information should additionally be entered and submitted via the EDC system.

11. PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf

The results of this study may be published or presented at scientific meetings. If this is foreseen, the physician must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the physician.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating physician will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors' authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the physician and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

12. REFERENCES

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Appendix 1
List of Stand-Alone Documents Not Included in the Protocol

- List of contact details of responsible parties and all physicians
- FIGO Staging
- RECIST (v 1.1) Criteria
- NCI-CTCAE (V 4.03)
- ECOG PS

Appendix 2
Data Collection Overview (as per Standard of Care)

In the routine care setting patients are seen regularly by their treating physicians either for treatment or for regular assessment after treatment. Thus no study specific visits or evaluations are required by this protocol either before or after start of medicinal product

[a] Written informed consent must be obtained before any data collection.

	Screening	**Treatment cycles (each cycle = 3 weeks)**									**Completion/Early Termination Visit** [b]	**Follow-Up** [c]
	At any time after bevacizumab is prescribed and Informed consent is taken/treatment is ongoing and Informed Consent is taken but before recording data/entering data	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9***		
Informed consent	x											
Demographic data	x											
General medical history and baseline conditions	x											
Vital signs [d]	x										x	
Weight	x	x	x	x	x	x	x	x	x	x	x	x
Height	x											
Physical examination [e]	x										x	
Hematology [f]	x	x	x	x	x	x	x	x	x	x	x	
Biochemistry [g]	x	x	x	x	x	x	x	x	x	x	x	

Treatment administration	x	x	x	x	x	x	x	x	x	x		
Response assessment	x			x			x			x		
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	
Adverse events (After ICF is signed)	x	x	x	x	x	x	x	x	x	x	x	x

Notes:

[a] No visit is specified by the protocol as it is an NIS.

[b] Patients who complete the study or discontinue from the study early will be followed up for AEs and survival. Adverse events will be collected for up to 30 days after last dose of bevacizumab treatment.

[c] Follow-up information will be collected via telephone calls and/or clinic visits (only if they happen during the normal course of treatment) until death, loss to follow-up, or study termination by the Sponsor.

[d] Respiratory rate, pulse rate, systolic and diastolic blood pressure while the patient is in a seated position *(whatever data is available in the medical records)*

[e] Any abnormalities present in medical records at baseline on the General Medical History and Baseline Conditions would be recorded only if available from medical records. New or worsening abnormalities should be recorded on the Adverse Event section.

[f] Includes the following data as available in medical records [hemoglobin, hematocrit, platelet count, RBC count, WBC count, absolute differential count (neutrophils, eosinophils, lymphocytes, monocytes, basophils, other cells)].

[g] Includes the following data as and whatever available in the medical records (sodium, potassium, chloride, bicarbonate, fasting glucose, Blood urea nitrogen or urea, creatinine, calcium, total and direct bilirubin, total protein, albumin, alanine transaminase, aspartate aminotransferase, alkaline phosphatase, phosphorus, magnesium, lactate dehydrogenase, creatine phosphokinase, uric acid).

* Treatment may continue post 9 cycles