GSK Vaccines Controlled Document

Documentum Name : EBOLA Z CHAD3-004 (202090) SAP Interim - Final (with wet ink sign-off)

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STATISTICAL ANALYSIS PLAN

202090 (EBOLA Z CHAD3-004)

A PHASE 2, RANDOMISED, OBSERVER-BLIND, CONTROLLED, MULTI-COUNTRY STUDY TO ASSESS THE SAFETY AND IMMUNOGENICITY OF A SINGLE INTRAMUSCULAR DOSE OF GSK BIOLOGICALS' INVESTIGATIONAL RECOMBINANT CHIMPANZEE ADENOVIRUS TYPE 3-VECTORED EBOLA ZAIRE VACCINE (CHAD3-EBO-Z) (GSK3390107A), IN CHILDREN 1 TO 17 YEARS OF AGE IN AFRICA

AUTHOR: PPD

VERSION NUMBER AND DATE: 1.0 18APR2016

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V1.0 (Dated 18APR2016 for Protocol 202090 (EBOLA Z CHAD3-004).

	Name	Signature	Date (DDMMMYYYY)
Author:	[redacted]		28APR2016
Position:	Statistical Team Lead		
Company:	Quintiles		

Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the interim and final analysis of this study.

	Name	Signature	Date (DDMMMYYYY)
Approved By:	[redacted]	[redacted]	21 APR 2016
Position:	Statistician		
Company:	GSK		
Approved By:	[redacted]	[redacted]	27 APR 2016
Position:	Clinical Research & Development Lead (CRDL)		
Company:	GSK		


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MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorised Version
1.0	18APR2016	PPD	Not Applicable – First Version

TABLE OF CONTENTS

1. INTRODUCTION

This document describes the rules and conventions that will be used in the planned presentation and analysis of safety and immunology data for Protocol 202090 (EBOLA Z CHAD3-004) as set out in the latest version of the interim and final analysis table, listing and figure (TLF) shells. It describes the data that will be summarised and analysed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on:

- Amendment 2 Final version of the protocol, dated 06MAY2015.
- Addendum Ghana, dated 07AUG2015.
- Latest version of the analysis cohort assignment documentation.

This version of the SAP is focused on the safety and immunology data for the unblinded interim analysis as well as the final analysis.

2. STUDY OBJECTIVES AND ENDPOINTS

The following relates to the overall study objectives as described in Section 2: Objectives, of the protocol, as well as the overall study endpoints as described in Section 11: Statistical Methods, of the protocol.

2.1. PRIMARY OBJECTIVE AND ENDPOINTS

2.1.1. PRIMARY OBJECTIVE

The primary objective is to assess the safety and reactogenicity of a single intramuscular dose of the ChAd3-EBO-Z vaccine:

- Overall.
- Separately in children aged:
  - 1 to 5 years.
  - 6 to 12 years.
  - 13 to 17 years.

2.1.2. PRIMARY ENDPOINTS

- Occurrence of each solicited local and general adverse event (AE), during a 7-day follow-up period after each vaccination (that is, the day of vaccination and 6 subsequent days), in all subjects, in both groups.
- Occurrence of any unsolicited AE, during a 30-day follow-up period after each vaccination (that is, the day of vaccination and 29 subsequent days), in all subjects, in both groups.
- Occurrence of haematological (complete blood count [CBC], including differential count and platelet count) and biochemical (alanine aminotransferase [ALT], creatinine) laboratory abnormalities at Screening, Day 3, Day 6, Day 30, Month 6, Month 6 + 6 days, Month 6 + 30 days and Month 12 in all subjects, in both groups.
- Occurrence of clinical symptoms of thrombocytopenia (AE of specific interest), during a 7-day follow-up period after vaccination at Day 0 (that is, Day 0 up to Day 6), in all subjects, in both groups.
- Occurrence of any serious adverse event (SAE), in all subjects, in both groups.

2.2. SECONDARY OBJECTIVE AND ENDPOINTS

2.2.1. SECONDARY OBJECTIVE

The secondary objective is to assess the humoral immunogenicity of a single intramuscular dose of the ChAd3EBO-Z vaccine, in terms of anti-glycoprotein (GP) Ebola Virus Zaire (EBOV) antibody responses:

- Overall.
- Separately in children aged:
  - 1 to 5 years.
  - 6 to 12 years.
  - 13 to 17 years.

2.2.2. SECONDARY ENDPOINT

- Anti-GP EBOV antibody concentrations, as measured by enzyme-linked immunosorbent assay (ELISA):
  - At Day 0 and Day 30, in all subjects, in both groups.
  - At Month 6 and Month 6 + 30 days, in all subjects in the Group MENACWY-TT/EBO-Z.

2.3. TERTIARY OBJECTIVES AND ENDPOINTS

2.3.1. TERTIARY OBJECTIVES

The exploratory objectives are:

- To assess the persistence of the humoral immune response induced by a single intramuscular dose of the ChAd3-EBO-Z vaccine, in terms of anti-GP EBOV antibody responses:
  - Overall.
  - Separately in children aged:
    - 1 to 5 years.
    - 6 to 12 years.
    - 13 to 17 years.
- To assess EBOV-specific cell-mediated immunity (CMI) of a single intramuscular dose of the ChAd3-EBO-Z vaccine:

- Overall.
- Separately in children aged:
  - 1 to 5 years.
  - 6 to 12 years.
  - 13 to 17 years.

- To assess the pre-existing immunity to the ChAd3 virus vaccine vector prior vaccination, ChAd3-specific immune responses after vaccination and explore its potential impact on Ebola-specific immune responses:
  - Overall.
  - Separately in children aged:
    - 1 to 5 years.
    - 6 to 12 years.
    - 13 to 17 years.

- If deemed necessary, to further characterise the immune response to/the safety profile of the investigational ChAd3-EBO-Z vaccine.

2.3.2. TERTIARY ENDPOINTS

- Anti-GP EBOV antibody concentrations, as measured by ELISA:
  - At Month 6 and Month 6 + 30 days, in all subjects, in the Group EBO-Z/MENAWY-TT. o At Month 12, in all subjects, in both groups.

- Magnitude, responder rate and cytokine co-expression profile of ChAd3-EBO Z-specific CD4+ or CD8+ T-cell responses, as assessed by intracellular cytokine staining (ICS) after stimulation with EBOV GP antigens:
  - At Day 0, Day 30, Month 6, Month 6 + 30 days and Month 12, in a sub-cohort of 30 subjects per age stratum, per group.

- ChAd3 neutralising antibody titres, as measured by a neutralisation assay:
  - At Day 0, Day 30 Month 6 and Month 6 + 30 days, in a subset of 30 subjects per age stratum, per group.

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

A phase 2, randomised, observer-blind, controlled, multi-country study with two groups and three age strata as described below in Table 1: Treatment Groups:

Table 1: Treatment Groups

Treatment Group	Age Stratum	Number of Subjects	Treatment Name	
			Day 0	Month 6
EBO-Z/MENACWY-TT	13 to 17 years	~100	ChAd3-EBO-Z	Nimenrix
	6 to 12 years	~100		
	1 to 5 years	~100		
	Total	~300		
MENACWY-TT/EBO-Z	13 to 17 years	~100	Nimenrix	ChAd3-EBO-Z
	6 to 12 years	~100		
	1 to 5 years	~100		
	Total	~300		

Randomised subjects will be followed for approximately 12 months from the Day 0 visit. Subjects will be randomised 1:1 to the two treatment groups. The randomisation will utilise stratification by age so that an equal number of children are randomised in each age stratum:

- 1 to 5 years.
- 6 to 12 years.
- 13 to 17 years.

In addition, the randomisation will utilise a minimisation procedure to account for the following factors:

- Gender.
- Centre (refer to Section 7.2: Multicentre Studies for details).

The study will have the following blinding implemented:

- Observer-blind:

- From study start until the interim analysis (refer to Section 4.2: Interim Analysis for additional information).

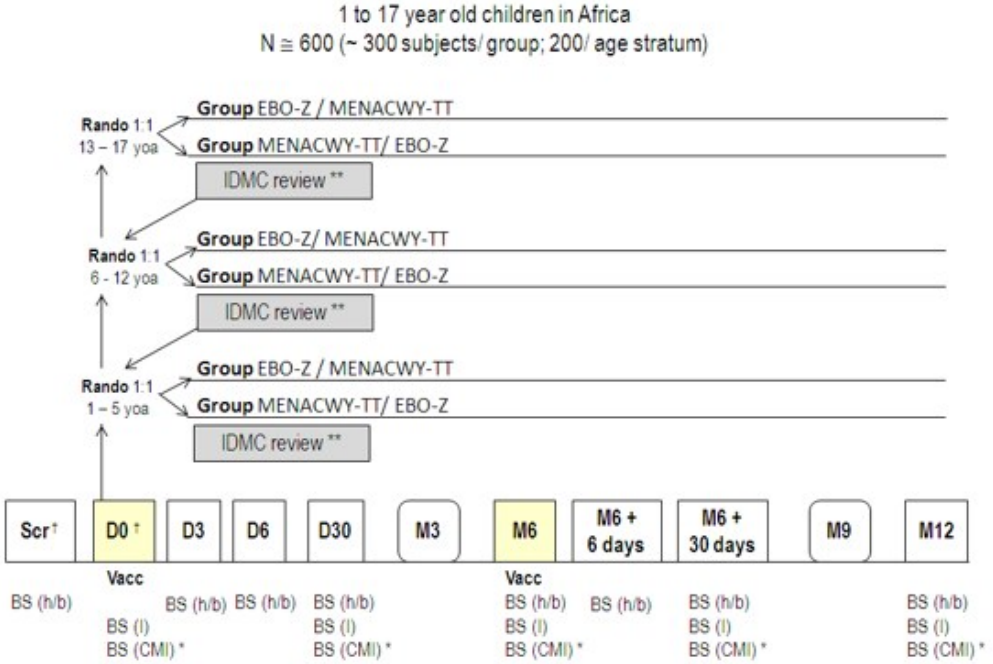
- Single-blind: o From the interim analysis.

Additionally, a sub-selection of subjects will be enrolled into a sub-cohort:

- Sub-cohort for CMI, refer to Section 5.5.1: Sub-cohort for Cell-mediated Immunity (CMI for additional information.

The study design is presented below in Figure 1: Study Design Overview.

Figure 1: Study Design Overview



Rando = randomisation; **yoa** = years of age; **Scr** = Screening; **D** = Day; **M** = Month; **BS (h/b)** = blood sample for haematology/ biochemistry parameters; **BS (I)** = blood sample for humoral immunity; **BS (CMI)** = blood sample for cell-mediated immunity.
Squares indicate visits to the vaccination centre. Rounded rectangles indicate study contacts (home visit or phone call).
Yellow-coloured visits indicate vaccination visits. At the Day 0 visit, subjects in the Group EBO-Z/ MENACWY-TT receive the investigational ChAd3-EBO-Z vaccine and subjects in Group MENACWY-TT/ EBO-Z receive *Nimenrix*. At the Month 6 visit, subjects in Group EBO-Z/ MENACWY-TT receive *Nimenrix* and subjects in the Group MENACWY-TT/ EBO-Z receive the investigational ChAd3-EBO-Z vaccine.
Subjects will be followed-up for adverse events (AEs) on a daily basis during the 7-day follow-up period after vaccination (day 0 to 6). During this period, AEs will be recorded on a Diary Card. On those days that no study visit is planned, a home visit will be scheduled.
† The Screening Visit and the Day 0 visit may take place on the same day (allowed interval 0 - 30 days).
* Only for subjects in the sub-cohort for CMI.
** IDMC review on all available safety data, which will include the safety data up to 7 days after vaccination at Day 0, from at least 50 children (25 per group) in an age stratum before proceeding to vaccination in the next (younger) age stratum (if applicable).

3.2. SCHEDULE OF EVENTS

Refer to Figure 1: Study Design Overview in the protocol, as well as Table 5: List of Study Procedures during Visits to the Vaccination Centre in the protocol.

3.3. CHANGES TO ANALYSIS FROM PROTOCOL

To be completed for the final analysis.

4. PLANNED ANALYSES

The following analyses are planned for this study:

- Independent Data Monitoring Committee (IDMC) analyses.
- Interim Analysis.
- Final Analysis.

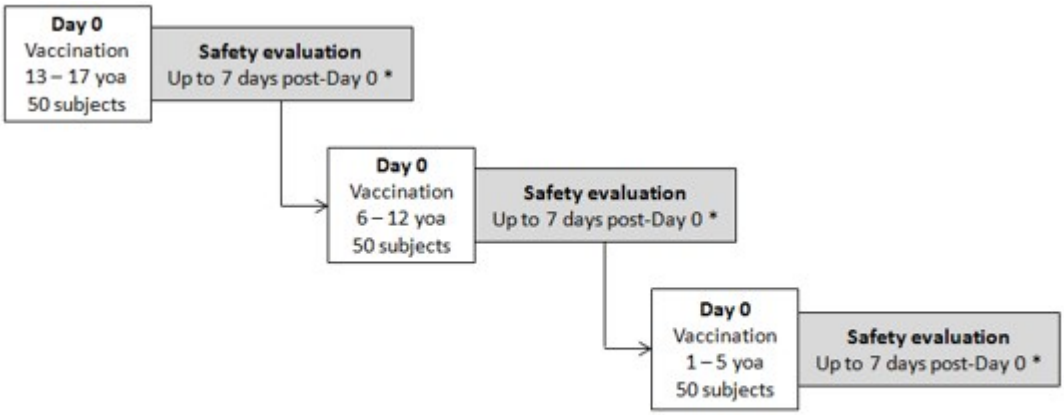
4.1. INDEPENDENT DATA MONITORING COMMITTEE (IDMC)

Unblinded IDMC analyses are planned for this study in order to ensure subject safety and monitor tolerability of the investigational vaccine. The IDMC will review safety and reactogenicity data from the current study as well as data from the EBOLA-Z ChAd3-005 study, which will be conducted in parallel with the current study.

Study vaccinations in this study will only start after a favourable outcome of an IDMC review of the safety and reactogenicity data from 100 adults after a 1-week follow-up in the EBOLA-Z ChAd3-005 study. In addition, vaccination at Day 0 will be done in a staggered manner, starting with the children in the oldest age stratum (13 to 17 years). For each age stratum, the IDMC will conduct a review of all available safety data once data is available up to at least 7 days after vaccination of at least 50 subjects, in that age stratum.

In order to proceed to vaccination of the subjects in the younger age stratum (6 to 12 years), a favourable outcome of the IDMC review of safety data up to at least 7 days after vaccination from at least 50 subjects (25 subjects per treatment group) in the oldest age stratum needs to be obtained. The same will be done for moving from the 6 to 12 years age stratum to vaccination of the youngest children (1 to 5 years). Refer to Figure 2: Overview of Staggered Design and Independent Data Monitoring Committee (IDMC) Safety Evaluations below for a description of the staggered approach per age stratum.

Figure 2: Overview of Staggered Design and Independent Data Monitoring Committee (IDMC) Safety Evaluations



* Safety evaluation on all available safety data from the entire study, which will include the safety data up to 7 days after vaccination at Day 0 from at least 50 subjects (25 subjects/ group) in the respective age stratum.

For the unblinded IDMC analyses the Quintiles Biostatistics blinded team will produce all the required programs and blinded outputs. These programs and outputs will be transferred to the Quintiles Biostatistics unblinded team. The Quintiles Biostatistics unblinded team will reproduce all outputs based on the actual randomisation schedule and will then be responsible for providing the unblinded outputs to the IDMC members as specified in the latest version of the Biostatistics Blinded to Unblinded Team Handover Document (CS_TP_BS0214) for the EBO-Z CHAD3-004 study. Refer to the latest version of the unblinding plan for additional details with regard to the handling of unblinded information.

A separate set of IDMC TLF shells (latest version of EBO-Z_CHAD3_IDMC_Shells) has been created specifically for the IDMC analyses. In addition, the IDMC charter can be referenced for additional information regarding the IDMC analyses.

4.2. INTERIM ANALYSIS

An unblinded interim analysis will be conducted when safety and immunology data up to Day 30 have been collected for all subjects. All available safety and immunogenicity data in the interim analysis transfer will be included in the interim analysis. As per protocol, the blinded team will be unblinded at the time of the interim analysis and will produce the unblinded interim analysis TLFs.

The cleaning of the 30-day safety data for each subject will be scheduled to be completed prior to the unblinding in order to keep the blind during data cleaning activities.

The interim analysis is planned once the following has been completed:

- GSK's authorization of the following:
  - o SAP. o Relevant TLF shells. o Analysis cohort assignments.

- Immunogenicity data availability:
  - At least the Day 30 anti-GP EBOV data should be available.
- Interim analysis data transfer from Data Management.

The interim analysis data transfer should comply with:

- All the data up to Day 30 is clean:
  - All outstanding data issues and queries resolved. o All unresolvable data issues documented in the Data Handling Report (DHR), a separate document produced by Data Management.
  - All coding, for example AEs, is completed. o All reconciliation of vendor data with eSource data completed successfully.
- Any additional data post-Day 30 should be as clean as possible.

4.3. FINAL ANALYSIS

All final, planned analyses identified in this SAP and relevant set of TLF shells will be performed by the Quintiles Biostatistics blinded team. The final analysis is planned for when all subjects had completed study participation, following:

- GSK's authorization of the following:
  - Final version of the SAP.
  - Relevant set of TLF shells. o Analysis cohort assignments.
- Final database lock.
- All immunology data are available.

The final analysis will be performed on a clean database transfer:

- All outstanding data issues and queries were resolved.
- All unresolvable data issues documented in the DHR, a separate document produced by Data Management.
- All coding, for example AEs, is completed.
- All reconciliation of vendor data with eSource data completed successfully.

5. ANALYSIS COHORTS

GSK's authorization of the analysis cohort assignments is required at two time points:

- Prior to the interim analysis: Interim analysis cohort authorization.
- Prior to the final analysis: Final analysis cohort authorization:
  - Prior to the final analysis there will only be a review of the interim analysis cohort assignments as a confirmation of the inclusion of all subjects in the relevant analysis cohorts.

Refer to the relevant analysis cohort assignment documentation (latest version of CHAD3-004-EBO-Z_Cohort_Assignment_Plan) for additional information.

5.1. TOTAL ENROLLED COHORT

The Total Enrolled Cohort is defined as all subjects who signed informed consent, regardless of being randomised to either:

- EBO-Z/MENACWY-TT.
- MENACWY-TT/EBO-Z.

The Total Enrolled Cohort will be programmatically derived based on the informed consent information recorded on the Screening form in eSource.

5.2. TOTAL RANDOMISED COHORT

The Total Randomised Cohort is defined as all subjects who were randomised to either EBO-Z/MENACWY-TT or MENACWY-TT/EBO-Z, regardless of whether they received a vaccination.

A subject will be programmatically included in the Total Randomised Cohort if the subject had been randomised based on the treatment allocation information recorded on the Visit Day 0 form in eSource or reported in the Interactive Web Randomisation System (IWRS).

For analyses and presentations based on the Total Randomised Cohort, subjects are to be analysed according to the treatment allocated regardless of the treatment received.

5.3. TOTAL VACCINATED COHORT (TVC)

The Total Vaccinated Cohort (TVC) is defined as all subjects included in the Total Randomised Cohort who received at least one vaccination. The TVC is defined separately for safety and immunogenicity analyses as described below:

- Safety Analysis:
  - A subject is to be programmatically included in the TVC if the subject has at least one date of vaccination available in the database.
  - Labelled as 'Total Vaccinated Cohort' in relevant TLF shells.
- Immunogenicity Analysis:
  - Immunogenicity analysis based on the TVC will include all vaccinated subjects for whom immunogenicity results are available, however, due to the fact that only subjects with data available are to be included per time point for the immunogenicity analysis, there will be no additional elimination required. The TVC for safety and immunogenicity analyses are defined as the same cohort of subjects.

Subjects who received a different treatment to that allocated are to be analysed as described below:

- Analyse subject according to the treatment received at Day 0 (first vaccination).

5.4. ACCORDING-TO-PROTOCOL COHORT (ATP)

The According-to-protocol (ATP) Cohort is defined as all evaluable subjects satisfying the following:

- Meet all eligibility criteria.
- Received at least one dose of study vaccine according to protocol procedures and randomisation.
- Randomisation code has not been broken for vaccination at Day 0.
- Comply with the procedures and intervals defined in the protocol.
- Did not receive a concomitant medication/product/vaccination leading to elimination from an ATP analysis (refer to relevant section in the protocol, Section 6.7.2).
- Did not present with a medical condition leading to elimination from an ATP analysis (refer to the relevant section in the protocol, Section 6.8).
- Data concerning immunogenicity endpoint measurements are available.

The ATP Cohort will be used for immunogenicity analyses and will be defined prior to:

- Planned Interim Analysis based on the elimination code process.

Subjects included in the ATP Cohort did not receive a different treatment to that allocated, therefore the analysis would be the same for subjects whether based on the randomised or allocated treatment.

5.5. SUB-COHORTS AND SUBSETS OF SUBJECTS

5.5.1. SUB-COHORT FOR CELL-MEDIATED IMMUNITY (CMI)

The first approximately 30 subjects randomised per age stratum and group, (180 subjects in total, 90 per group)

will be included in this sub-cohort. Subjects will be included from selected centres (refer to Section 7.2: Multicentre Studies) only. A blood sample for assessment of CMI should be taken from the subjects at the following visits:

- Day 0.
- Day 30.
- Month 6.
- Month 6 + 30 days.
- Month 12.

This sub-cohort will be programmatically assigned based on the relevant treatment allocation information recorded on the Visit Day 0 form in eSource. This sub-cohort will be labelled as the CMI Sub-cohort in the relevant presentations.

5.5.2. SUBSET FOR ADDITIONAL TESTING

A subset of the subjects will have additional humoral immunogenicity assays performed. These will be the same subjects as the subjects in the sub-cohort for CMI. These subjects will have the neutralizing antibodies assays performed. Other subjects will have the same samples available, however these samples will be used for other testing and not analysed within this protocol. This subset will be labelled as the Subset for Additional Testing in the relevant presentations.

6. GENERAL CONSIDERATIONS

6.1. REFERENCE START DATE AND RELATIVE DAY

Reference start date is defined as the date of first vaccination, and equals the Day 0 date. Relative day is calculated relative to the reference start date and is to be used to show start and stop day of an assessment or event. Relative day is calculated as follows:

- Relative day = (date of assessment/event – reference start date).

Unless otherwise specified, if the date of the assessment/event is partial or missing, relative day and any corresponding durations will not calculated and will be presented as missing in the listings. Imputed AE dates will be used in order to assign the AEs as either within or outside the relevant collection period and will not be used to calculate an imputed relative day (refer to APPENDIX 2: Partial Date Conventions).

Some presentations might include the relative day relative to the most recent vaccination (refer to Section 6.7.2: Most Recent Vaccination) and will be calculated as follows:

- If the date of the assessment/event is on or after the most recent vaccination:
  - Relative day to most recent vaccination = (date of event – date of most recent vaccination).

6.2. BASELINE

Unless otherwise specified, Baseline is defined as the last non-missing assessment (scheduled or unscheduled) prior to the first vaccination. In the case where the last non-missing assessment and the reference start date coincide, that assessment will be considered pre-baseline (unless specified as post-vaccination). However, adverse events (AEs) starting on the reference start date will be considered post-baseline.

6.3. DERIVED TIME POINTS

6.3.1. CHAD3-EBO-Z POST-VACCINATION TIME POINTS

As a first step, safety and/or immunogenicity results will be presented by treatment administered at Day 0.

In a second step, all available data post-vaccination with the investigational vaccine (Day 0 for the EBOZ/MENACWY-TT and Month 6 for the MENACWY-TT/EBO-Z treatment groups, respectively) will be pooled. All available safety and immunogenicity data following the ChAd3-EBO-Z vaccination in both the treatment groups will be pooled at the time points as specified in Table 2: Derivation of ChAd3-EBO-Z Post-vaccination Time Points:

Table 2: Derivation of ChAd3-EBO-Z Post-vaccination Time Points

ChAd3-EBO-Z Post-vaccination Time Point	Treatment Group	Visit
0 Days Post-vaccination with EBO-Z	EBO-Z/MENACWY-TT	Day 0
	MENACWY-TT/EBO-Z	Month 6
6 Days Post-vaccination with EBO-Z	EBO-Z/MENACWY-TT	Day 6

	MENACWY-TT/EBO-Z	Month 6 + 6 Days
30 Days Post-vaccination with EBO-Z	EBO-Z/MENACWY-TT	Day 30
	MENACWY-TT/EBO-Z	Month 6 + 30 Days
3 Months Post-vaccination with EBO-Z	EBO-Z/MENACWY-TT	Month 3
	MENACWY-TT/EBO-Z	Month 9
6 Months Post-vaccination with EBO-Z	EBO-Z/MENACWY-TT	Month 6
	MENACWY-TT/EBO-Z	Month 12

6.4. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

In general, for by-visit summaries, data recorded at the scheduled visit will be presented. Unscheduled assessments will not be included in by-visit summaries, but may contribute to the Baseline value.

In the case of a retest (same visit number assigned), the latest available test result as provided in the data transfer for that visit/time point will be used for by-visit summaries.

Listings will include scheduled and unscheduled assessments.

6.5. WINDOWING CONVENTIONS

No visit windowing will be performed for this study.

6.6. STATISTICAL TESTS

Unless otherwise specified, the default summary statistics will be the following:

- Quantitative variables:
  - Number of subjects in each category (n).
    - Mean.
  - Standard deviation (SD). o Median. o Minimum. o Maximum. o First quartile (Q1). o Third quartile (Q3).

- In case of log-transformed data for quantitative variables, the default summary statistics are to be as follows:
  - Number of subjects in each category (n).
    - Geometric mean. o Geometric SD.
  - Median. o Minimum. o Maximum. o Q1. o Q3.
- Qualitative variables:
  - Number of subjects in each category (n). o The percentage of subjects in each category (%) can be presented relative to either one of the following:
    - The total number of subjects in the relevant analysis cohort (and sub-cohort).
    - The total number of subjects in the relevant analysis cohort (and sub-cohort), with assessments available (observed cases).
    - Total number of subjects in the relevant analysis cohort with returned diary cards.
  - In the event of missing assessments, a 'Missing' category showing the number of subjects with missing assessments will be presented. Percentage of subjects with missing data will not be presented.

6.7. COMMON CALCULATIONS

6.7.1. CHANGE FROM BASELINE

For quantitative measurements, change from Baseline will be calculated as:

- Change from Baseline at Day x = (Result at Day x – Baseline Result).

If a result/value is missing, the change from Baseline will be presented as missing in the listing; hence no imputation for a missing change from Baseline will be performed.

6.7.2. MOST RECENT VACCINATION

Most recent vaccination prior to assessment/event:

- Calculate the difference in the assessment/start date and all available vaccination dates.

- Assessments: Days since vaccination (Day 0/Month 6) = (Assessment date – vaccination date [Day 0/Month 6]).
- Events: Days since vaccination (Day 0/Month 6) = (Event start date – vaccination date [Day 0/Month 6]).

- For previous calculation (difference in assess/start date and available vaccination dates), only consider those vaccinations where the days since vaccination is >= 0 and determine the vaccination (Day 0/Month 6) for which the days since vaccination (as calculated in the previous step) is a minimum.
- Assign the vaccination selected in the previous step (minimum days since vaccination determination) as the most recent.

6.7.3. DURATION

- Duration = End Date/Day – Start Date/Day + 1.
- The start and end date/days are defined in each of the relevant sections where the duration calculation is required.

6.8. SOFTWARE VERSION

All analyses will be conducted using SAS version 9.4.

7. STATISTICAL CONSIDERATIONS

7.1. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

Not applicable.

7.2. MULTICENTRE STUDIES

This study will be conducted by more than one investigators at more than one centre internationally. Among others, centre will be accounted for in the randomisation minimisation procedure. The following centres are included in this study:

Table 3: Study Centres

Country	Centre Number	Investigator	CMI Sub-cohort Enrolment (Yes/No)
Mali	P P	Prof Samba Sow	Yes
Senegal	P P	Prof Cheikh Ndour	Yes

All centres will be pooled in all analyses.

7.3. MISSING DATA

Missing safety data will not be imputed. For handling of partial or missing AE start dates, refer to Section APPENDIX 2: Partial Date Conventions.

7.4. MULTIPLE COMPARISONS/ MULTIPLICITY

Not applicable, the study does not include any confirmatory objectives. All analyses are descriptive.

7.5. EXAMINATION OF SUBGROUPS

No subgroup analyses will be performed for this study.

8. OUTPUT PRESENTATIONS

APPENDIX 1: Programming Conventions for Outputs describes the conventions for presentation of data in outputs.

The TLF shells provided together with this SAP describe the presentations for the interim/final analysis and therefore the format and content of the TLFs to be provided by Quintiles Biostatistics.

Note that verbatim terms, specifications (for example the reason a specific assessment was not done) and all variables in the TLF shells that contain the suffix (eSource) contain verbatim text that may include spelling mistakes. Verbatim text is to be presented in the listings 'as is' and no manual 'hard-coding' corrections of such data are to be made.

9. DISPOSITION AND WITHDRAWALS

All subjects who provide informed consent will be accounted for in this study.

Subject disposition and withdrawals will be presented for the Total Enrolled Cohort or Total Randomised Cohort, as indicated below.

The following listings are planned for presentation:

- Subject disposition (Total Enrolled Cohort).
- Protocol violations (Total Enrolled Cohort).
- Inclusion and/or exclusion criteria exceptions (Total Enrolled Cohort).
- Analysis cohorts (Total Enrolled Cohort).

The following tables are planned for presentation:

- Subject enrolment and primary reason for screen failures (Total Enrolled Cohort).
- Subject disposition and primary reason for premature study withdrawal (Total Randomised Cohort as well as Total Vaccinated Cohort).
- Major protocol violations (Total Randomised Cohort).
- Analysis cohorts (Total Enrolled Cohort).

The following disposition variable, as presented in the planned TLF shells, will be collected on the Informed Consent form in eSource:

- Informed consent/assent date and time.

The following disposition variables, as presented in the planned TLF shells, will be collected on the Treatment Allocation and Vaccination form in eSource:

- No-sub-cohort:
  - o Yes.
- Sub-cohort for CMI:
  - o Yes.
- Randomised: o Yes. o No.

The following disposition variables, as presented in the planned TLF shells, will be collected on the Screening Conclusion form in eSource:

- Is the subject a screening failure:
  - o Yes. o No.

- Primary reason for screen failure:
  - o Eligibility criteria not fulfilled. o Protocol violation, specify. o Serious adverse event (SAE): o Related to study participation or GSK concurrent medication. o Not related to study participation or GSK concurrent medication, specify. o Consent withdrawal (not due to SAE). o Migrated/moved from the study area. o Lost to follow-up. o Other, specify.
- Date of screening conclusion completion.

The following disposition variables, as presented in the planned TLF shells, will be collected on the Study Conclusion form in eSource:

- Did the subject complete all study related visits:
  - o Yes. o No.
- Primary reason for premature study withdrawal:
  - o SAE/AE. o Protocol violation, specify.
  - o Consent withdrawal (not due to an AE). o Moved from the study area. o Lost to follow-up. o Other, specify.
- Date of study conclusion completion.

The following disposition variable, as presented in the planned TLF shells, will be collected on the Emergency Unblinding form in eSource:

- Date and time of emergency unblinding.

The following eligibility criteria variables, as presented in the planned TLF shells, will be collected on the Eligibility Criteria form in eSource:

- Criterion category:

- o Inclusion. o Exclusion.

- Criterion number.
- Criterion met:
  - o Yes. o No. o Not done.

The following protocol deviation variables, as presented in the planned TLF shells, will be collected in Clinical Trial Management System (CTMS) and provided by the project manager:

- Protocol deviation type.
- Protocol deviation description.
- Date of protocol deviation.
- Protocol deviation severity.

The following variables, as presented in the planned TLF shells, will be imported from an EXCEL spreadsheet created for review of each analysis cohort assignment and as authorised by GSK (refer to Section 5: Analysis Cohorts):

- Included in analysis cohort (Yes/No):
  - o Total Enrolled Cohort. o Total Randomised Cohort. o Total Vaccinated Cohort. o According-to-protocol Cohort.
- Reason(s) for exclusion from each analysis cohort.

9.1. DERIVATIONS

Based on the aforementioned variables the following variables, as presented in the planned TLF shells, will be derived:

- Reason not randomised:
  - o Assigned as the primary reason for screen failure.
- Emergency unblinding (Yes/No):
  - o Yes: If the date of emergency unblinding is reported. o No: If the date of emergency unblinding is not reported.

- Subject ongoing in the study (only applicable to the interim analysis):
  - Yes: Screening completed and study conclusion information not completed at the time of data transfer for analysis.
- Relative day:
  - Calculated relative to Day 0 vaccination (refer to Section 6.1: Reference Start Date and Relative Day).

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the Total Enrolled Cohort for the listings.

No statistical testing will be performed for demographic or other Baseline characteristics.

The following listing is planned for presentation:

- Demographics and other Baseline characteristics.

The following tables are planned for presentation:

- Demographics and other Baseline characteristics (Total Vaccinated Cohort).
  - This table will also be repeated for the following:
    - CMI sub-cohort.
    - According to Protocol Cohort.
    - According to Protocol Cohort and CMI sub-cohort.
- Number of subjects by country (Total Enrolled Cohort).
- Number of subjects by age category:
  - Toddler (1-2 years). o Early childhood (3-5 years). o Middle childhood (6-11 years).
  - Early adolescence (12-17 years).

The following demography variables, as presented in the planned TLF shells, will be collected on the Demography and Medical History Review eSource form:

- Age (years):
  - Calculated relative to Screening in eSource.
- Race (geographic ancestry):
  - African heritage/African American. o American Indian or Alaskan native.
  - Asian:
    - Central/South Asian heritage.
    - East Asian heritage.
    - Japanese heritage.
    - South East Asian heritage.

- Native Hawaiian or other Pacific islander. o White:
  - Arabic/North African heritage.
  - Caucasian/European heritage.
- Other, specify.

- Ethnicity: o American Hispanic or Latino.
- Not American Hispanic or Latino.

The following demography variables, as presented in the planned TLF shells, will be collected on the Subject Information form in eSource:

- Date of birth:
  - Transferred as MMMYYYY.
- Gender: o Female (F).
- Male (M).

The following Baseline characteristic variables, as presented in the planned TLF shells, will be collected on the Vital Signs form in eSource (refer to Section 6.2: Baseline for additional details):

- Baseline height (cm).
- Baseline weight (kg).

The following Baseline characteristic variables, as presented in the planned TLF shells will be collected on the Reproductive Status and Contraception Use for Females form in eSource:

- Childbearing potential:
  - Yes. o No, hysterectomy, bilateral ovariectomy or current tubal ligation. o No, pre-menarche.
- Adequate contraception use:
  - Yes. o No. o NA- same sex partners is their preferred and usual lifestyle.

The following demography variables, as presented in the planned TLF shells, will be imported from an EXCEL spreadsheet with the centre information provided by the project manager:

- Country and investigator information (refer to Section 7.2: Multicentre Studies for additional details).

The following demography variable, as presented in the planned TLF shells, will be included in the data transferred from eSource:

- Centre number.

10.1. DERIVATIONS

Based on the aforementioned variables, the following variable, as presented in the planned TLF shells is derived:

- Age category: o 1-2 years. o 3-5 years. o 6-11 years.
  - o 12-17 years.

All listings, as presented in the relevant TLF shells, will include the following demographic information:

- Age (years).
- Gender.
- Race.

These demographic variables will be concatenated to form one demographic variable in the following format:

- Age (years)/Gender/Race:
  - o For example: 13/M/WHITE.

11. MEDICAL HISTORY

The following medical history listing is planned for presentation for the Total Enrolled Cohort:

- Medical history.

The following medical history table is planned for presentation for the Total Vaccinated Cohort:

- Medical history:
  - Number and percentage of subjects with at least one medical history finding in each of the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class.
  - Subjects with more than one occurrence are counted only once per MedDRA System Organ Class.
  - Percentage will be calculated relative to the total number of subjects in the relevant analysis cohort.

Medical history will not be coded, however the MedDRA System Organ Class will be provided on the Medical History form in eSource, along with the following medical history variables, as presented in the TLF shells:

- MedDRA System Organ Class:
  - Blood and lymphatic system.
  - Cardiac.
  - Ear and labyrinth. o Endocrine. o Eye. o Gastrointestinal. o Hepatobiliary. o Immune system (including allergies, autoimmune disorders). o Infections and infestations. o Metabolism and nutrition. o Musculoskeletal and connective tissue. o Neoplasms benign, malignant and unspecified (including cysts, polyps). o Nervous system. o Psychiatric. o Renal and urinary. o Reproductive system and breast. o Skin and subcutaneous tissue.
  - Respiratory, thoracic and mediastinal.
  - Surgical and medical procedures.
  - Vascular. o Other.
- Verbatim term (diagnosis).
- Start date.
- End date.
- Ongoing: o Yes. o No.
- Intensity:
  - Mild. o Moderate. o Severe. o Not applicable.

11.1. DERIVATIONS

Based on the aforementioned variables, the following variable will be derived:

- Relative day:
  - Calculated relative to Day 0 vaccination (refer to Section 6.1: Reference Start Date and Relative Day).

12. CONCOMITANT MEDICATION AND VACCINATIONS

The following concomitant medication and vaccination listing is planned for presentation for the Total Enrolled Cohort:

- Concomitant medication and vaccinations.

Concomitant medication and vaccinations will only be coded with Anatomical Therapeutic Chemical (ATC) codes using the WHO Drug Dictionary Enhanced version SEP2015. The following concomitant medication and vaccination variables, as presented in the planned TLF shells, will be collected on the Concomitant Medication and Vaccination form in eSource:

- Type: o Concomitant medication. o Concomitant vaccination.
- Verbatim term (drug/vaccination name).
- Dose.
- Dose unit.
- Frequency.
- Route: o Medication route. o Vaccine route.
- Start date.
- End date.
- Ongoing: o Yes. o No.
- Medication indication:
  - o Treatment of a SAE. o Cause of SAE. o Not applicable.

12.1. DERIVATIONS

Based on the aforementioned variables, the following variable will be derived:

- Relative day:
  - o Calculated relative to Day 0 vaccination (refer to Section 6.1: Reference Start Date and Relative Day).

13. STUDY VACCINATION

The following listing is planned for presentation for Total Randomised Cohort:

- Vaccination administration.

The following table is planned for presentation for the Total Randomised Cohort:

- Vaccination administration:
  - Number and percentage of subjects with a vaccination administration at each relevant visit. o Percentage will be calculated relative to the total number of subjects in the relevant analysis cohort.

The following vaccination variables, as presented in the planned TLF shells, will be collected on the Treatment Allocation and Vaccination form in eSource:

- Vaccination administered:
  - Yes. o No.
- Vaccination site:
  - Deltoid. o Thigh. o Other, specify.
- Vaccination side:
  - Right. o Left.
- Vaccination route:
  - Intramuscular. o Other, specify.
- Date and time of vaccination.

- Comment on vaccination administration.
- Reason for non-administration:
  - o Serious Adverse Event related to study participation or to a GSK concurrent medication. o Serious Adverse Event not related to study participation or to a GSK concurrent medication. o Non-Serious Adverse Event. o Other, specify.
- Decision maker for non-administration:
  - o Investigator. o Subject. o Legally acceptable representative.

The following contraindication variables, as presented in the planned TLF shells, will be recorded on the Contraindication Review form in eSource:

- Fever (temperature ≥ 37.5˚C):
  - o Yes. o No.
- Clinically significant immunosuppressive or immunodeficient condition:
  - o Yes. o No.
- Pregnant: o Yes. o No.

- Had anaphylaxis following vaccine administration:
  - Yes.
  - No.

The following vaccination variables, as presented in the planned TLF shells, will be imported from the EXCEL spreadsheet received from Cenduit:

- Actual vaccination administered:
  - EBO-Z. o
    Nimenrix.

13.1. DERIVATIONS

Based on the aforementioned variables, the following variable will be derived:

- Relative day:
  - Calculated relative to Day 0 vaccination (refer to Section 6.1: Reference Start Date and Relative Day).

14. IMMUNOGENICITY

The following immunogenicity assays will be completed for the relevant sub-cohort as indicated below:

- Humoral immune response:
  - Anti-GP EBOV. o ChAd3 neutralising antibody (subset for additional testing).
- CMI against Ebola:
  - CD4+ or CD8+ T-cell response specific to EBOV (subset for additional testing)

Refer to Table 11: Immunological Read-outs (Humoral Immunity) as well as Table 12: Immunological Read-outs (Cell-medicated Immunity) in the protocol for the specific details with regards to the collection of immunogenicity samples.

No imputation will be performed for missing immunogenicity data. Therefore, any analysis will exclude subjects with missing measurements at the specific time points.

All immunogenicity tables will be repeated for the derived time points as defined in Section 6.3.1: ChAd3-EBO-Z Post-vaccination Time Points.

All immunogenicity tables mentioned below will be repeated for the Total Vaccinated Cohort: Immunogenicity if at least 5 % of subjects in any treatment group are excluded from the According-to-protocol Cohort.

14.1. HUMORAL IMMUNE RESPONSE

14.1.1. ANTI-GLYCOPROTEIN (GP) EBOLA VIRUS ZAIRE (EBOV)

The following listing is planned for presentation for the Total Vaccinated Cohort: Immunogenicity:

- Anti-GP EBOV results.

The following tables are planned for presentation for the According-to-protocol Cohort:

- Anti-GP EBOV: Serological status:
  - The number and percentage (%) of subjects in each status category (seronegative, seropositive and seroconversion for post-vaccination time points).
  - Percentage (%) calculated relative to the number of subjects with results available in order to assign a status at each time point.
  - 95% CIs for the seropositivity and -negativity rates will be presented for each treatment group.
- Anti-GP EBOV: Response:
  - The number and percentage (%) of subjects in each category (Yes and No).
  - Percentage (%) calculated relative to the number of subjects with results available at both pre-and post-vaccination time points at each time point.
  - 95% CIs for the response rate will be presented for each treatment group.
- Anti-GP EBOV: Above threshold (only completed if possible at the time of the analysis, otherwise will be completed at a later stage):
  - The number and percentage (%) of subjects with results equal to at least to a specific threshold value.
  - Percentage (%) calculated relative to the number of subjects with results available at both pre-and post-vaccination time points at each time point.
  - 95% CIs for the proportion of subjects with concentration results equal to or above the threshold will be presented for each treatment group.
- Anti-GP EBOV: Geometric mean concentrations (GMC) (depending on the outcome of validation):
  - Summary statistics, refer to Section 6.6: Statistical Tests, based on the log-transformed concentration values.
  - 95% CIs will presented for the GMCs per each treatment group. o GMC calculations are performed by taking the anti-log of the mean of the log10 concentration transformation.

The following figures are planned for presentation for the According-to-protocol Cohort:

- Reverse cumulative distribution curves:
  - Each plot shows antibody concentrations (on a log-scale) on the X-axis and the proportion of individuals exhibiting that concentrations or higher on the Y-axis.

- Concentration and GMCs:
  - Individual antibody concentrations at Day 0 and Day 30, with dot plots, per treatment group. o GMCs and 95% confidence intervals will also be plotted.
- Kinetic plot (only applicable to the final analysis):
  - GMCs, including 95% CIs at the EBO-Z post-vaccination time points. o Time points will be connected with straight lines.

All anti-GP EBOV tables will be presented by Baseline serological status, including the following categories:

- Seronegative.
- Seropositive.
- Total.

The following immunology variables, as presented in the planned TLF shells, will be collected on the Blood Sampling form in eSource:

- Were humoral immunity blood samples collected:
  - Yes. o No.
- Date and time of sample collection.

The following immunology variable, as presented in the planned TLF shells, will be imported from the laboratory report:

- Concentration value.

14.1.1.1. Derivations

Based on the aforementioned immunogenicity variables, the following variables, as presented in the planned TLF shells, will be derived:

- Log-transformed concentration values:
  - Log10 of the concentration values will be derived. o Results below the cut-off of the assay will be assigned as half of the cut-off* value before taking the log for analysis purposes.
- Serological status:
  - Seronegative:
    - Concentration value is below the cut-off* value.
  - Seropositive:
    - Concentration value is greater or equal to the cut-off* value.
  - Seroconversion:
    - Seropositive result post-vaccination for any subjects defined as seronegative pre-vaccination.

- Response: o Yes:
  - For seronegative pre-vaccination: Post-vaccination concentration value of at least the assay cutoff* value.
  - For seropositive pre-vaccination: Post-vaccination concentration value of at least x-fold* increase over the pre-vaccination concentration value. o No:
  - For seronegative pre-vaccination: Post-vaccination concentration value of less than the assay cutoff* value.
  - For seropositive pre-vaccination: Post-vaccination concentration value of less than x-fold* increase over the pre-vaccination concentration value.

  The x-fold increase will be calculated as:

$$= \frac{\_}{\_}$$

*Both the assay cut-off value and x will be defined once the Anti-GP ELISA assay has been validated and information is available (prior to the interim analysis).

- Above threshold:
  - o Yes:
    - Post-vaccination value >= defined threshold. o No:
    - Post-vaccination value < defined threshold.

  Threshold will be defined prior to the interim analysis.

14.1.2. ChAd3 Neutralising Antibody

All analyses will be the same as described for the anti-GP EBOV data. The same tables as described for the antiGP EBOV data will be prepared for the ChAd3 neutralisation data. The ChAd3 neutralisation result will be the reciprocal antibody titres corresponding to the inhibitory concentration 90% (IC90, the titre at which 90% of infectivity is inhibited).

In addition, the association of the pre-existing (baseline) ChAd3 neutralisation antibodies with each of the following vaccine-induced (Day 30 post-vaccination) results will be evaluated by the Spearman-rank correlation method:

- Anti-GP EBOV: Concentration.
- Frequency of CD4+ T-cell specific to EBOV:
  - o CD4+/IFN.
  - o CD4+/I

  L2. o

CD4+/T
NF.

- Frequency of CD8+ T-cell specific to EBOV:
  - CD8+/IFN.
  - CD8+/IL2.
  - CD8+/TNF.

Three scatter plots will be presented per cytokine (IFN, IL2, TNF), one plot for each of the aforementioned sets of results. The vaccine-induced results will be based on the result observed at Day 30. The figure will be repeated for the 30 Days Post-vaccination derived time point as defined in Section 6.3.1: ChAd3-EBO-Z Post-vaccination Time Points.

14.1.2.1. Derivations

Refer to Section 14.1.1.1: Derivations for relevant derivations, the following information is specific to the ChAd3 neutralisation data:

- Log-transformed titre values and serological status:
  - The relevant cut-off value is the reciprocal titre of 12.
- Response: o Yes:
  - For seronegative pre-vaccination: Post-vaccination titre value of at least the assay cut-off* value.
  - For seropositive pre-vaccination: Post-vaccination titre value of at least x-fold* increase over the pre-vaccination titre value. o No:
  - For seronegative pre-vaccination: Post-vaccination titre value of less than the assay cut-off* value.
  - For seropositive pre-vaccination: Post-vaccination titre value of less than x-fold* increase over the pre-vaccination titre value.

*Both the assay cut-off value and x will be defined once the neutralisation assay has been validated and information is available (prior to the interim analysis).

- Above threshold:
  - The threshold value is 200.

14.2. CELL-MEDIATED IMMUNITY (CMI) AGAINST EBOLA

14.2.1. CHAD3-EBOV-SPECIFIC CD4+ OR CD8+ T-CELL RESPONSE

The following listing is planned for presentation for the Total Vaccinated Cohort: Immunogenicity:

- ChAd3-EBOV-specific results.

The following table is planned for presentation for the According-to-protocol Cohort:

- ChAd3-EBOV-specific response.
  - The number and percentage (%) of subjects in each response category (yes, no). o Percentage (%) calculated relative to the number of subjects with results available in order to assign a status at each time point.
  - 95% CIs for the response rates will be presented for each treatment group.
  - This table will be presented by T-cell:
    - CD4+.
    - CD8+.
  - The overall post-baseline response rate will also be included (response at any time point postbaseline).
- Frequency of ChAd3-EBOV-specific T-cells per subset.
  - Summary statistics, refer to Section 6.6: Statistical Tests, based on the percentage results per subset.

All CMI tables will be presented by Baseline anti-GP EBOV serological status, including the following categories:

- Seronegative.
- Seropositive.
- Total.

The following immunology variables, as presented in the planned TLF shells, will be collected on the Blood Sampling form in eSource:

- Were CMI blood samples collected:
  - Yes. o No.
- Date and time of sample collection.

The following immunology variables, as presented in the planned TLF shells, will be imported from the laboratory report:

- Subset: o CD4+/IFN. o CD4+/IL2. o CD4+/TNF. o CD8+/IFN. o CD8+/IL2. o CD8+/TNF.

- Antigen: o GP(Z1). o GP(Z2). o NEG.
- Results, per T-cell and antigen:
  - o Total number of cells (NSUB result).
- Results, per subset and antigen:
  - o Percentage result (PCTPOS result).
  - o Adjusted result (%) (AD_PCTPOS result):
    - Per subset and antigen, percentage result minus the NEG antigen percentage result.

14.2.1.1. Derivations

Based on the aforementioned immunogenicity variables, the following variables, as presented in the planned TLF shells, will be derived:

- Baseline serological status:
  - o Based on the pre-vaccination anti-GP EBOV serological status: ▪ Seronegative. ▪ Seropositive.
- T-cell frequency (%):
  - o Per subset, sum of the GP(Z1) and GP(Z2) adjusted result (%) for analysis. o Negative T-cell frequencies will be set to 0.0001% for analysis purposes.
- Number of positive cells:
  - o Per subset and antigen the number of positive cells is derived by multiplying the total number of cells (NSUB) with the percentage of cells (PCTPOS), if this result is not an integer due to rounding issues, the result will be rounded to the nearest integer:
    - Positive cells = ROUND(NSUB × (PCTPOS × 0.01), 1.0).
- Number of negative cells:
  - o Per subset and antigen, once the number of positive cells is calculated, the negative cells is derived as the difference between the total number of cells (NSUB) and the positive number of cells.
- Response:
  - o No:
    - Per subset and antigen (excluding the NEG antigen), a Fisher's exact test is performed for the 2x2 table consisting of positive and negative cells compared to that of the negative control (NEG antigen) and the one-sided p-value is > 0.01.
    - OR
    - The one-sided p-value is <= 0.01 and adjusted result (%) is smaller than or equal to the values provided in Table 4: Adjusted Result (%) Response Criteria below. o Yes:

- Per subset and antigen (excluding the NEG antigen), a Fisher's exact test is performed for the 2x2 table consisting of positive and negative cells compared to that of the negative control (NEG antigen) and the one-sided p-value is <= 0.01.
- AND
- The adjusted result (%) is larger than the value provided in Table 4: Adjusted Result (%) Response Criteria below.

Table 4: Adjusted Result (%) Response Criteria

T-cell	Cytokine	Criteria
CD4+	IFN	0.05
	IL-2	
	TNF	
CD8	IFN	0.08
	IL-2	0.05
	TNF	0.08

If at least one of the subset and antigen combinations has a response derived as Yes, the subject is considered as a responder for that visit. If the subject is response at least one post-baseline visit, the subject will be regarded as an overall responder.

For the table pooled following the EBO-Z vaccination the overall response rate will only consider post-vaccination responses with 6 month of the EBO-Z vaccination:

- EBO-Z/MENACWY-TT treatment group:
  - Day 30. o Month 6.
- MENACWY-TT/EBO-Z treatment group:
  - Month 6 + 30 days. o Month 12.

If either of the aforementioned post-vaccination responses has been derived as Yes, the subject will be considered as an overall responder for the pooled table.

15. SAFETY OUTCOMES

The Total Vaccinated Cohort will be used as primary analysis cohort for all safety analyses.

15.1. UNSOLICITED ADVERSE EVENTS

Unsolicited AEs will be coded using the latest version of MedDRA at the time of the data transfer.

For analysis of unsolicited adverse events, all vaccinated subjects will be considered. Subjects who did not report the event will be considered as subjects without the event.

The following AE variables, as presented in the planned TLF shells, will be collected on the Adverse Event form in eSource:

- Site of AE: o Non-administration site. o Administration site.
- Adverse event of special interest (AESI) within 7 days post-vaccination at Day 0 (symptoms of thrombocytopenia):
  - o Yes (available AESI terms are provided in APPENDIX 3: Adverse Events of Specific Interest (AESIs) Terms):
    - AESI term.
    - Additional AESI term. o No.
- Verbatim term (diagnosis).
- Start date and time.
- End date and time.
- Ongoing: o Yes. o No.
- Intensity:
  - o Mild.
  - o Moderate. o Severe.
- Action taken with vaccination:
  - o Investigational product withdrawn. o Dose delayed. o No action taken.
- Outcome: o Recovered/Resolved.
  - o Recovered/Resolved with sequelae. o Recovering/Resolving. o Fatal. o Not recovered/not resolved. o Unknown.
- Led to study discontinuation:

- o Yes. o No.

- Serious: o Yes:
  - Fatal.
  - Life-threatening.
  - Requires/prolonged hospitalisation.
  - Substantial/Permanent disability.
  - Congenital anomaly/birth defect.
  - Other. o No.

The following AE variable, as presented on the planned TLFs, will be collected on the Adverse Event Relationship form in eSource:

- Relationship to study vaccine, as judged by the investigator:
  - Yes.
  - No.

The following laboratory variable, as presented in the planned TLFs, will be collected on the Laboratory Results form in eSource:

- Platelet counts at each relevant visit.

The following AE coding variables, as presented in the planned TLF shells, are to be provided by Data Management as part of the data transfer to Quintiles Biostatistics:

- Primary System Organ Class (SOC).
- Preferred Term.

Unsolicited AEs will be coded using the latest version of MedDRA at the time of the data transfer. If the AE is uncoded at the time of the analysis, the AE will be analysed as 'Uncoded'. Coded items will be presented in listings and will be used in descriptive statistics.

15.1.1. DERIVATIONS

Based on the aforementioned variables, the following variables will be derived:

- Most recent vaccination (refer to Section 6.7.2: Most Recent Vaccination).
- Relative day of the most recent vaccination:
  - Calculated relative to Day 0 vaccination (refer to Section 6.1: Reference Start Date and Relative Day).
- Relative days (start and stop):
  - Calculated relative to most recent vaccination (refer to Section 6.1: Reference Start Date and Relative Day).

- Within post-vaccination reporting window flag (refer to Section 15.1.6: Adverse Event (AE) Postvaccination Reporting Window).
- Dose at onset:
  - Dose at onset will be assigned for all unsolicited AEs and is defined as the most recent dose prior to the onset of the AE:
    - Total (only applicable to SAE tables).
    - EBO-Z.
    - Nimenrix.
- Number of events will be calculated as the total number of events reported in the database per relevant category. Therefore multiple events per subject would be counted for each occurrence and not just once per subject.

Refer to APPENDIX 2: Partial Date Conventions for handling of partial dates for AEs.

15.1.2. ALL UNSOLICITED ADVERSE EVENTS

The following listings are planned for presentation for Total Vaccinated Cohort:

- Unsolicited AEs.
- Serious adverse events (SAEs).
- Severe (grade 3) AEs.
- Adverse events of specific interest (AESIs):
  - All available platelet counts will also be displayed in this listing.

The following tables are planned for presentation for the Total Vaccinated Cohort and AE and Humoral Immunity Sub-cohort:

- Overview of unsolicited AEs:
  - Number and percentage (%) of subjects in each of the following categories: ▪ Unsolicited AE.
    - Severe (grade 3) unsolicited AE.
    - Related unsolicited AE.
    - Severe (grade 3) related unsolicited AE.
    - Unsolicited AE leading to premature study withdrawal.
  - In this table AESIs (refer to Section 15.1.4: Adverse Events Of Specific Interest (AESIs)) and *any AEs (refer to Section 15.3: Solicited and Unsolicited Adverse Events (AEs)) will be included as well.
  - Percentage (%) of subjects will be calculated relative to the total number of subjects in the relevant analysis cohort and sub-cohort per treatment group.

- A 95% confidence interval (CI) for the proportion of subjects with AEs in each category will be obtained by using the exact binomial option.
- Subjects with multiple events in each category are counted only once in each category.

- Incidence of unsolicited AEs:
  - Number and percentage (%) subjects with unsolicited AEs summarised by SOC and PT.
- Incidence of unsolicited AEs by severity:
  - Number and percentage (%) subjects with unsolicited AEs summarised by SOC, PT and severity. o This table will be repeated for related unsolicited AEs.
- Incidence of unsolicited AEs by relationship:
  - Number and percentage (%) subjects with unsolicited AEs summarised by SOC, PT and relationship.

For all unsolicited AEs the SOCs will be sorted by descending frequency of the total number of subjects with at least one unsolicited AE in the overall category. Within each SOC, PTs will be sorted by descending frequency of the total number of subjects with at least one unsolicited AE in each category. Ties will be sorted alphabetically.

All unsolicited AE incidence tables will be repeated for the following pooling of AEs, presented per age stratum:

- AEs following the active ChAd3-EBO-Z vaccination; hence:
  - EBO-Z/MENACWY-TT subjects: Unsolicited AEs within the reporting window following Day 0 vaccination. o MENACWY-TT/EBO-Z subjects: Unsolicited AEs within the reporting window following Month 6 vaccination.

15.1.2.1. Severity

Severity is classed as mild, moderate or severe (increasing severity) and will be obtained from the Intensity variable recorded on the Adverse Events form in eSource. If there are any missing intensities at the time of the analysis, an unknown category will be used to summarise those SOC/PTs terms.

15.1.2.2. Relationship to Study Vaccine

Relationship, as indicated by the Investigator, is categorised as not related or related (increasing severity of relationship) and will be obtained from the relationship to study vaccine variable on the Adverse Event Relationship form in eSource. Missing relationships should be queried prior to the analysis transfer is made to Biostatistics. If there is any missing relationship to study vaccine at the time of the analysis, an unknown category will be used to summarise those SOC/PTs.

15.1.3. UNSOLICITED AES LEADING TO PREMATURE STUDY WITHDRAWAL

Unsolicited AEs leading to premature study withdrawal, as indicated by the investigator, will be obtained from

the led to study discontinuation variable on the Adverse Events form in eSource. These AEs will be included in the unsolicited AE overview and also indicated in the unsolicited AE listing.

15.1.4. Adverse Events Of Specific Interest (AESIs)

Adverse events of specific interest (AESIs), as indicated by the investigator, will be obtained from the clinical symptoms of thrombocytopenia within 7 days post vaccination Day 0 variable on the Adverse Events form in eSource.

The following tables are planned for presentation for the Total Vaccinated Cohort and AE and Humoral Immunity sub-cohort:

- Overview of AESIs:
  - These will be presented together with the overview of unsolicited AEs (refer to Section 15.1.2: All Unsolicited Adverse Events):
    - Any AESI.
    - Any severe (grade 3) AESI.
    - Any related AESI.
    - Any severe (grade 3) related AESI.
    - Any AESI leading to premature study withdrawal.
- Incidence of AESIs.
- Incidence of AESIs by severity.
- Incidence of related AESIs by severity.
- Incidence of AESIs by relationship.

For all AESIs the SOCs will be sorted by descending frequency of the total number of subjects with at least one AESI in the overall category. Within each SOC, PTs will be sorted by descending frequency of the total number of subjects with at least one AESI in each category. Ties will be sorted alphabetically.

Adverse event of specific interest (AESIs) tables will not be repeated for any pooled AESIs as AESIs are only following Day 0 vaccination and hence the MENACWY-TT/EBO-Z subjects will not have AESIs reported following Month 6 vaccination. Refer to APPENDIX 3: Adverse Events of Specific Interest (AESIs) Terms for a list of AE terms considered as AESIs.

15.1.5. Serious Adverse Events (SAEs)

Serious adverse events (SAEs) as indicated by the investigator, will be obtained from the serious variable on the Adverse Events form in eSource. These AEs will be included in the unsolicited AE overview as well as in the unsolicited AE listing.

The following tables are planned for presentation for the Total Vaccinated Cohort:

- Overview of SAEs by dose:
  - Number and percentage (%) of subjects in each of the following categories: ▪ Any SAE.
    - SAE with outcome of death.
    - Severe (grade 3) SAE.
    - Related SAE.
    - Related SAE with outcome of death. ▪ Severe (grade 3) related SAE. o Percentage (%) of subjects will be calculated relative to the total number of subjects in the relevant analysis cohort per treatment group.
  - A 95% confidence interval (CI) for the proportion of subjects with AEs in each category will be obtained by using the exact binomial option.
  - Subjects with multiple events in each category are counted only once in each category.

  The following by dose (Total, EBO-Z, Nimenrix) tables are similar to those described for the unsolicited AEs in Section 15.1: Unsolicited Adverse Events:

- Incidence of SAEs.
- Incidence of SAEs by severity.
- Incidence of related SAEs by severity.
- Incidence of SAEs by relationship.
- Number and percentage of SAEs including the number of events.
- Number and percentage of related SAEs including the number of events.

For all SAEs the SOCs will be sorted by descending frequency of the total number of subjects with at least one SAE in the overall category. Within each SOC, PTs will be sorted by descending frequency of the total number of subjects with at least one SAE in each category. Ties will be sorted alphabetically.

15.1.5.1. Serious Adverse Events (SAEs) with Outcome of Death

Adverse events (AEs) with outcome of death are those events which are recorded as resulting in death on the Adverse Events form in eSource. These AEs will be included in the unsolicited AE overview and also indicated in the SAE listing.

15.1.6. ADVERSE EVENT (AE) POST-VACCINATION REPORTING WINDOW

All AE incidence tables will only include AEs (SAEs, AESIs and unsolicited AEs) which occurred within the protocol defined post-vaccination reporting window, as defined in Table 5: Unsolicited Adverse Event (AE) Postvaccination Reporting Windows, below. All AE listings will include all the AEs reported, regardless whether it was reported within the reporting window. All AEs reported outside the reporting window will be indicated in the listing.

Table 5: Unsolicited Adverse Event (AE) Post-vaccination Reporting Windows

Adverse Event Type	Post-vaccination Reporting Window
SAEs	Through data cut-off
AESIs	7-day window following Day 0
Unsolicited AEs	30-day window following each vaccination

15.2. SOLICITED ADVERSE EVENTS (AES)

Solicited AEs will not be coded by data management and as per coding will be assigned based on the information provided in Table 6: Solicited Adverse Events MedDRA Coding.

For a given subject, missing or non-evaluable measurements will not be replaced. Therefore the analysis of the solicited symptoms will include only vaccinated subjects with documented safety data (that is; symptom screen completed after the vaccination). More specifically the following rules will be used:

- Subjects who documented the absence of a solicited symptom after a vaccination will be considered not having that symptom after that vaccination.
- Subjects who documented the presence of a solicited symptom and fully or partially recorded daily measurement over the solicited period will be included in the summaries for that vaccination and classified according to their maximum observed daily recording over the solicited period.
- Subjects who documented the presence of a solicited symptom after a vaccination without having recorded any daily measurement will be assigned to the lowest intensity category for that vaccination (that is; 37.5°C for fever or grade 1 for other symptoms).
- Vaccinations without symptom sheets documented will be excluded.

The following AE variables, as presented in the planned TLF shells, will be collected on the Solicited Adverse Events Local Signs and Symptoms form in eSource:

- Any signs or symptoms between Day 0 and Day 6:
  - o Yes. o No.
- Per day (Day 0 to Day 6) presence of each of the following signs or symptoms:
  - o Redness:
    - Diameter measurement (mm). o Swelling:
    - Diameter measurement (mm). o Pain:
    - Intensity (0 to 3).

Per sign or symptom:

- Ongoing after Day 6:
  - Yes:
    - Maximum diameter/intensity after Day 6.
    - End date after Day 6.
  - No.
- Did the subject discontinue due to the event:
  - Yes.
  - No.

The following AE variable, as presented on the planned TLFs, will be collected on the Solicited Adverse Events General Signs and Symptoms form in eSource:

- Any signs or symptoms between Day 0 and Day 6:
  - Yes.
  - No.
- Per study day (Day 0 to Day 6) presence of each of the following signs or symptoms for children aged 6 to 17 years of age:
  - Fever:
    - Temperature reading (˚C).
  - Headache:
    - Intensity (0 to 3).
  - Fatigue:
    - Intensity (0 to 3).
  - Gastrointestinal symptoms:
    - Intensity (0 to 3).
- Per study day (Day 0 to Day 6) presence of each of the following signs or symptoms for children aged 1 to 5 years of age:
  - Fever:
    - Temperature reading (˚C).
  - Loss of Appetite:
    - Intensity (0 to 3).
  - Drowsiness:
    - Intensity (0 to 3).
  - Irritability/Fussiness:
    - Intensity (0 to 3).

Per sign or symptom:

- Ongoing after Day 6:

- Yes:
  - Maximum reading/intensity after Day 6.
  - End date after Day 6. o No.

- Did the subject discontinue due to the event:
  - Yes. o No.
- Relationship to study vaccine:
  - Yes.
  - No.

The following diary card variable will be collected on the Diary Card Review form in eSource:

- Did the field worker/site personnel return the diary card:
  - Yes. o No.

15.2.1. DERIVATIONS

Based on the aforementioned variables, the following variables will be derived:

- End date after Day 6 relative day:
  - Calculated relative to the most recent vaccination (refer to Section 6.1: Reference Start Date and Relative Day).
- Duration of solicited sign or symptom (refer to Section 6.7.3: Duration):
  - If ongoing after Day 6:
    - End date/day: End date after Day 6 as recorded in eSource.
    - Start date/day: Start date of sign or symptom (derived from the first study day where sign or symptom is present relative to the study vaccination date). o If not ongoing after Day 6:
    - End date/day: Last date of sign or symptom (derived from the study day where sign or symptom is present relative to the study vaccination date).
    - Start date/day: Start date of sign or symptom (derived from the first study day where sign or symptom is present relative to the study vaccination date).
    -
- Relationship to study vaccine for local solicited signs or symptoms:
  - All local signs or symptoms will be regarded as related to study vaccine.
- Intensity for fever, redness and swelling:

Refer to APPENDIX 4: Solicited Adverse Event (AE) Intensity Grading, for the required intensity grade assignment for fever, redness and swelling.

- Dose at onset:
  - Dose at onset will be assigned for all solicited AEs and is defined as the most recent dose prior to the onset of the AE:
    - EBO-Z:
    - Day 0.
    - Month 6.
    - Nimenrix:
    - Day 0.
    - Month 6.
- MedDRA System Organ Class as well as Preferred Term will be assigned based on Table 6: Solicited Adverse Events MedDRA Coding, below.

Table 6: Solicited Adverse Events MedDRA Coding

Solicited AE	MedDRA System Organ Class	MedDRA Preferred Term
Redness	Skin and subcutaneous tissue disorders	Erythema
Swelling	General disorders and administration site conditions	Swelling
Pain	General disorders and administration site conditions	Pain
Fever	General disorders and administration site conditions	Pyrexia
Headache	Nervous system disorders	Headache
Fatigue	General disorders and administration site conditions	Fatigue
Gastrointestinal Symptoms	Gastrointestinal disorders	Gastrointestinal disorder
Loss of Appetite	Metabolism and nutrition disorders	Decreased appetite
Drowsiness	Nervous system disorders	Somnolence
Irritability/Fussiness	Psychiatric disorders	Irritability

15.2.2. ALL SOLICITED ADVERSE EVENTS

The following listing is planned for presentation for the Total Vaccinated Cohort:

- Solicited AEs.

The following tables are planned for presentation for the Total Vaccinated Cohort:

- Overview of Solicited AEs:
  - Number and percentage (%) of subjects in each of the following categories: ▪ Solicited AE.
    - Solicited severe (grade 3) AE.
    - Solicited related AE.
    - Solicited severe (grade 3) related AE. ▪ Solicited local AE.
    - Severe (grade 3) solicited local AE.
    - Solicited general AE.
    - Severe (grade 3) solicited general AE.
    - Related solicited general AE.
    - Severe (grade 3) related solicited general AE.
    - Solicited AE leading to premature study withdrawal.
    - Severe (grade 3) solicited AE leading to premature study withdrawal.
    - Related solicited AE leading to premature study withdrawal.
    - Severe (grade 3) related solicited AE leading to premature study withdrawal.
  - Percentage (%) of subjects will be calculated relative to the total number of subjects in the relevant analysis cohort, per treatment group with returned diary cards.
  - A 95% confidence interval (CI) for the proportion of subjects with AEs in each category will be obtained by using the exact binomial option.
  - Subjects with multiple events in each category are counted only once in each category.
- Incidence of solicited AEs:
  - Number and percentage (%) subjects with solicited AEs summarised by category and sign or symptom.
- Incidence of solicited AEs by severity:
  - Number and percentage (%) subjects with solicited AEs summarised by category, sign or symptom and severity.
  - This table will be repeated for related solicited AEs (including general solicited AEs only).
- Incidence of solicited AEs by relationship:
  - Number and percentage (%) subjects with solicited AEs summarised by category, sign or symptom and relationship.
- Duration of fever (days):

- Descriptive statistics for the duration of fever will be provided, based on all subjects with at least one fever event reported.

For all solicited AEs the categories and signs or symptoms will be sorted as listed below:

- Local: o Pain. o Redness. o Swelling.
- General: o Fever. o Fatigue (only applicable to age strata: 13 to 17 years of age and 6 to 12 years of age). o Gastrointestinal symptoms (only applicable to age strata: 13 to 17 years of age and 6 to 12 years of age).
  - Headache (only applicable to age strata: 13 to 17 years of age and 6 to 12 years of age). o Drowsiness (only applicable to age stratum: 1 to 5 years of age). o Irritability/Fussiness (only applicable to age stratum: 1 to 5 years of age). o Loss of appetite (only applicable to age stratum: 1 to 5 years of age).

All solicited AE incidence tables will be repeated for the following pooling of AEs:

- AEs following the active ChAd3-EBO-Z vaccination; hence:
  - EBO-Z/MENACWY-TT subjects: Solicited AEs within the reporting window following Day 0 vaccination.
  - MENACWY-TT/EBO-Z subjects: Solicited AEs within the reporting window following Month 6 vaccination.

15.2.2.1. Severity

Severity will be derived based on the intensity grading:

- Mild: Intensity grade of 1.
- Moderate: Intensity grade of 2.
- Severe: Intensity grade of 3.

In addition, for the intensity it can also be reported as the following:

- Redness:
  - Unknown. o Uninterpretable.
- Swelling, and fever:
  - Unknown.

Severity is therefore classed as unknown, uninterpretable, mild, moderate or severe (increasing severity). If there are any missing intensities at the time of the analysis, those will be summarised in the unknown category.

15.2.2.2. Relationship to Study Vaccine

Relationship, as indicated by the Investigator, is classified as not related or related (increasing severity of relationship) and will be obtained from the relationship to study vaccine variable on the Solicited Adverse Events

General forms in eSource. Missing relationships should be queried prior to the analysis transfer to Biostatistics. If there are any AEs with a missing relationship to study vaccine at the time of the analysis, an unknown category will be used to summarise those solicited AEs.

15.2.3. SOLICITED AES LEADING TO PREMATURE STUDY WITHDRAWAL

Solicited AEs leading to premature study withdrawal, as indicated by the investigator, will be obtained from the led to study discontinuation variable on the Solicited Adverse Events Local and General forms in eSource. These AEs will be included in the solicited AE overview.

15.3. SOLICITED AND UNSOLICITED ADVERSE EVENTS (AES)

The following tables are planned for presentation for the Total Vaccinated Cohort:

- Overview of solicited and unsolicited AEs:
  - These will be presented together with the overview of unsolicited AEs (refer to Section 15.1.2: All Unsolicited Adverse Events):
    - *Any AE.
    - *Any severe (grade 3) AE.
    - *Any related AE.
    - *Any severe (grade 3) related AE.
    - *Any AE leading to premature study withdrawal.
    - *Any Severe (grade 3) AE leading to premature study withdrawal.
    - *Any Related AE leading to premature study withdrawal.
    - *Any Severe (grade 3) AE related leading to premature study withdrawal.
- Solicited and unsolicited AEs experienced by at least 5% of subjects within the 30 day post-vaccination window, including the number of events:
  - Multiple events are counted as multiple events for the calculation of the number of events (n*). o AEs will be presented by MedDRA System Organ Class and Preferred Term. o SAEs will be excluded from this table.

15.4. LABORATORY EVALUATIONS

The list of laboratory assessments to be included in the analysis is provided in APPENDIX 5: Laboratory Assessments.

The following listings are planned for presentation based on the Total Randomised Cohort:

- Clinical laboratory results, including change from Baseline and toxicity grading.
- Clinical laboratory results: Platelets, including an indication of subjects with AESIs.
- Malaria rapid diagnosis test (RDT) results.
- Pregnancy test results:
  - Based on the Total Enrolled Cohort and only includes female subjects with results available.

The following tables are planned for presentation based on the Total Vaccinated Cohort:

- Clinical laboratory results, including change from Baseline:
  - Descriptive statistics, including the interquartile range.
- Out of range clinical laboratory results:
  - Number and percentage (%) of subjects with results above or below the normal range. o Percentage (%) is relative to the number of subjects with result available for the specific test and the relevant time point.
- Toxicity grade shift from Baseline to post-baseline, the table will include the following categories:
  - Grade 0. o Grade 1. o Grade 2. o Grade 3.
  - Grade 4.

All laboratory tables will be repeated for the following pooling of results:

- Results following the active ChAd3-EBO-Z vaccination; hence:
  - EBO-Z/MENACWY-TT subjects: Laboratory results following Day 0 vaccination.
  - MENACWY-TT/EBO-Z subjects: Laboratory results following Month 6 vaccination.

The following laboratory variables, as presented in the planned TLF shells, will be recorded on the Blood Sampling form in eSource:

- Date and time of sample collection:
  - Haematology samples.
  - Biochemistry samples.

The following laboratory variables, as presented in the planned TLF shells, will be recorded on the Laboratory Results form in eSource:

- Date of sample collection:
  - Haematology samples. o Biochemistry samples.
- Result and unit.
- Significance:
  - Not clinically significant (NCS). o Clinically significant (CS).

The following laboratory variables, as presented in the planned TLF shells, will be recorded on the Malaria RDT and Results form in eSource:

- Date and time of assessment.
- Result: o Positive. o Negative.
- Malaria treatment prescribed per local/national requirements:
  - o Yes. o No.
- Prescribed malaria treatment completed:
  - o Yes.
  - o No.

The following laboratory variables, as presented in the planned TLF shells, will be recorded on the Pregnancy Test form in eSource:

- Date and time of assessment.
- Result: o Positive.
  - o Negative.

The following pregnancy variables, as presented in the planned TLF shells, will be recorded on the Pregnancy Report form in eSource:

- Date and time of outcome.
- Outcome: o Live infant NO apparent congenital anomaly. o Live infant congenital anomaly. o Elective termination NO apparent congenital anomaly.
  - o Elective termination congenital anomaly.
  - o Spontaneous abortion NO apparent congenital anomaly. o Spontaneous abortion congenital anomaly. o Stillbirth NO apparent congenital anomaly. o Stillbirth congenital anomaly. o Ectopic pregnancy. o Molar pregnancy. o Lost to follow-up. o Pregnancy ongoing.
- Relevant family history.

The following laboratory variables, as presented in the planned TLF shells, will be included in the data transfer from Data Management:

- Local laboratory references ranges in reported units.
- Local laboratory reference ranges in SI units.
- Laboratory results in SI units.

15.4.1. DERIVATIONS

Based on the aforementioned variables, the following variables will be derived:

- Relative day:
  - Calculated relative to Day 0 vaccination (refer to Section 6.1: Reference Start Date and Relative Day).
- Change from Baseline for results in System of International (SI) units (refer to Section 6.7.1: Change from Baseline).
- Toxicity grade for selected laboratory tests (refer to APPENDIX 6: Laboratory Toxicity Grading for derivation details).
  - Maximum grade overall will also be derived as the highest post-vaccination toxicity grade across all post-baseline visits and time points.
- Reference range indicator based on the results in SI units.
  - Low: Result < reference range lower limit.
  - Normal: Result >= reference range lower limit AND result <= reference range upper limit. o High: Result > reference range upper limit.

For clinical laboratory results below or above the limit of quantification will be handled as follows:

- Assign as equal to the limit of quantification, for example '<x' will be assigned as x for analysis purposes. SI conversions can be applied to the derived result. In the listings the result will be presented as the SI value (after conversion) with the qualifier symbol concatenated, for example '<y' in SI unit.

15.5. VITAL SIGNS

The list of vital signs assessments to be included in the analysis is provided in APPENDIX 7: Vital Signs Assessments.

The following listing is planned for presentation based on the Total Randomised Cohort:

- Vital signs results.

The following table is planned for presentation based on the Total Vaccinated Cohort:

- Vital signs results.

The following vital signs variables, as presented in the planned TLF shells, will be recorded on the Vital Signs form in eSource:

- Date and time of assessment.
- Result and unit for each of the vital signs assessments.
- Location of temperature assessment:

- Axillary (preferred). o Oral. o Rectal. o Tympanic (not recommended).

The following vital signs variables, as presented in the planned TLF shells, will be recorded on the Pre Vaccination Temperature form in eSource:

- Date and time of assessment.
- Location of temperature assessment.
  - Axillary (preferred). o Oral. o Rectal. o Tympanic (not recommended).
- Pre-vaccination temperature and unit.

No standardisation of temperatures based on the location of assessment will be performed.

15.5.1. DERIVATIONS

Based on the aforementioned variables, the following variable will be derived:

- Relative day:
  - Calculated relative to Day 0 vaccination (refer to Section 6.1: Reference Start Date and Relative Day).

15.6. PHYSICAL EXAMINATION

The list of physical examination assessments to be included in the analysis is provided in APPENDIX 8: Physical Assessments.

The following listing is planned for presentation based on the Total Enrolled Cohort:

- Physical assessment results.

The following physical assessment variables, as presented in the planned TLF shells, will be recorded on the Physical Assessment form in eSource:

- Date and time of assessment.
- Physical assessment:
  - Normal. o Abnormal. o Not done.

- Finding one classification:
  - Clinically significant.
  - Not clinically significant.
- Finding two classification:
  - Clinically significant.
  - Not clinically significant.

15.6.1. DERIVATIONS

Based on the aforementioned variables, the following variable will be derived:

- Relative day:
  - Calculated relative to Day 0 vaccination (refer to Section 6.1: Reference Start Date and Relative Day).

15.7. SUSPECTED EBOLA VIRUS DISEASE (EVD)

The following listing is planned for presentation based on the Total Randomised Cohort:

- Suspected Ebola virus disease (EVD).

The following EVD variables, as presented in the planned TLF shells, will be recorded on the Management of Suspected EVD form in eSource:

- Subject travelled to a country affected by the EBOV epidemic since last visit:
  - Yes:
    - Date of return.
  - No.
- Subject in direct contact with a person with EVD within 21 days prior to the study visit:
  - Yes.
  - No.

16. DATA NOT SUMMARISED OR PRESENTED

The other variables and/or domains not summarised or presented are:

- Pregnancy report (the pregnancy test results will be reported in a listing including selected pregnancy report variable (outcome, date of outcome and relevant family history).

17. REFERENCES

202090 (EBOLA Z CHAD3-004) Protocol:

- Amendment 2 Final version of the protocol, dated 06MAY2015.
- Addendum Ghana, dated 07AUG2015.

GSK-EBOLA-CHAD3-004_Annotated Source PDF_21SEP2015.

ICS Positivity Criteria-CAD3-EBOZ.doc.

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

Refer to the latest version of the relevant TLF shells for additional guidance on the output conventions.

SPELLING FORMAT

English UK.

PRESENTATION OF TREATMENT GROUPS

- Not Randomised.
- EBO-Z/MENAWY-TT.
- MENAWY-TT /EBO-Z.
- Total.

PRESENTATION OF VISITS

All study visits will be included as visit in the relevant outputs (TLFs). The visits will be presented as follows:

- Screening.
- Day x, where x = 0, 3, 6, 30.
- Month x, where x = 3, 6.
- Month 6 + x days, where x = 6, 30.
- Month x, where x = 9, 12.

DECIMAL PRECISION:

All values are to be rounded using the SAS® function ROUND, as the last step prior to presentation. All computed percentages (%) are to be presented using one decimal place. If the original data has N decimal places (as derived from the raw data), then the summary statistics for quantitative data are to contain the following number of decimal places (with a maximum of 4 decimal places):

- Minimum and maximum: N.
- Mean, geometric mean and median: (N+1).

- Standard deviation and geometric standard deviation: (N+2).

APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings and will simply be used to determine whether the within reporting window for AEs as Yes or No.

AE Start Date			Criterion	Action
Day	Month	Year		
Missing	Known	Known	AE start month and year are the same as the month and year of one vaccination (Day 0 or Month 6)	Assign the missing day as the day of the relevant vaccination in the coinciding month and year
			AE start month and year are not the same as the month and year of any of the vaccinations (Day 0 or Month 6) and known to be in between vaccinations	Assign the missing day as the first day of the month
			AE start month and year are not the same as the month and year of any of the vaccinations (Day 0 or Month 6) and known to be prior to all vaccinations	Assign the missing day as the last day of the month
			AE start month and year are not the same as the month and year of any of the vaccinations (Day 0 or Month 6) and known to be after all vaccinations	Assign the missing day as the first day of the month
Missing	Missing	Known	AE start year is the same as the year of one vaccination (Day 0 or Month 6)	Assign the missing day and month as the day and month of the relevant vaccination in the coinciding year
			AE start year is the same as the year of more than one vaccination (Day 0 or Month 6)	Assign the missing day and month as the day and month of the earliest vaccination in the coinciding year
			AE start year is not the same as the year of any of the vaccinations (Day 0 or Month 6) and known to be prior to all vaccinations	Assign the missing day and month as 31 December

			AE start year is not the same as the year of any of the vaccinations (Day 0 or Month 6) and known to be after all vaccinations	Assign the missing day and month as 01 January
AE Start Date				
Day	Month	Year	Criterion	Action
Missing	Missing	Missing	-	Assign the missing date as the date of vaccination at Day 0

APPENDIX 3. ADVERSE EVENTS OF SPECIFIC INTEREST (AESIS) TERMS

MedDRA 17.1 Preferred Term	Preferred Term Code	MedDRA 17.1 Preferred Term	Preferred Term Code
Abdominal wall haematoma	10067383	Iris haemorrhage	10057418
Abdominal wall haemorrhage	10067788	Kidney contusion	10023413
Abnormal withdrawal bleeding	10069195	Lacrimal haemorrhage	10069930
Acute haemorrhagic leukoencephalitis	10058994	Large intestinal haemorrhage	10052534
Administration site haematoma	10075100	Large intestinal ulcer haemorrhage	10061262
Administration site haemorrhage	10075101	Laryngeal haematoma	10070885
Adrenal haematoma	10059194	Laryngeal haemorrhage	10065740
Adrenal haemorrhage	10001361	Lip haematoma	10066304
Anal haemorrhage	10049555	Lip haemorrhage	10049297
Anal ulcer haemorrhage	10063896	Liver contusion	10067266
Anastomotic haemorrhage	10056346	Lower gastrointestinal haemorrhage	10050953
Anastomotic ulcer haemorrhage	10002244	Lymph node haemorrhage	10074270
Aneurysm ruptured	10048380	Mallory-Weiss syndrome	10026712
Anorectal varices haemorrhage	10068925	Mediastinal haematoma	10049941
Aortic aneurysm rupture	10002886	Mediastinal haemorrhage	10056343
Aortic dissection rupture	10068119	Melaena	10027141
Aortic intramural haematoma	10067975	Melaena	10027141
Aortic rupture	10060874	Melaena neonatal	10049777
Aponeurosis contusion	10075330	Meningorrhagia	10052593
Application site bruise	10050114	Menometrorrhagia	10027295

Application site haematoma	10068317	Menorrhagia	10027313
Application site haemorrhage	10072694	Menorrhagia	10027313

MedDRA 17.1 Preferred Term	Preferred Term Code	MedDRA 17.1 Preferred Term	Preferred Term Code
Arterial haemorrhage	10060964	Mesenteric haematoma	10071557
Arterial intramural haematoma	10074971	Mesenteric haemorrhage	10060717
Arterial rupture	10003173	Metrorrhagia	10027514
Arteriovenous fistula site haematoma	10055150	Mouth haemorrhage	10028024
Arteriovenous fistula site haemorrhage	10055123	Mouth haemorrhage	10028024
Arteriovenous graft site haematoma	10055152	Mucosal haemorrhage	10061298
Arteriovenous graft site haemorrhage	10055126	Muscle contusion	10070757
Astringent therapy	10067372	Muscle haemorrhage	10028309
Atrial rupture	10048761	Myocardial haemorrhage	10048849
Auricular haematoma	10003797	Myocardial rupture	10028604
Basal ganglia haemorrhage	10067057	Naevus haemorrhage	10062955
Bladder tamponade	10062656	Nail bed bleeding	10048891
Bleeding time abnormal	10049227	Nasal septum haematoma	10075027
Bleeding time abnormal	10049227	Neonatal gastrointestinal haemorrhage	10074159
Bleeding time prolonged	10005140	Nephritis haemorrhagic	10029132
Bleeding varicose vein	10005144	Nipple exudate bloody	10029418
Blood blister	10005372	Ocular retrobulbar haemorrhage	10057571
Blood urine	10005863	Oesophageal haemorrhage	10030172
Blood urine present	10018870	Oesophageal ulcer haemorrhage	10030202
Bloody discharge	10057687	Oesophageal varices haemorrhage	10030210

Bloody peritoneal effluent	10067442	Oesophagitis haemorrhagic	10030219
Bone contusion	10066251	Optic disc haemorrhage	10030919
Bone marrow haemorrhage	10073581	Optic nerve sheath haemorrhage	10030941
Brain stem haematoma	10073230	Oral mucosa haematoma	10074779

MedDRA 17.1 Preferred Term	Preferred Term Code	MedDRA 17.1 Preferred Term	Preferred Term Code
Brain stem haemorrhage	10006145	Osteorrhagia	10051937
Breast haematoma	10064753	Ovarian haematoma	10033263
Breast haemorrhage	10006254	Ovarian haemorrhage	10065741
Broad ligament haematoma	10006375	Pancreatic haemorrhage	10033625
Bronchial haemorrhage	10065739	Pancreatitis haemorrhagic	10033650
Cardiac contusion	10073356	Papillary muscle haemorrhage	10059164
Carotid aneurysm rupture	10051328	Paranasal sinus haematoma	10069702
Catheter site bruise	10063587	Parathyroid haemorrhage	10059051
Catheter site haematoma	10055662	Parotid gland haemorrhage	10051166
Catheter site haemorrhage	10051099	Pelvic haematoma	10054974
Central nervous system haemorrhage	10072043	Pelvic haematoma obstetric	10034248
Cephalhaematoma	10008014	Pelvic haemorrhage	10063678
Cerebellar haematoma	10061038	Penile contusion	10073352
Cerebellar haemorrhage	10008030	Penile haematoma	10070656
Cerebral aneurysm ruptured syphilitic	10008076	Penile haemorrhage	10034305
Cerebral arteriovenous malformation haemorrhagic	10008086	Peptic ulcer haemorrhage	10034344
Cerebral haematoma	10053942	Pericardial haemorrhage	10034476
Cerebral haemorrhage	10008111	Perineal haematoma	10034520

Cerebral haemorrhage foetal	10050157	Periorbital contusion	10062515
Cerebral haemorrhage neonatal	10008112	Periorbital haematoma	10034544
Cerebral microhaemorrhage	10067277	Peripartum haemorrhage	10072693
Cervix haematoma uterine	10050020	Perirenal haematoma	10049450
Cervix haemorrhage uterine	10050022	Peritoneal haematoma	10058095
Choroidal haematoma	10068642	Peritoneal haemorrhage	10034666

MedDRA 17.1 Preferred Term	Preferred Term Code	MedDRA 17.1 Preferred Term	Preferred Term Code
Choroidal haemorrhage	10008786	Petechiae	10034754
Chronic gastrointestinal bleeding	10050399	Petechiae	10034754
Ciliary body haemorrhage	10057417	Pharyngeal haematoma	10068121
Coital bleeding	10065019	Pharyngeal haemorrhage	10034827
Colonic haematoma	10009996	Pituitary haemorrhage	10049760
Conjunctival haemorrhage	10010719	Placenta praevia haemorrhage	10035121
Conjunctival haemorrhage	10010719	Platelet count decreased	10035528
Contusion	10050584	Polymenorrhagia	10064050
Corneal bleeding	10051558	Post abortion haemorrhage	10036246
Cullen's sign	10059029	Post procedural contusion	10073353
Cystitis haemorrhagic	10011793	Post procedural haematoma	10063188
Deep dissecting haematoma	10074718	Post procedural haematuria	10066225
Diarrhoea haemorrhagic	10012741	Post procedural haemorrhage	10051077
Disseminated intravascular coagulation	10013442	Post transfusion purpura	10072265
Diverticulitis intestinal haemorrhagic	10013541	Postmenopausal haemorrhage	10055870
Diverticulum intestinal haemorrhagic	10013560	Postpartum haemorrhage	10036417

Duodenal ulcer haemorrhage	10013839	Premature separation of placenta	10036608
Duodenitis haemorrhagic	10013865	Procedural haemorrhage	10071229
Dysfunctional uterine bleeding	10013908	Proctitis haemorrhagic	10036778
Ear haemorrhage	10014009	Prostatic haemorrhage	10036960
Ear haemorrhage	10014009	Pulmonary alveolar haemorrhage	10037313
Ecchymosis	10014080	Pulmonary contusion	10037370
Encephalitis haemorrhagic	10014589	Pulmonary haematoma	10054991
Enterocolitis haemorrhagic	10014896	Pulmonary haemorrhage	10037394

MedDRA 17.1 Preferred Term	Preferred Term Code	MedDRA 17.1 Preferred Term	Preferred Term Code
Epidural haemorrhage	10073681	Puncture site haemorrhage	10051101
Epistaxis	10015090	Purpura	10037549
Epistaxis	10015090	Purpura	10037549
Exsanguination	10015719	Purpura neonatal	10037557
Extradural haematoma	10015769	Purpura senile	10037560
Extravasation blood	10015867	Putamen haemorrhage	10058940
Eye contusion	10073354	Radiation associated haemorrhage	10072281
Eye haemorrhage	10015926	Rectal haemorrhage	10038063
Eyelid bleeding	10053196	Rectal ulcer haemorrhage	10038081
Eyelid contusion	10075018	Renal cyst haemorrhage	10059846
Eyelid haematoma	10064976	Renal haematoma	10038459
Foetal-maternal haemorrhage	10016871	Renal haemorrhage	10038460
Gastric haemorrhage	10017788	Respiratory tract haemorrhage	10038727
Gastric ulcer haemorrhage	10017826	Respiratory tract haemorrhage neonatal	10038728

Gastric ulcer haemorrhage, obstructive	10017829	Retinal haemorrhage	10038867
Gastric varices haemorrhage	10057572	Retinopathy haemorrhagic	10051447
Gastritis alcoholic haemorrhagic	10017857	Retroperitoneal haematoma	10058360
Gastritis haemorrhagic	10017866	Retroperitoneal haemorrhage	10038980
Gastroduodenal haemorrhage	10053768	Retroplacental haematoma	10054798
Gastroduodenitis haemorrhagic	10048712	Ruptured cerebral aneurysm	10039330
Gastrointestinal angiodysplasia haemorrhagic	10017929	Scleral haemorrhage	10050508
Gastrointestinal haemorrhage	10017955	Scrotal haematocoele	10061517
Gastrointestinal haemorrhage	10017955	Scrotal haematoma	10039749

MedDRA 17.1 Preferred Term	Preferred Term Code	MedDRA 17.1 Preferred Term	Preferred Term Code
Gastrointestinal polyp haemorrhage	10074437	Shock haemorrhagic	10049771
Gastrointestinal ulcer haemorrhage	10056743	Skin haemorrhage	10064265
Genital contusion	10073355	Skin ulcer haemorrhage	10050377
Genital haemorrhage	10061178	Small intestinal haemorrhage	10052535
Gingival bleeding	10018276	Small intestinal ulcer haemorrhage	10061550
Gingival bleeding	10018276	Soft tissue haemorrhage	10051297
Graft haemorrhage	10063577	Soft tissue haemorrhage	10051297
Grey Turner's sign	10075426	Spermatic cord haemorrhage	10065742
Haemarthrosis	10018829	Spinal cord haemorrhage	10048992
Haematemesis	10018830	Spinal epidural haematoma	10050162
Haematochezia	10018836	Spinal epidural haemorrhage	10049236
Haematochezia	10018836	Spinal haematoma	10048464
Haematoma	10018852	Spinal subarachnoid haemorrhage	10073564

Haematoma evacuation	10060733	Spinal subdural haematoma	10050164
Haematoma infection	10051564	Spinal subdural haemorrhage	10073563
Haematosalpinx	10050468	Spleen contusion	10073533
Haematospermia	10018866	Splenic haematoma	10041646
Haematotympanum	10063013	Splenic haemorrhage	10041647
Haematuria	10018867	Splenic varices haemorrhage	10068662
Haematuria	10018867	Splinter haemorrhages	10041663
Haematuria traumatic	10018871	Spontaneous haematoma	10065304
Haemobilia	10058947	Spontaneous haematoma	10065304
Haemophilic arthropathy	10065057	Spontaneous haemorrhage	10074557
Haemoptysis	10018964	Spontaneous haemorrhage	10074557

MedDRA 17.1 Preferred Term	Preferred Term Code	MedDRA 17.1 Preferred Term	Preferred Term Code
Haemorrhage	10055798	Stoma site haemorrhage	10074508
Haemorrhage coronary artery	10055803	Stomatitis haemorrhagic	10042132
Haemorrhage foetal	10061191	Subarachnoid haemorrhage	10042316
Haemorrhage in pregnancy	10018981	Subarachnoid haemorrhage neonatal	10042317
Haemorrhage intracranial	10018985	Subchorionic haematoma	10072596
Haemorrhage neonatal	10061993	Subcutaneous haematoma	10042345
Haemorrhage subcutaneous	10018999	Subdural haematoma	10042361
Haemorrhage subepidermal	10019001	Subdural haematoma evacuation	10042363
Haemorrhage urinary tract	10055847	Subdural haemorrhage	10042364
Haemorrhagic anaemia	10052293	Subdural haemorrhage neonatal	10042365

Haemorrhagic arteriovenous malformation	10064595	Subgaleal haematoma	10069510
Haemorrhagic ascites	10059766	Subretinal haematoma	10071935
Haemorrhagic cerebral infarction	10019005	Testicular haemorrhage	10051877
Haemorrhagic diathesis	10062713	Thalamus haemorrhage	10058939
Haemorrhagic disease of newborn	10019008	Third stage postpartum haemorrhage	10043449
Haemorrhagic disorder	10019009	Thoracic haemorrhage	10062744
Haemorrhagic erosive gastritis	10067786	Thrombocytopenia	10043554
Haemorrhagic hepatic cyst	10067796	Thrombocytopenia	10043554
Haemorrhagic infarction	10019013	Thrombocytopenic purpura	10043561
Haemorrhagic ovarian cyst	10060781	Thrombocytopenic purpura	10043561
Haemorrhagic stroke	10019016	Thrombotic thrombocytopenic purpura	10043648
Haemorrhagic thyroid cyst	10072256	Thyroid haemorrhage	10064224

MedDRA 17.1 Preferred Term	Preferred Term Code	MedDRA 17.1 Preferred Term	Preferred Term Code
Haemorrhagic transformation stroke	10055677	Tongue haematoma	10043959
Haemorrhagic tumour necrosis	10054096	Tongue haemorrhage	10049870
Haemorrhagic urticaria	10059499	Tonsillar haemorrhage	10057450
Haemorrhagic vasculitis	10071252	Tooth pulp haemorrhage	10072228
Haemorrhoidal haemorrhage	10054787	Tooth socket haemorrhage	10064946
Haemostasis	10067439	Tracheal haemorrhage	10062543
Haemothorax	10019027	Traumatic haematoma	10044522
Henoch-Schonlein purpura	10019617	Traumatic haemorrhage	10053476

Hepatic haemangioma rupture	10054885	Traumatic haemothorax	10074487
Hepatic haematoma	10019676	Traumatic intracranial haemorrhage	10061387
Hepatic haemorrhage	10019677	Tumour haemorrhage	10049750
Hereditary haemorrhagic telangiectasia	10019883	Ulcer haemorrhage	10061577
Hyperfibrinolysis	10074737	Umbilical cord haemorrhage	10064534
Hyphaema	10020923	Umbilical haematoma	10068712
Iliac artery rupture	10072789	Umbilical haemorrhage	10045455
Immune thrombocytopenic purpura	10074667	Upper gastrointestinal haemorrhage	10046274
Implant site bruising	10063850	Ureteric haemorrhage	10065743
Implant site haematoma	10063780	Urethral haemorrhage	10049710
Implant site haemorrhage	10053995	Urinary bladder haemorrhage	10046528
Incision site haematoma	10059241	Urogenital haemorrhage	10050058
Incision site haemorrhage	10051100	Urogenital haemorrhage	10050058
Increased tendency to bruise	10021688	Uterine haematoma	10063875
Increased tendency to bruise	10021688	Uterine haemorrhage	10046788
MedDRA 17.1 Preferred Term	Preferred Term Code	MedDRA 17.1 Preferred Term	Preferred Term Code
Induced abortion haemorrhage	10052844	Vaccination site bruising	10069484
Infusion site bruising	10059203	Vaccination site haematoma	10069472
Infusion site haematoma	10065463	Vaccination site haemorrhage	10069475
Infusion site haemorrhage	10065464	Vaginal haematoma	10046909
Injection site bruising	10022052	Vaginal haemorrhage	10046910
Injection site haematoma	10022066	Varicose vein ruptured	10046999

Injection site haemorrhage	10022067	Vascular pseudoaneurysm ruptured	10053949
Instillation site haematoma	10073609	Vascular purpura	10047097
Instillation site haemorrhage	10073610	Vascular rupture	10053649
Internal haemorrhage	10075192	Venous haemorrhage	10065441
Intestinal haematoma	10069829	Ventricle rupture	10047279
Intestinal haemorrhage	10059175	Vessel puncture site bruise	10063881
Intra-abdominal haematoma	10056457	Vessel puncture site haematoma	10065902
Intra-abdominal haemorrhage	10061249	Vessel puncture site haemorrhage	10054092
Intracerebral haematoma evacuation	10062025	Vitreous haematoma	10071936
Intracranial haematoma	10059491	Vitreous haemorrhage	10047655
Intracranial tumour haemorrhage	10022775	Vulval haematoma	10047756
Intraocular haematoma	10071934	Vulval haematoma evacuation	10047757
Intrapartum haemorrhage	10067703	Vulval haemorrhage	10063816
Intraventricular haemorrhage	10022840	Wound haematoma	10071504
Intraventricular haemorrhage neonatal	10022841	Wound haemorrhage	10051373

APPENDIX 4. SOLICITED ADVERSE EVENT (AE) INTENSITY GRADING

Adverse Event	Age	Intensity Grade	Parameter
Pain at injection site	< 6 years of age	0: None	-
		1: Mild	Minor reaction to touch
		2: Moderate	Cries/protests on touch
		3: Severe	Cries when limb is moved/spontaneously painful
	≥ 6 years of age	0: None	-
		1: Mild	Any pain neither interfering with nor preventing normal every day activities
		2: Moderate	Painful when limb is moved and interferes with every day activities

		3: Severe	Significant pain at rest. Prevents normal every day activities
Redness * at injection site	All		Record greatest surface diameter in mm
Swelling at injection site	All		Record greatest surface diameter in mm
Fever **	All		Record temperature in °C/°F
Fatigue	≥ 6 years of age	0: Normal	-
		1: Mild	Fatigue that is easily tolerated
		2: Moderate	Fatigue that interferes with normal activity
		3: Severe	Fatigue that prevents normal activity
Gastrointestinal symptoms (nausea, vomiting, diarrhoea and/ or abdominal pain)	≥ 6 years of age	0: Normal	-
		1: Mild	Gastrointestinal symptoms that are easily tolerated
		2: Moderate	Gastrointestinal symptoms that interfere with normal activity
		3: Severe	Gastrointestinal symptoms that prevent normal activity
Headache	≥ 6 years of age	0: Normal	-
		1: Mild	Headache that is easily tolerated
		2: Moderate	Headache that interferes with normal activity
		3: Severe	Headache that prevents normal activity
Drowsiness	< 6 years of age	0: None	Behaviour as usual
		1: Mild	Drowsiness easily tolerated
		2: Moderate	Drowsiness that interferes with normal activity
		3: Severe	Drowsiness that prevents normal activity
Irritability/Fussiness	< 6 years of age	0: None	Behaviour as usual
		1: Mild	Crying more than usual/no effect on normal activity
		2: Moderate	Crying more than usual/interferes with normal activity
		3: Severe	Crying that cannot be comforted/prevents normal activity
Loss of appetite	< 6 years of age	0: None	Appetite as usual
		1: Mild	Eating less than usual/no effect on normal activity
		2: Moderate	Eating less than usual/interferes with normal activity
		3: Severe	Not eating at all

***** In case it is not possible to determine the extent of redness on darkly pigmented skin, it will be reported as uninterpretable on the Diary Card and in eSource.

** Fever is defined as temperature ≥ 37.5°C / 99.5°F. The preferred route for recording temperature in this study will be axillary.

The intensity of local vaccination site redness/swelling will be scored as follows:

Age	Intensity Grade	Diameter Measurement (mm)
1 to 5 years of age	0: None	-
	1: Mild	> 0 to ≤ 10
	2: Moderate	> 10 to ≤ 30
	3: Severe	> 30
6 to 12 years of age	0: None	-
	1: Mild	> 0 to ≤ 20
	2: Moderate	> 20 to ≤ 50
	3: Severe	> 50
13 to 17 years of age	0: None	≤ 20
	1: Mild	> 20 to ≤ 50
	2: Moderate	> 50 to ≤ 100
	3: Severe	> 100

The intensity of fever will be scored as follows:

Age	Intensity Grade	Temperature Reading (˚C)
All	0: None	< 37.5
	1: Mild	≥ 37.5 to ≤ 38.5
	2: Moderate	> 38.5 to ≤ 39.5
	3: Severe	> 39.5

APPENDIX 5. LABORATORY ASSESSMENTS

Category	Test	Reported Unit	Conversion Factor	SI Unit	Toxicity Grading
Haematology	Basophils	%	1	%	
	Basophils absolute	/mm^3	0.001	10^9/L	
	Eosinophils	%	1	%	
	Eosinophils absolute	/mm^3	0.001	10^9/L	
	Haemoglobin	g/dL	10	g/L	Haemoglobin
	Lymphocytes	%	1	%	
	Lymphocytes absolute	/mm^3	0.001	10^9/L	
	Mean cell volume	fL	1	fL	
	Monocytes	%	1	%	
	Monocytes absolute	/mm^3	0.001	10^9/L	
	Neutrophils	%	1	%	

	Neutrophils absolute	/mm^3	0.001	10^9/L	
	Platelets	/mm^3	0.001	10^9/L	Platelets
	Red blood cells	/mm^3	0.000001	10^12/L	
	White blood cells	x10^3/µL	0.001	10^9/L	White blood cells - decrease
Biochemistry	Alanine aminotransferase	U/L	1	U/L	Alanine aminotransferase increase by factor
	Creatinine	umol/L	1	umol/L	Creatinine
		mg/dL	88.4	umol/L	

APPENDIX 6. LABORATORY TOXICITY GRADING

Category	Test (Unit)	Age	Gender	Grade			
				1	2	3	4
Haematology	Haemoglobin (g/dL)	≤ 12 years of age	Both	7.5 to 8.49	6.5 to 7.49	5 to 6.49	< 5
		> 12 years of age	Male	10 to 10.9	9 to 9.9	8 to 8.9	< 8
			Female	8.5 to 9.4	7.5 to 8.4	6.5 to 7.4	< 6.5

	Platelets ($x10^3/\mu L$)	≤ 12 years of age	Both	75 to 99.999	50 to 74.999	25 to 49.999	< 25
		> 12 years of age	Both	75 to 100	50 to 74.999	25 to 49.999	< 25
	White blood cells - decrease ($x10^3/\mu L$)	≤ 12 years of age	Both	2.5 to 3.999	1.50 to 2.499	1 to 1.499	< 1
		> 12 years of age	Both	2 to 2.749	1.50 to 1.999	1 to 1.499	< 1
Biochemistry	Creatinine (mg/dL)	≤ 12 years of age	Both	1.2 to 1.7	> 1.7 to 2.1	> 2.1 to 2.5	> 2.5
		> 12 years of age	Both	1.5 to 1.7	> 1.7 to 2	> 2.0 to 2.5	> 2.5
	Alanine aminotransferase increase by factor	≤ 12 years of age	Both	1.1 to 2.5xULN	> 2.5 to 5.0xULN	> 5.0 to 10xULN	> 10xULN
		> 12 years of age	Both	1.1 to 2.5xULN	> 2.5 to 5.0xULN	> 5.0 to 10xULN	> 10xULN

ULN: Upper limit of the normal range.

Note: acceptable limits for eligibility and grading scale adapted from Division of AIDS table for grading severity of adult and pediatric adverse events December 2004; WHO Toxicity Grading Scale for Determining Severity of Adverse Events, February 2003; Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, Guidance for Industry, 2007.

APPENDIX 7. VITAL SIGNS ASSESSMENTS

Assessment	Unit
Temperature	C
Height	cm

Weight	kg
Heart rate	beats per minute
Respiratory rate	breaths per minute

APPENDIX 8. PHYSICAL ASSESSMENTS

Assessment
Abdomen
Anorectal
Breast
Cardiovascular
Eyes/Ears/Nose/Throat
Genitalia
Head/Neck/Thyroid
Lymph nodes
Musculoskeletal
Neurological
Respiratory
Skin

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STATISTICAL ANALYSIS PLAN

202090 (EBOLA Z CHAD3-004)

A PHASE 2, RANDOMISED, OBSERVER-BLIND, CONTROLLED, MULTI-COUNTRY STUDY TO ASSESS THE SAFETY AND IMMUNOGENICITY OF A SINGLE INTRAMUSCULAR DOSE OF GSK BIOLOGICALS' INVESTIGATIONAL RECOMBINANT CHIMPANZEE ADENOVIRUS TYPE 3-VECTORED EBOLA ZAIRE VACCINE (CHAD3-EBO-Z) (GSK3390107A), IN CHILDREN 1 TO 17 YEARS OF AGE IN AFRICA

AUTHOR: PPD

VERSION NUMBER AND DATE: 2.0 14JUN2017

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Effective Date: 01May2012

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V2.0 (dated 14JUN2017) for Protocol 202090 (EBOLA Z CHAD3-004).

	Name	Signature	Date (DDMMMYYYY)
Author:	[redacted]	[redacted]	19JUN2017
Position:	Statistical Team Lead		
Company:	QuintilesIMS		

Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the interim and final analysis of this study.

	Name	Signature	Date (DDMMMYYYY)
Approved By:	[redacted]	[redacted]	19 JUN 2017
Position:	Statistician		
Company:	GSK		
Approved By:	[redacted]	[redacted]	19 JUN 2017
Position:	Clinical Research & Development Lead (CRDL)		
Company:	GSK		

MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorised Version
1.0	18APR2016	PPD	Not Applicable – First Version

2.0	14JUN2017	PPD	Added the additional analysis as was prepared on an ad hoc basis for the interim analysis as well as some pooled tables and figures based on the additional analysis. Added pregnancy summary. Removed the anti-GP above threshold analyses. Update the Quintiles logo to the QuintilesIMS logo.

TABLE OF CONTENTS

1. INTRODUCTION

This document describes the rules and conventions that will be used in the planned presentation and analysis of safety and immunology data for Protocol 202090 (EBOLA Z CHAD3-004) as set out in the latest version of the interim and final analysis table, listing and figure (TLF) shells. It describes the data that will be summarised and analysed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on:

- Amendment 2 Final version of the protocol, dated 06MAY2015.
- Addendum Ghana, dated 07AUG2015.
- Latest version of the analysis cohort assignment documentation.

This version of the SAP is focused on the safety and immunology data for the unblinded interim analysis as well as the final analysis.

2. STUDY OBJECTIVES AND ENDPOINTS

The following relates to the overall study objectives as described in Section 2: Objectives, of the protocol, as well as the overall study endpoints as described in Section 11: Statistical Methods, of the protocol.

2.1. PRIMARY OBJECTIVE AND ENDPOINTS

2.1.1. PRIMARY OBJECTIVE

The primary objective is to assess the safety and reactogenicity of a single intramuscular dose of the ChAd3-EBO-Z vaccine:

- Overall.
- Separately in children aged:
  - 1 to 5 years.
  - 6 to 12 years.
  - 13 to 17 years.

2.1.2. PRIMARY ENDPOINTS

- Occurrence of each solicited local and general adverse event (AE), during a 7-day follow-up period after each vaccination (that is, the day of vaccination and 6 subsequent days), in all subjects, in both groups.
- Occurrence of any unsolicited AE, during a 30-day follow-up period after each vaccination (that is, the day of vaccination and 29 subsequent days), in all subjects, in both groups.
- Occurrence of haematological (complete blood count [CBC], including differential count and platelet count) and biochemical (alanine aminotransferase [ALT], creatinine) laboratory abnormalities at Screening, Day 3, Day 6, Day 30, Month 6, Month 6 + 6 days, Month 6 + 30 days and Month 12 in all subjects, in both groups.
- Occurrence of clinical symptoms of thrombocytopenia (AE of specific interest), during a 7-day follow-up period after vaccination at Day 0 (that is, Day 0 up to Day 6), in all subjects, in both groups.
- Occurrence of any serious adverse event (SAE), in all subjects, in both groups.

2.2. SECONDARY OBJECTIVE AND ENDPOINTS

2.2.1. SECONDARY OBJECTIVE

The secondary objective is to assess the humoral immunogenicity of a single intramuscular dose of the ChAd3EBO-Z vaccine, in terms of anti-glycoprotein (GP) Ebola Virus Zaire (EBOV) antibody responses:

- Overall.
- Separately in children aged:
  - 1 to 5 years.
  - 6 to 12 years.
  - 13 to 17 years.

2.2.2. SECONDARY ENDPOINT

- Anti-GP EBOV antibody concentrations, as measured by enzyme-linked immunosorbent assay (ELISA):
  - At Day 0 and Day 30, in all subjects, in both groups.
  - At Month 6 and Month 6 + 30 days, in all subjects in the Group MENACWY-TT/EBO-Z.

2.3. TERTIARY OBJECTIVES AND ENDPOINTS

2.3.1. TERTIARY OBJECTIVES

The exploratory objectives are:

- To assess the persistence of the humoral immune response induced by a single intramuscular dose of the ChAd3-EBO-Z vaccine, in terms of anti-GP EBOV antibody responses:
  - Overall.
  - Separately in children aged:
    - 1 to 5 years.
    - 6 to 12 years.
    - 13 to 17 years.
- To assess EBOV-specific cell-mediated immunity (CMI) of a single intramuscular dose of the ChAd3-EBO-Z vaccine:
  - Overall.
  - Separately in children aged:
    - 1 to 5 years.
    - 6 to 12 years.
    - 13 to 17 years.
- To assess the pre-existing immunity to the ChAd3 virus vaccine vector prior vaccination, ChAd3-specific immune responses after vaccination and explore its potential impact on Ebola-specific immune responses:
  - Overall.
  - Separately in children aged:

1 to 5 years.
6 to 12 years.
13 to 17 years.

- If deemed necessary, to further characterise the immune response to/the safety profile of the investigational ChAd3-EBO-Z vaccine.

2.3.2. TERTIARY ENDPOINTS

- Anti-GP EBOV antibody concentrations, as measured by ELISA:
  - o At Month 6 and Month 6 + 30 days, in all subjects, in the Group EBO-Z/MENAWY-TT. o At Month 12, in all subjects, in both groups.
- Magnitude, responder rate and cytokine co-expression profile of ChAd3-EBO Z-specific CD4+ or CD8+ T-cell responses, as assessed by intracellular cytokine staining (ICS) after stimulation with EBOV GP antigens:
  - o At Day 0, Day 30, Month 6, Month 6 + 30 days and Month 12, in a sub-cohort of 30 subjects per age stratum, per group.
- ChAd3 neutralising antibody titres, as measured by a neutralisation assay:
  - o At Day 0, Day 30 Month 6 and Month 6 + 30 days, in a subset of 30 subjects per age stratum, per group.

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

A phase 2, randomised, observer-blind, controlled, multi-country study with two groups and three age strata as described below in Table 1: Treatment Groups:

Table 1: Treatment Groups

Treatment Group	Age Stratum	Number of Subjects	Treatment Name	
			Day 0	Month 6
EBO-Z/MENACWY-TT	13 to 17 years	~100	ChAd3-EBO-Z	Nimenrix
	6 to 12 years	~100		
	1 to 5 years	~100		

	Total	~300		
MENACWY-TT/EBO-Z	13 to 17 years	~100	Nimenrix	ChAd3-EBO-Z
	6 to 12 years	~100		
	1 to 5 years	~100		
	Total	~300		

Randomised subjects will be followed for approximately 12 months from the Day 0 visit. Subjects will be randomised 1:1 to the two treatment groups. The randomisation will utilise stratification by age so that an equal number of children are randomised in each age stratum:

- 1 to 5 years.
- 6 to 12 years.
- 13 to 17 years.

In addition, the randomisation will utilise a minimisation procedure to account for the following factors:

- Gender.
- Centre (refer to Section 7.2: Multicentre Studies for details).

The study will have the following blinding implemented:

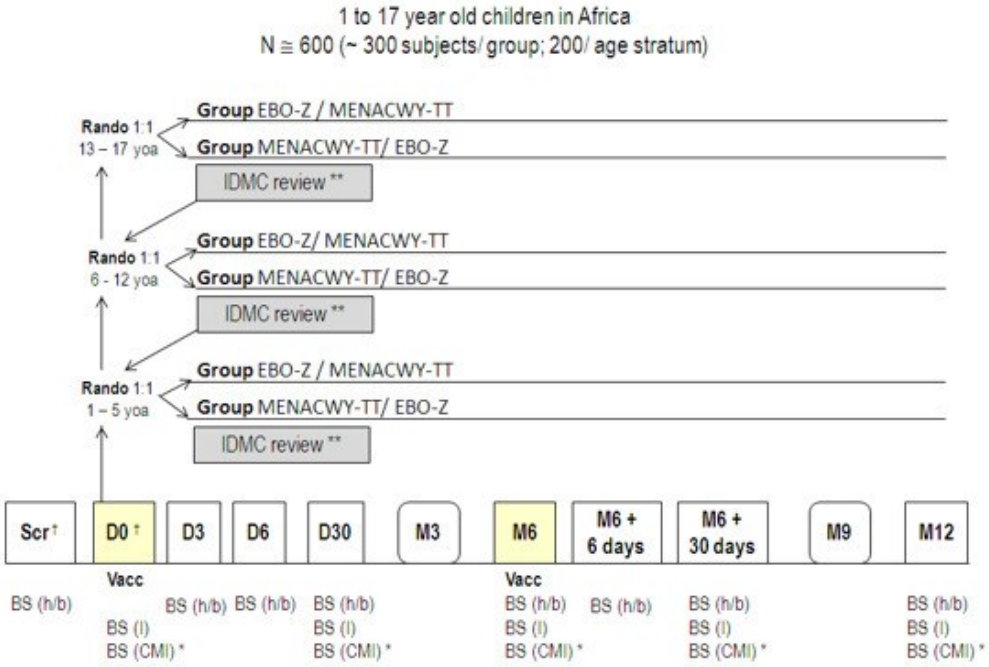
- Observer-blind:
  - From study start until the interim analysis (refer to Section 4.2: Interim Analysis for additional information).
- Single-blind:
  - From the interim analysis.

Additionally, a sub-selection of subjects will be enrolled into a sub-cohort:

- Sub-cohort for CMI, refer to Section 5.5.1: Sub-cohort for Cell-mediated Immunity (CMI for additional information.

The study design is presented below in Figure 1: Study Design Overview.

Figure 1: Study Design Overview



Rando = randomisation; **yoa** = years of age; **Scr** = Screening; **D** = Day; **M** = Month; **BS (h/b)** = blood sample for haematology/ biochemistry parameters; **BS (I)** = blood sample for humoral immunity; **BS (CMI)** = blood sample for cell-mediated immunity.

Squares indicate visits to the vaccination centre. Rounded rectangles indicate study contacts (home visit or phone call). Yellow-coloured visits indicate vaccination visits. At the Day 0 visit, subjects in the Group EBO-Z/ MENACWY-TT receive the investigational ChAd3-EBO-Z vaccine and subjects in Group MENACWY-TT/ EBO-Z receive *Nimenrix*. At the Month 6 visit, subjects in Group EBO-Z/ MENACWY-TT receive *Nimenrix* and subjects in the Group MENACWY-TT/ EBO-Z receive the investigational ChAd3-EBO-Z vaccine.

Subjects will be followed-up for adverse events (AEs) on a daily basis during the 7-day follow-up period after vaccination (day 0 to 6). During this period, AEs will be recorded on a Diary Card. On those days that no study visit is planned, a home visit will be scheduled.

† The Screening Visit and the Day 0 visit may take place on the same day (allowed interval 0 - 30 days).

* Only for subjects in the sub-cohort for CMI.

** IDMC review on all available safety data, which will include the safety data up to 7 days after vaccination at Day 0, from at least 50 children (25 per group) in an age stratum before proceeding to vaccination in the next (younger) age stratum (if applicable).

3.2. SCHEDULE OF EVENTS

Refer to Figure 1: Study Design Overview in the protocol, as well as Table 5: List of Study Procedures during Visits to the Vaccination Centre in the protocol.

3.3. CHANGES TO ANALYSIS FROM PROTOCOL

None.

4. PLANNED ANALYSES

The following analyses are planned for this study:

- Independent Data Monitoring Committee (IDMC) analyses.
- Interim Analysis.
- Final Analysis.

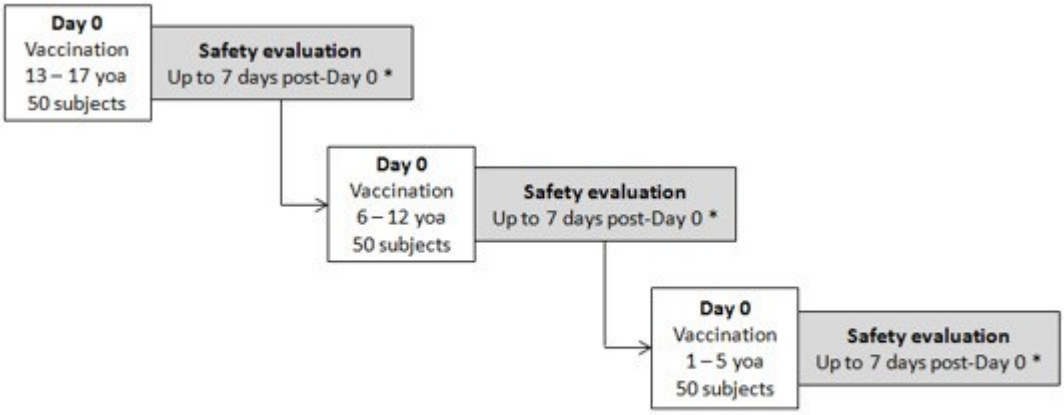
4.1. INDEPENDENT DATA MONITORING COMMITTEE (IDMC)

Unblinded IDMC analyses are planned for this study in order to ensure subject safety and monitor tolerability of the investigational vaccine. The IDMC will review safety and reactogenicity data from the current study as well as data from the EBOLA-Z ChAd3-005 study, which will be conducted in parallel with the current study.

Study vaccinations in this study will only start after a favourable outcome of an IDMC review of the safety and reactogenicity data from 100 adults after a 1-week follow-up in the EBOLA-Z ChAd3-005 study. In addition, vaccination at Day 0 will be done in a staggered manner, starting with the children in the oldest age stratum (13 to 17 years). For each age stratum, the IDMC will conduct a review of all available safety data once data is available up to at least 7 days after vaccination of at least 50 subjects, in that age stratum.

In order to proceed to vaccination of the subjects in the younger age stratum (6 to 12 years), a favourable outcome of the IDMC review of safety data up to at least 7 days after vaccination from at least 50 subjects (25 subjects per treatment group) in the oldest age stratum needs to be obtained. The same will be done for moving from the 6 to 12 years age stratum to vaccination of the youngest children (1 to 5 years). Refer to Figure 2: Overview of Staggered Design and Independent Data Monitoring Committee (IDMC) Safety Evaluations below for a description of the staggered approach per age stratum.

Figure 2: Overview of Staggered Design and Independent Data Monitoring Committee (IDMC) Safety Evaluations



* Safety evaluation on all available safety data from the entire study, which will include the safety data up to 7 days after vaccination at Day 0 from at least 50 subjects (25 subjects/ group) in the respective age stratum.

For the unblinded IDMC analyses the QuintilesIMS Biostatistics blinded team will produce all the required programs and blinded outputs. These programs and outputs will be transferred to the QuintilesIMS Biostatistics unblinded team. The QuintilesIMS Biostatistics unblinded team will reproduce all outputs based on the actual randomisation schedule and will then be responsible for providing the unblinded outputs to the IDMC members as specified in the latest version of the Biostatistics Blinded to Unblinded Team Handover Document (CS_TP_BS0214) for the EBO-Z CHAD3-004 study. Refer to the latest version of the unblinding plan for additional details with regard to the handling of unblinded information.

A separate set of IDMC TLF shells (latest version of EBO-Z_CHAD3_IDMC_Shells) has been created specifically for the IDMC analyses. In addition, the IDMC charter can be referenced for additional information regarding the IDMC analyses.

4.2. INTERIM ANALYSIS

An unblinded interim analysis will be conducted when safety and immunology data up to Day 30 have been collected for all subjects. All available safety and immunogenicity data in the interim analysis transfer will be included in the interim analysis. As per protocol, the blinded team will be unblinded at the time of the interim analysis and will produce the unblinded interim analysis TLFs.

The cleaning of the 30-day safety data for each subject will be scheduled to be completed prior to the unblinding in order to keep the blind during data cleaning activities.

The interim analysis is planned once the following has been completed:

- GSK's authorization of the following:
  - o SAP. o Relevant TLF shells. o Analysis cohort assignments.
- Immunogenicity data availability:

- At least the Day 30 anti-GP EBOV data should be available.

- Interim analysis data transfer from Data Management.

The interim analysis data transfer should comply with:

- All the data up to Day 30 is clean:
  - All outstanding data issues and queries resolved.
  - All unresolvable data issues documented in the Data Handling Report (DHR), a separate document produced by Data Management.
  - All coding, for example AEs, is completed. o All reconciliation of vendor data with eSource data completed successfully.

- Any additional data post-Day 30 should be as clean as possible.

4.3. FINAL ANALYSIS

All final, planned analyses identified in this SAP and relevant set of TLF shells will be performed by the QuintilesIMS Biostatistics blinded team. The final analysis is planned for when all subjects had completed study participation, following:

- GSK's authorization of the following:
  - Final version of the SAP. o Relevant set of TLF shells.
  - Analysis cohort assignments.

- Final database lock.

- All immunology data are available.

The final analysis will be performed on a clean database transfer:

- All outstanding data issues and queries were resolved.

- All unresolvable data issues documented in the DHR, a separate document produced by Data Management.

- All coding, for example AEs, is completed.

- All reconciliation of vendor data with eSource data completed successfully.

5. ANALYSIS COHORTS

GSK's authorization of the analysis cohort assignments is required at two time points:

- Prior to the interim analysis: Interim analysis cohort authorization.
- Prior to the final analysis: Final analysis cohort authorization:
  - Prior to the final analysis there will only be a review of the interim analysis cohort assignments as a confirmation of the inclusion of all subjects in the relevant analysis cohorts.

Refer to the relevant analysis cohort assignment documentation (latest version of CHAD3-004-EBO-Z_Cohort_Assignment_Plan) for additional information.

5.1. TOTAL ENROLLED COHORT

The Total Enrolled Cohort is defined as all subjects who signed informed consent, regardless of being randomised to either:

- EBO-Z/MENACWY-TT.
- MENACWY-TT/EBO-Z.

The Total Enrolled Cohort will be programmatically derived based on the informed consent information recorded on the Screening form in eSource.

5.2. TOTAL RANDOMISED COHORT

The Total Randomised Cohort is defined as all subjects who were randomised to either EBO-Z/MENACWY-TT or MENACWY-TT/EBO-Z, regardless of whether they received a vaccination.

A subject will be programmatically included in the Total Randomised Cohort if the subject had been randomised based on the treatment allocation information recorded on the Visit Day 0 form in eSource or reported in the Interactive Web Randomisation System (IWRS).

For analyses and presentations based on the Total Randomised Cohort, subjects are to be analysed according to the treatment allocated regardless of the treatment received.

5.3. TOTAL VACCINATED COHORT (TVC)

The Total Vaccinated Cohort (TVC) is defined as all subjects included in the Total Randomised Cohort who received at least one vaccination. The TVC is defined separately for safety and immunogenicity analyses as described below:

- Safety Analysis:

- A subject is to be programmatically included in the TVC if the subject has at least one date of vaccination available in the database.
- Labelled as 'Total Vaccinated Cohort' in relevant TLF shells.

- Immunogenicity Analysis:
  - Immunogenicity analysis based on the TVC will include all vaccinated subjects for whom immunogenicity results are available, however, due to the fact that only subjects with data available are to be included per time point for the immunogenicity analysis, there will be no additional elimination required. The TVC for safety and immunogenicity analyses are defined as the same cohort of subjects.

Subjects who received a different treatment to that allocated are to be analysed as described below:

- Analyse subject according to the treatment received at Day 0 (first vaccination).

5.4. ACCORDING-TO-PROTOCOL COHORT (ATP)

The According-to-protocol (ATP) Cohort is defined as all evaluable subjects satisfying the following:

- Meet all eligibility criteria.
- Received at least one dose of study vaccine according to protocol procedures and randomisation.
- Randomisation code has not been broken for vaccination at Day 0.
- Comply with the procedures and intervals defined in the protocol.
- Did not receive a concomitant medication/product/vaccination leading to elimination from an ATP analysis (refer to relevant section in the protocol, Section 6.7.2).
- Did not present with a medical condition leading to elimination from an ATP analysis (refer to the relevant section in the protocol, Section 6.8).
- Data concerning immunogenicity endpoint measurements are available.

The ATP Cohort will be used for immunogenicity analyses and will be defined prior to:

- Planned Interim Analysis based on the elimination code process.

Subjects included in the ATP Cohort did not receive a different treatment to that allocated, therefore the analysis would be the same for subjects whether based on the randomised or allocated treatment.

5.5. SUB-COHORTS AND SUBSETS OF SUBJECTS

5.5.1. SUB-COHORT FOR CELL-MEDIATED IMMUNITY (CMI)

The first approximately 30 subjects randomised per age stratum and group, (180 subjects in total, 90 per group) will be included in this sub-cohort. Subjects will be included from selected centres (refer to Section 7.2: Multicentre Studies) only. A blood sample for assessment of CMI should be taken from the subjects at the following visits:

- Day 0.
- Day 30.
- Month 6.
- Month 6 + 30 days.
- Month 12.

This sub-cohort will be programmatically assigned based on the relevant treatment allocation information recorded on the Visit Day 0 form in eSource. This sub-cohort will be labelled as the CMI Sub-cohort in the relevant presentations.

5.5.2. SUBSET FOR ADDITIONAL TESTING

A subset of the subjects will have additional humoral immunogenicity assays performed. These will be the same subjects as the subjects in the sub-cohort for CMI. These subjects will have the neutralizing antibodies assays performed. Other subjects will have the same samples available, however these samples will be used for other testing and not analysed within this protocol. This subset will be labelled as the Subset for Additional Testing in the relevant presentations.

6. GENERAL CONSIDERATIONS

6.1. REFERENCE START DATE AND RELATIVE DAY

Reference start date is defined as the date of first vaccination, and equals the Day 0 date. Relative day is calculated relative to the reference start date and is to be used to show start and stop day of an assessment or event. Relative day is calculated as follows:

- Relative day = (date of assessment/event – reference start date).

Unless otherwise specified, if the date of the assessment/event is partial or missing, relative day and any corresponding durations will not calculated and will be presented as missing in the listings. Imputed AE dates will be used in order to assign the AEs as either within or outside the relevant collection period and will not be used to calculate an imputed relative day (refer to APPENDIX 2: Partial Date Conventions).

Some presentations might include the relative day relative to the most recent vaccination (refer to Section 6.7.2: Most Recent Vaccination) and will be calculated as follows:

- If the date of the assessment/event is on or after the most recent vaccination:
  - Relative day to most recent vaccination = (date of event – date of most recent vaccination).

6.2. BASELINE

Unless otherwise specified, Baseline is defined as the last non-missing assessment (scheduled or unscheduled) prior to the first vaccination. In the case where the last non-missing assessment and the reference start date coincide, that assessment will be considered pre-baseline (unless specified as post-vaccination). However, adverse events (AEs) starting on the reference start date will be considered post-baseline.

6.3. DERIVED TIME POINTS

6.3.1. CHAD3-EBO-Z POST-VACCINATION TIME POINTS

As a first step, safety and/or immunogenicity results will be presented by treatment administered at Day 0.

In a second step, all available data post-vaccination with the investigational vaccine (Day 0 for the EBOZ/MENACWY-TT and Month 6 for the MENACWY-TT/EBO-Z treatment groups, respectively) will be pooled. All available safety and immunogenicity data following the ChAd3-EBO-Z vaccination in both the treatment groups will be pooled at the time points as specified in Table 2: Derivation of ChAd3-EBO-Z Post-vaccination Time Points:

Table 2: Derivation of ChAd3-EBO-Z Post-vaccination Time Points

ChAd3-EBO-Z Post-vaccination Time Point	Treatment Group	Visit
0 Days Post-vaccination with EBO-Z	EBO-Z/MENACWY-TT	Day 0
	MENACWY-TT/EBO-Z	Month 6
6 Days Post-vaccination with EBO-Z	EBO-Z/MENACWY-TT	Day 6
	MENACWY-TT/EBO-Z	Month 6 + 6 Days
30 Days Post-vaccination with EBO-Z	EBO-Z/MENACWY-TT	Day 30
	MENACWY-TT/EBO-Z	Month 6 + 30 Days
3 Months Post-vaccination with EBO-Z	EBO-Z/MENACWY-TT	Month 3
	MENACWY-TT/EBO-Z	Month 9
6 Months Post-vaccination with EBO-Z	EBO-Z/MENACWY-TT	Month 6
	MENACWY-TT/EBO-Z	Month 12

6.4. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

In general, for by-visit summaries, data recorded at the scheduled visit will be presented. Unscheduled assessments will not be included in by-visit summaries, but may contribute to the Baseline value.

In the case of a retest (same visit number assigned), the latest available test result as provided in the data transfer for that visit/time point will be used for by-visit summaries.

Listings will include scheduled and unscheduled assessments.

6.5. WINDOWING CONVENTIONS

No visit windowing will be performed for this study.

6.6. STATISTICAL TESTS

Unless otherwise specified, the default summary statistics will be the following:

- Quantitative variables:

- Number of subjects in each category (n).
- Mean.
- Standard deviation (SD).
- Median.
- Minimum.
- Maximum.
- First quartile (Q1).
- Third quartile (Q3).

- In case of log-transformed data for quantitative variables, the default summary statistics are to be as follows:
  - Number of subjects in each category (n).
  - Geometric mean.
  - Geometric SD.
  - Median.
  - Minimum.
  - Maximum.
  - Q1.
  - Q3.

- Qualitative variables:
  - Number of subjects in each category (n).
  - The percentage of subjects in each category (%) can be presented relative to either one of the following:
    - The total number of subjects in the relevant analysis cohort (and sub-cohort).
    - The total number of subjects in the relevant analysis cohort (and sub-cohort), with assessments available (observed cases).
    - Total number of subjects in the relevant analysis cohort with returned diary cards.
  - In the event of missing assessments, a 'Missing' category showing the number of subjects with missing assessments will be presented. Percentage of subjects with missing data will not be presented.

6.7. COMMON CALCULATIONS

6.7.1. CHANGE FROM BASELINE

For quantitative measurements, change from Baseline will be calculated as:

- Change from Baseline at Day x = (Result at Day x – Baseline Result).

If a result/value is missing, the change from Baseline will be presented as missing in the listing; hence no imputation for a missing change from Baseline will be performed.

6.7.2. MOST RECENT VACCINATION

Most recent vaccination prior to assessment/event:

- Calculate the difference in the assessment/start date and all available vaccination dates.
  - Assessments: Days since vaccination (Day 0/Month 6) = (Assessment date – vaccination date [Day 0/Month 6]).
  - Events: Days since vaccination (Day 0/Month 6) = (Event start date – vaccination date [Day 0/Month 6]).
- For previous calculation (difference in assess/start date and available vaccination dates), only consider those vaccinations where the days since vaccination is >= 0 and determine the vaccination (Day 0/Month 6) for which the days since vaccination (as calculated in the previous step) is a minimum.
- Assign the vaccination selected in the previous step (minimum days since vaccination determination) as the most recent.

6.7.3. DURATION

- Duration = End Date/Day – Start Date/Day + 1.
- The start and end date/days are defined in each of the relevant sections where the duration calculation is required.

6.8. SOFTWARE VERSION

All analyses will be conducted using SAS version 9.4.

7. STATISTICAL CONSIDERATIONS

7.1. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

Not applicable.

7.2. MULTICENTRE STUDIES

This study will be conducted by more than one investigators at more than one centre internationally. Among others, centre will be accounted for in the randomisation minimisation procedure. The following centres are included in this study:

Table 3: Study Centres

Country	Centre Number	Investigator	CMI Sub-cohort Enrolment (Yes/No)
Mali	P	Prof Samba Sow	Yes
Senegal	P	Prof Cheikh Ndour	Yes

All centres will be pooled in all analyses.

7.3. MISSING DATA

Missing safety data will not be imputed. For handling of partial or missing AE start dates, refer to Section APPENDIX 2: Partial Date Conventions.

7.4. MULTIPLE COMPARISONS/ MULTIPLICITY

Not applicable, the study does not include any confirmatory objectives. All analyses are descriptive.

7.5. EXAMINATION OF SUBGROUPS

No subgroup analyses will be performed for this study.

8. OUTPUT PRESENTATIONS

APPENDIX 1: Programming Conventions for Outputs describes the conventions for presentation of data in outputs.

The TLF shells provided together with this SAP describe the presentations for the interim/final analysis and therefore the format and content of the TLFs to be provided by QuintilesIMS Biostatistics.

Note that verbatim terms, specifications (for example the reason a specific assessment was not done) and all variables in the TLF shells that contain the suffix (eSource) contain verbatim text that may include spelling mistakes. Verbatim text is to be presented in the listings 'as is' and no manual 'hard-coding' corrections of such data are to be made.

9. DISPOSITION AND WITHDRAWALS

All subjects who provide informed consent will be accounted for in this study.

Subject disposition and withdrawals will be presented for the Total Enrolled Cohort or Total Randomised Cohort, as indicated below.

The following listings are planned for presentation:

- Subject disposition (Total Enrolled Cohort).
- Protocol violations (Total Enrolled Cohort).
- Inclusion and/or exclusion criteria exceptions (Total Enrolled Cohort).
- Analysis cohorts (Total Enrolled Cohort).

The following tables are planned for presentation:

- Subject enrolment and primary reason for screen failures (Total Enrolled Cohort).
- Subject disposition and primary reason for premature study withdrawal (Total Randomised Cohort as well as Total Vaccinated Cohort).
- Major protocol violations (Total Randomised Cohort).
- Analysis cohorts (Total Enrolled Cohort).

The following disposition variable, as presented in the planned TLF shells, will be collected on the Informed Consent form in eSource:

- Informed consent/assent date and time.

The following disposition variables, as presented in the planned TLF shells, will be collected on the Treatment Allocation and Vaccination form in eSource:

- No-sub-cohort: o Yes.
- Sub-cohort for CMI: o Yes.
- Randomised:
  - o Yes.
  - o No.

The following disposition variables, as presented in the planned TLF shells, will be collected on the Screening Conclusion form in eSource:

- Is the subject a screening failure:
  - o Yes.
  - o No.
- Primary reason for screen failure:

- o Eligibility criteria not fulfilled. o Protocol violation, specify. o Serious adverse event (SAE): o Related to study participation or GSK concurrent medication. o Not related to study participation or GSK concurrent medication, specify. o Consent withdrawal (not due to SAE). o Migrated/moved from the study area. o Lost to follow-up.
- o Other, specify.

- Date of screening conclusion completion.

The following disposition variables, as presented in the planned TLF shells, will be collected on the Study Conclusion form in eSource:

- Did the subject complete all study related visits:

  o Y
  es. o

  No.

- Primary reason for premature study withdrawal:

  - o SAE/AE. o Protocol violation, specify.
  - o Consent withdrawal (not due to an AE).
    - o Moved from the study area. o Lost to follow-up.
  - o Other, specify.

- Date of study conclusion completion.

The following disposition variable, as presented in the planned TLF shells, will be collected on the Emergency Unblinding form in eSource:

- Date and time of emergency unblinding.

The following eligibility criteria variables, as presented in the planned TLF shells, will be collected on the Eligibility Criteria form in eSource:

- Criterion category:

  - o Inclusion.
  - o Exclusion.

- Criterion number.

- Criterion met:

  - o Yes.
  - o No. o

Not done.

The following protocol deviation variables, as presented in the planned TLF shells, will be collected in Clinical Trial Management System (CTMS) and provided by the project manager:

- Protocol deviation type.
- Protocol deviation description.
- Date of protocol deviation.
- Protocol deviation severity.

The following variables, as presented in the planned TLF shells, will be imported from an EXCEL spreadsheet created for review of each analysis cohort assignment and as authorised by GSK (refer to Section 5: Analysis Cohorts):

- Included in analysis cohort (Yes/No):
  - Total Enrolled Cohort.
  - Total Randomised Cohort.
  - Total Vaccinated Cohort.
  - According-to-protocol Cohort.
- Reason(s) for exclusion from each analysis cohort.

9.1. DERIVATIONS

Based on the aforementioned variables the following variables, as presented in the planned TLF shells, will be derived:

- Reason not randomised:
  - Assigned as the primary reason for screen failure.
- Emergency unblinding (Yes/No):
  - Yes: If the date of emergency unblinding is reported.
  - No: If the date of emergency unblinding is not reported.
- Subject ongoing in the study (only applicable to the interim analysis):
  - Yes: Screening completed and study conclusion information not completed at the time of data transfer for analysis.
- Relative day:
  - Calculated relative to Day 0 vaccination (refer to Section 6.1: Reference Start Date and Relative Day).

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the Total Enrolled Cohort for the listings.

No statistical testing will be performed for demographic or other Baseline characteristics.

The following listing is planned for presentation:

- Demographics and other Baseline characteristics.

The following tables are planned for presentation:

- Demographics and other Baseline characteristics (Total Vaccinated Cohort).
    - This table will also be repeated for the following:
        CMI sub-cohort.
        According to Protocol Cohort.
        According to Protocol Cohort and CMI sub-cohort.
- Number of subjects by country (Total Enrolled Cohort).
- Number of subjects by age category:
    - Toddler (1-2 years). o Early childhood (3-5 years). o Middle childhood (6-11 years).
    - Early adolescence (12-17 years).

The following demography variables, as presented in the planned TLF shells, will be collected on the Demography and Medical History Review eSource form:

- Age (years):
    - Calculated relative to Screening in eSource.
- Race (geographic ancestry):
    - African heritage/African American. o American Indian or Alaskan native.
    - Asian:
        Central/South Asian heritage.
        East Asian heritage.
        Japanese heritage.
        South East Asian heritage.
    - Native Hawaiian or other Pacific islander. o White:
        Arabic/North African heritage.
        Caucasian/European heritage.
    - Other, specify.
- Ethnicity:
    - American Hispanic or Latino.

- Not American Hispanic or Latino.

The following demography variables, as presented in the planned TLF shells, will be collected on the Subject Information form in eSource:

- Date of birth: o Transferred as MMMYYYY.
- Gender:
  - Female (F).
  - Male (M).

The following Baseline characteristic variables, as presented in the planned TLF shells, will be collected on the Vital Signs form in eSource (refer to Section 6.2: Baseline for additional details):

- Baseline height (cm).
- Baseline weight (kg).

The following Baseline characteristic variables, as presented in the planned TLF shells will be collected on the Reproductive Status and Contraception Use for Females form in eSource:

- Childbearing potential:
  - Yes. o No, hysterectomy, bilateral ovariectomy or current tubal ligation. o No, pre-menarche.
- Adequate contraception use:
  - Yes. o No. o NA- same sex partners is their preferred and usual lifestyle.

The following demography variables, as presented in the planned TLF shells, will be imported from an EXCEL spreadsheet with the centre information provided by the project manager:

- Country and investigator information (refer to Section 7.2: Multicentre Studies for additional details).

The following demography variable, as presented in the planned TLF shells, will be included in the data transferred from eSource:

- Centre number.

10.1. DERIVATIONS

Based on the aforementioned variables, the following variable, as presented in the planned TLF shells is derived:

- Age category:
  - 1-2 years. o 3-5 years. o 6-11

years. o 12-17
years.

All listings, as presented in the relevant TLF shells, will include the following demographic information:

- Age (years).
- Gender.
- Race.

These demographic variables will be concatenated to form one demographic variable in the following format:

- Age (years)/Gender/Race:
  - For example:

13/M/WHITE.

11. MEDICAL HISTORY

The following medical history listing is planned for presentation for the Total Enrolled Cohort:

- Medical history.

The following medical history table is planned for presentation for the Total Vaccinated Cohort:

- Medical history:
  - Number and percentage of subjects with at least one medical history finding in each of the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class.
  - Subjects with more than one occurrence are counted only once per MedDRA System Organ Class.
  - Percentage will be calculated relative to the total number of subjects in the relevant analysis cohort.

Medical history will not be coded, however the MedDRA System Organ Class will be provided on the Medical History form in eSource, along with the following medical history variables, as presented in the TLF shells:

- MedDRA System Organ Class:
  - Blood and lymphatic system.
  - Cardiac. o Ear and labyrinth. o Endocrine. o Eye. o Gastrointestinal. o Hepatobiliary. o Immune system (including allergies, autoimmune disorders). o Infections and infestations. o Metabolism and nutrition. o Musculoskeletal and connective tissue. o Neoplasms benign, malignant and unspecified (including cysts, polyps). o Nervous system.
  - Psychiatric. o Renal and urinary. o Reproductive system and breast. o Skin and subcutaneous tissue.
  - Respiratory, thoracic and mediastinal. o Surgical and medical procedures.
  - Vascular. o Other.
- Verbatim term (diagnosis).
- Start date.
- End date.
- Ongoing:
  - Y

es. o

No.

- Intensity:
  - o Mild.
  - o Moderate. o Severe. o Not applicable.

11.1. DERIVATIONS

Based on the aforementioned variables, the following variable will be derived:

- Relative day:
  - o Calculated relative to Day 0 vaccination (refer to Section 6.1: Reference Start Date and Relative Day).

12. CONCOMITANT MEDICATION AND VACCINATIONS

The following concomitant medication and vaccination listing is planned for presentation for the Total Enrolled Cohort:

- Concomitant medication and vaccinations.

Concomitant medication and vaccinations will only be coded with Anatomical Therapeutic Chemical (ATC) codes using the WHO Drug Dictionary Enhanced version SEP2015. The following concomitant medication and vaccination variables, as presented in the planned TLF shells, will be collected on the Concomitant Medication and Vaccination form in eSource:

- Type:
  - Concomitant medication.
  - Concomitant vaccination.
- Verbatim term (drug/vaccination name).
- Dose.
- Dose unit.
- Frequency.
- Route:
  - Medication route.
  - Vaccine route.
- Start date.
- End date.
- Ongoing:
  - Yes.
  - No.
- Medication indication:
  - Treatment of a SAE.
  - Cause of SAE. o Not applicable.

12.1. DERIVATIONS

Based on the aforementioned variables, the following variable will be derived:

- Relative day:
  - Calculated relative to Day 0 vaccination (refer to Section 6.1: Reference Start Date and Relative Day).

13. STUDY VACCINATION

The following listing is planned for presentation for Total Randomised Cohort:

- Vaccination administration.

The following table is planned for presentation for the Total Randomised Cohort:

- Vaccination administration:
  - Number and percentage of subjects with a vaccination administration at each relevant visit. o Percentage will be calculated relative to the total number of subjects in the relevant analysis cohort.

The following vaccination variables, as presented in the planned TLF shells, will be collected on the Treatment Allocation and Vaccination form in eSource:

- Vaccination administered:
  - Y
  es. o
  No.
- Vaccination site:
  - Deltoid. o
  Thigh. o
  Other,
  specify.
- Vaccination side:
  - Right.
  - Left.
- Vaccination route:
  - Intramuscular.
  - Other, specify.
- Date and time of vaccination.
- Comment on vaccination administration.
- Reason for non-administration:
  - Serious Adverse Event related to study participation or to a GSK concurrent medication. o Serious Adverse Event not related to study participation or to a GSK concurrent medication. o Non-Serious Adverse Event. o Other, specify.
- Decision maker for non-administration:

- Investigator.
- Subject.
- Legally acceptable representative.

The following contraindication variables, as presented in the planned TLF shells, will be recorded on the Contraindication Review form in eSource:

- Fever (temperature ≥ 37.5˚C):
  - Yes.
  - No.
- Clinically significant immunosuppressive or immunodeficient condition:
  - Yes.
  - No.
- Pregnant:
  - Yes.
  - No.
- Had anaphylaxis following vaccine administration:
  - Yes.
  - No.

The following vaccination variables, as presented in the planned TLF shells, will be imported from the EXCEL spreadsheet received from Cenduit:

- Actual vaccination administered:
  - EBO-Z.
  - Nimenrix.

13.1. DERIVATIONS

Based on the aforementioned variables, the following variable will be derived:

- Relative day:
  - Calculated relative to Day 0 vaccination (refer to Section 6.1: Reference Start Date and Relative Day).

14. IMMUNOGENICITY

The following immunogenicity assays will be completed for the relevant sub-cohort as indicated below:

- Humoral immune response:

o Anti-GP EBOV. o ChAd3 neutralising antibody (subset for additional testing).

- CMI against Ebola:
  - o CD4+ or CD8+ T-cell response specific to EBOV (sub-cohort for CMI)

Refer to Table 11: Immunological Read-outs (Humoral Immunity) as well as Table 12: Immunological Read-outs (Cell-medicated Immunity) in the protocol for the specific details with regards to the collection of immunogenicity samples.

No imputation will be performed for missing immunogenicity data. Therefore, any analysis will exclude subjects with missing measurements at the specific time points.

All immunogenicity tables will be repeated for the derived time points as defined in Section 6.3.1: ChAd3-EBO-Z Post-vaccination Time Points.

All immunogenicity tables mentioned below will be repeated for the Total Vaccinated Cohort: Immunogenicity if at least 5 % of subjects in any treatment group are excluded from the According-to-protocol Cohort.

14.1. Humoral Immune Response

14.1.1. Anti-glycoprotein (GP) Ebola Virus Zaire (EBOV)

The following listing is planned for presentation for the Total Vaccinated Cohort: Immunogenicity:

- Anti-GP EBOV results.

The following tables are planned for presentation for the According-to-protocol Cohort:

- Anti-GP EBOV: Serological status:
  - o The number and percentage (%) of subjects in each status category (seronegative, seropositive and seroconversion for post-vaccination time points).
  - o Percentage (%) calculated relative to the number of subjects with results available in order to assign a status at each time point.
  - o 95% CIs for the seropositivity and -negativity rates will be presented for each treatment group.
- Anti-GP EBOV: Response:
  - o The number and percentage (%) of subjects in each category (Yes and No).
  - o Percentage (%) calculated relative to the number of subjects with results available at both pre-and post-vaccination time points at each time point.
  - o 95% CIs for the response rate will be presented for each treatment group.
- Anti-GP EBOV: Geometric mean concentrations (GMC) (depending on the outcome of validation):
  - o Summary statistics, refer to Section 6.6: Statistical Tests, based on the log-transformed concentration values.

- 95% CIs will be presented for the GMCs per each treatment group.
- GMC calculations are performed by taking the anti-log of the mean of the log10 concentration transformation.

- Anti-GP EBOV: Day 0 Geometric Mean Concentration
  - Summary statistics, refer to Section 6.6: Statistical Tests, based on the log-transformed concentration values.
  - This outputs would only contain the Baseline seropositive subjects.
  - Only Day 0 results will be presented. o 95% CIs for the GMCs will be presented for each treatment group.
  - GMC calculations are performed by taking the anti-log of the mean of the log10 concentration transformation.

The following figures are planned for presentation for the According-to-protocol Cohort:

- Reverse cumulative distribution curves:
  - Each plot shows antibody concentrations (on a log-scale) on the X-axis and the proportion of individuals exhibiting that concentrations or higher on the Y-axis.
- Day 0 Reverse Cumulative Distribution curve:
  - The plot shows antibody concentrations (on a log-scale) on the X-axis and the proportion of individuals exhibiting that concentrations or higher on the Y-axis.
  - This output would only contain the Baseline seropositive subjects. o Only Day 0 results will be presented.
- Concentration and GMCs:
  - Individual antibody concentrations at Day 0 and Day 30, with dot plots, per treatment group. o GMCs and 95% confidence intervals will also be plotted.
- Kinetic plot (only applicable to the final analysis):
  - GMCs, including 95% CIs at the EBO-Z post-vaccination time points. o Time points will be connected with straight lines.

All anti-GP EBOV tables will be presented by Baseline serological status, including the following categories:

- Seronegative.
- Seropositive.
- Total.

The following immunology variables, as presented in the planned TLF shells, will be collected on the Blood Sampling form in eSource:

- Were humoral immunity blood samples collected:
  - Y

es. o

No.

- Date and time of sample collection.

The following immunology variable, as presented in the planned TLF shells, will be imported from the laboratory report:

- Concentration value.

14.1.1.1. Derivations

Based on the aforementioned immunogenicity variables, the following variables, as presented in the planned TLF shells, will be derived:

- Log-transformed concentration values:
  - Log10 of the concentration values will be derived.
  - Results below the cut-off of the assay will be assigned as half of the cut-off* value before taking the log for analysis purposes.
- Serological status:
  - Seronegative:
    Concentration value is below the cut-off* value.
  - Seropositive:
    Concentration value is greater or equal to the cut-off* value.
  - Seroconversion:
    Seropositive result post-vaccination for any subjects defined as seronegative pre-vaccination.
- Response:
  - Yes:
    For seronegative pre-vaccination: Post-vaccination concentration value of at least the assay cutoff value.
    For seropositive pre-vaccination: Post-vaccination concentration value of at least x-fold increase over the pre-vaccination concentration value. o No:
    For seronegative pre-vaccination: Post-vaccination concentration value of less than the assay cutoff value.
    For seropositive pre-vaccination: Post-vaccination concentration value of less than x-fold increase over the pre-vaccination concentration value.

    The x-fold increase will be calculated as:

$$= \frac{-}{-}$$

NOTE: Assay cut-off value is defined as 36.11 EU/mL.

NOTE: x-fold is defined as 3-fold.

14.1.2. ChAd3 Neutralising Antibody

All analyses will be the same as described for the anti-GP EBOV data. The same tables as described for the antiGP EBOV data will be prepared for the ChAd3 neutralisation data. The ChAd3 neutralisation result will be the reciprocal antibody titres corresponding to the inhibitory concentration 90% (IC90, the titre at which 90% of infectivity is inhibited).

In addition, the association of the pre-existing (baseline) ChAd3 neutralisation antibodies with each of the following vaccine-induced (Day 30 post-vaccination) results will be evaluated by the Spearman-rank correlation method:

- Anti-GP EBOV: Concentration.
- Frequency of CD4+ T-cell specific to EBOV:
  - CD4+/IFN. o CD4+/IL2.
  - CD4+/TNF.
- Frequency of CD8+ T-cell specific to EBOV:
  - CD8+/IFN. o CD8+/IL2. o CD8+/TNF.

Three scatter plots will be presented per cytokine (IFN, IL2, TNF), one plot for each of the aforementioned sets of results. The vaccine-induced results will be based on the result observed at Day 30. The figure will be repeated for the 30 Days Post-vaccination derived time point as defined in Section 6.3.1: ChAd3-EBO-Z Post-vaccination Time Points.

14.1.2.1. Derivations

Refer to Section 14.1.1.1: Derivations for relevant derivations, the following information is specific to the ChAd3 neutralisation data:

- Log-transformed titre values and serological status:
  - The relevant cut-off value is the reciprocal titre of 12.
- Response:
  - Yes:

    For seronegative pre-vaccination: Post-vaccination titre value of at least the assay cut-off* value.

For seropositive pre-vaccination: Post-vaccination titre value of at least x-fold* increase over the pre-vaccination titre value. o No:

For seronegative pre-vaccination: Post-vaccination titre value of less than the assay cut-off* value.

For seropositive pre-vaccination: Post-vaccination titre value of less than x-fold* increase over the pre-vaccination titre value.

NOTE: Assay cut-off value is defined as 12.

NOTE: x-fold is defined as 3-fold.

- Above threshold:
  - Yes:
    Post-vaccination value >= defined threshold.
  - No:
    Post-vaccination value < defined threshold.
  - The threshold value is 200.

14.2. CELL-MEDIATED IMMUNITY (CMI) AGAINST EBOLA

14.2.1. CHAD3-EBOV-SPECIFIC CD4+ OR CD8+ T-CELL RESPONSE

The following listing is planned for presentation for the Total Vaccinated Cohort: Immunogenicity:

- ChAd3-EBOV-specific results.

The following table is planned for presentation for the According-to-protocol Cohort:

- ChAd3-EBOV-specific response.
  - The number and percentage (%) of subjects in each response category (yes, no).
  - Percentage (%) calculated relative to the number of subjects with results available in order to assign a status at each time point.
  - 95% CIs for the response rates will be presented for each treatment group.
  - This table will be presented by T-cell:
    CD4+.
    CD8+.
  - The overall post-baseline response rate will also be included (response at any time point postbaseline).
- Frequency of ChAd3-EBOV-specific T-cells per subset.
  - Summary statistics, refer to Section 6.6: Statistical Tests, based on the percentage results per subset.

- Coexpression profile of Ebola Zaire antigen specific CD4+ T-cells using each possible combination of cytokines (IFN, IL2, TNF) and levels expressed in percentages:
  - Summary statistics, refer to Section 6.6: Statistical Tests, based on the percentage results per subset.
  - Immune markers with at least one positive cytokine will be presented:
    IFN+IL2+TNF+
    IFN+IL2+TNF-
    IFN+IL2-TNF+
    IFN+IL2-TNF- IFN-
    IL2+TNF+
    IFN-IL2+TNF-
    IFN-IL2-TNF+ o This table will be repeated for the CD8+ T-cells. o
    This table will be repeated for the pooled data following the EBO-Z vaccination.
- Percentage of Ebola Zaire antigen-specific CD4+ T-cells using expressing at least 1 cytokine, 1, 2 and 3 cytokines:
  - Summary statistics, refer to Section 6.6: Statistical Tests, based on the percentage results per subset.
  - Immune markers with at least one positive cytokine will be presented:
    CD4+ T cells expressing at least 1 cytokine
    CD4+ T cells expressing 1 cytokine
    CD4+ T cells expressing 2 cytokines
    CD4+ T cells expressing 3 cytokines o This table will be repeated for the CD8+ T-cells. o This table will be repeated for the pooled data following the EBO-Z vaccination.

All CMI tables will be presented by Baseline anti-GP EBOV serological status, including the following categories:

- Seronegative.
- Seropositive.
- Total.

The following figures are planned for presentation for the According-to-protocol Cohort (CMI sub-cohort):

- Coexpression profile of Ebola Zaire antigen specific CD4+ T cells using each possible combination of cytokines (IFN, IL2, TNF) and levels expressed in percentages:
  - The % of cell expressing 1, 2 or 3 markers would be presented o Median and Q1 as well as Q3 will be presented.
  - This figure will be repeated for the CD8+ T-cells.
- Percentage of Ebola Zaire antigen specific CD4+ T-cells using expressing at least 1 cytokine, 1, 2, and 3 cytokines:
  - Pie charts presenting the relative % of cells expressing 1, 2 or 3 cytokine.

- Size of the pie chart will be scaled to the geometric mean. o Day 0 and Day 30 results presented next to one another on the same figure. o Separate pie charts presented for the treatment groups on the same page. o This figure will be repeated for the CD8+ T-cells.

The following immunology variables, as presented in the planned TLF shells, will be collected on the Blood Sampling form in eSource:

- Were CMI blood samples collected:
  - Yes.
  - No.
- Date and time of sample collection.

The following immunology variables, as presented in the planned TLF shells, will be imported from the laboratory report:

- Subset:
  - CD4+/IFN. o CD4+/IL2. o CD4+/TNF. o CD8+/IFN. o CD8+/IL2.
  - CD8+/TNF.
- Antigen:
  - GP(Z1). o GP(Z2).
  - NEG.
- Results, per T-cell and antigen:
  - Total number of cells (NSUB result).
- Results, per subset and antigen:
  - Percentage result (PCTPOS result).
  - Adjusted result (%) (AD_PCTPOS result):
    Per subset and antigen, percentage result minus the NEG antigen percentage result.

14.2.1.1. Derivations

Based on the aforementioned immunogenicity variables, the following variables, as presented in the planned TLF shells, will be derived:

- Baseline serological status:
  - Based on the pre-vaccination anti-GP EBOV serological status:
    Seronegative.
    Seropositive.
- T-cell frequency (%):

- Per subset, sum of the GP(Z1) and GP(Z2) adjusted result (%) for analysis.
- Negative T-cell frequencies will be set to 0.0001% for analysis purposes.

- Number of positive cells:
  - Per subset and antigen the number of positive cells is derived by multiplying the total number of cells (NSUB) with the percentage of cells (PCTPOS), if this result is not an integer due to rounding issues, the result will be rounded to the nearest integer:
    Positive cells = ROUND(NSUB × (PCTPOS × 0.01), 1.0).

- Number of negative cells:
  - Per subset and antigen, once the number of positive cells is calculated, the negative cells is derived as the difference between the total number of cells (NSUB) and the positive number of cells.

- Response:
  - No:
    Per subset and antigen (excluding the NEG antigen), a Fisher's exact test is performed for the 2x2 table consisting of positive and negative cells compared to that of the negative control (NEG antigen) and the one-sided p-value is > 0.01.
    OR
    The one-sided p-value is <= 0.01 and adjusted result (%) is smaller than or equal to the values provided in Table 4: Adjusted Result (%) Response Criteria below. o Yes:
    Per subset and antigen (excluding the NEG antigen), a Fisher's exact test is performed for the 2x2 table consisting of positive and negative cells compared to that of the negative control (NEG antigen) and the one-sided p-value is <= 0.01.
    AND
    The adjusted result (%) is larger than the value provided in Table 4: Adjusted Result (%) Response Criteria below.

Table 4: Adjusted Result (%) Response Criteria

T-cell	Cytokine	Criteria
CD4+	IFN	0.05
	IL-2	
	TNF	
CD8	IFN	0.08
	IL-2	0.05
	TNF	0.08

If at least one of the subset and antigen combinations has a response derived as Yes, the subject is considered as a responder for that visit. If the subject is response at least one post-baseline visit, the subject will be regarded as an overall responder.

For the table pooled following the EBO-Z vaccination the overall response rate will only consider post-vaccination responses with 6 month of the EBO-Z vaccination:

- EBO-Z/MENACWY-TT treatment group:
  - Day 30. o
    Month 6.
- MENACWY-TT/EBO-Z treatment group:
  - Month 6 +
    30 days. o
    Month 12.

If either of the aforementioned post-vaccination responses has been derived as Yes, the subject will be considered as an overall responder for the pooled table.

15. SAFETY OUTCOMES

The Total Vaccinated Cohort will be used as primary analysis cohort for all safety analyses.

15.1. UNSOLICITED ADVERSE EVENTS

Unsolicited AEs will be coded using the latest version of MedDRA at the time of the data transfer.

For analysis of unsolicited adverse events, all vaccinated subjects will be considered. Subjects who did not report the event will be considered as subjects without the event.

The following AE variables, as presented in the planned TLF shells, will be collected on the Adverse Event form in eSource:

- Site of AE:
  - Non-administration site. o Administration site.
- Adverse event of special interest (AESI) within 7 days post-vaccination at Day 0 (symptoms of thrombocytopenia):
  - Yes (available AESI terms are provided in APPENDIX 3: Adverse Events of Specific Interest (AESIs) Terms):
    AESI term.
    Additional AESI term. o
    No.
- Verbatim term (diagnosis).

- Start date and time.
- End date and time.
- Ongoing:
  - Yes. o No.
- Intensity:
  - Mild.
  - Moderate. o Severe.
- Action taken with vaccination:
  - Investigational product withdrawn.
  - Dose delayed. o No action taken.
- Outcome:
  - Recovered/Resolved.
  - Recovered/Resolved with sequelae. o Recovering/Resolving. o Fatal. o Not recovered/not resolved. o Unknown.
- Led to study discontinuation:
  - Yes.
  - No.
- Serious:
  - Yes:
    - Fatal.
    - Life-threatening.
    - Requires/prolonged hospitalisation.
    - Substantial/Permanent disability.
    - Congenital anomaly/birth defect.
    - Other.
  - No.

The following AE variable, as presented on the planned TLFs, will be collected on the Adverse Event Relationship form in eSource:

- Relationship to study vaccine, as judged by the investigator:
  - Yes.
  - No.

The following laboratory variable, as presented in the planned TLFs, will be collected on the Laboratory Results form in eSource:

- Platelet counts at each relevant visit.

The following AE coding variables, as presented in the planned TLF shells, are to be provided by Data Management as part of the data transfer to QuintilesIMS Biostatistics:

- Primary System Organ Class (SOC).
- Preferred Term.

Unsolicited AEs will be coded using the latest version of MedDRA at the time of the data transfer. If the AE is uncoded at the time of the analysis, the AE will be analysed as 'Uncoded'. Coded items will be presented in listings and will be used in descriptive statistics.

15.1.1. DERIVATIONS

Based on the aforementioned variables, the following variables will be derived:

- Most recent vaccination (refer to Section 6.7.2: Most Recent Vaccination).
- Relative day of the most recent vaccination:
  - Calculated relative to Day 0 vaccination (refer to Section 6.1: Reference Start Date and Relative Day).
- Relative days (start and stop):
  - Calculated relative to most recent vaccination (refer to Section 6.1: Reference Start Date and Relative Day).
- Within post-vaccination reporting window flag (refer to Section 15.1.6: Adverse Event (AE) Postvaccination Reporting Window).
- Dose at onset:
  - Dose at onset will be assigned for all unsolicited AEs and is defined as the most recent dose prior to the onset of the AE:
    Total (only applicable to SAE tables).
    EBO-Z.
    Nimenrix.
- Number of events will be calculated as the total number of events reported in the database per relevant category. Therefore multiple events per subject would be counted for each occurrence and not just once per subject.

Refer to APPENDIX 2: Partial Date Conventions for handling of partial dates for AEs.

15.1.2. ALL UNSOLICITED ADVERSE EVENTS

The following listings are planned for presentation for Total Vaccinated Cohort:

- Unsolicited AEs.
- Serious adverse events (SAEs).

- Severe (grade 3) AEs.
- Adverse events of specific interest (AESIs):
  - All available platelet counts will also be displayed in this listing.

The following tables are planned for presentation for the Total Vaccinated Cohort:

- Overview of unsolicited AEs:
  - Number and percentage (%) of subjects in each of the following categories:
    Unsolicited AE.
    Severe (grade 3) unsolicited AE.
    Related unsolicited AE.
    Severe (grade 3) related unsolicited AE.
    Unsolicited AE leading to premature study withdrawal.
  - In this table AESIs (refer to Section 15.1.4: Adverse Events Of Specific Interest (AESIs)) and *any AEs (refer to Section 15.3: Solicited and Unsolicited Adverse Events (AEs)) will be included as well.
  - Percentage (%) of subjects will be calculated relative to the total number of subjects in the relevant analysis cohort and sub-cohort per treatment group.
  - A 95% confidence interval (CI) for the proportion of subjects with AEs in each category will be obtained by using the exact binomial option.
  - Subjects with multiple events in each category are counted only once in each category.
- Incidence of unsolicited AEs:
  - Number and percentage (%) subjects with unsolicited AEs summarised by SOC and PT.
- Incidence of unsolicited AEs by severity:
  - Number and percentage (%) subjects with unsolicited AEs summarised by SOC, PT and severity. o This table will be repeated for related unsolicited AEs.
- Incidence of unsolicited AEs by relationship:
  - Number and percentage (%) subjects with unsolicited AEs summarised by SOC, PT and relationship.

For all unsolicited AEs the SOCs will be sorted by descending frequency of the total number of subjects with at least one unsolicited AE in the overall category. Within each SOC, PTs will be sorted by descending frequency of the total number of subjects with at least one unsolicited AE in each category. Ties will be sorted alphabetically.

All unsolicited AE incidence tables will include AEs reported during the collection period following the vaccination at Day 0. Therefore AEs reported during the collection period following the Month 6 vaccination will be excluded from the unsolicited AE incidence tables, unless otherwise specified.

All unsolicited AE incidence tables will be repeated for the following pooling of AEs, presented per age stratum:

- AEs following the active ChAd3-EBO-Z vaccination; hence:

- EBO-Z/MENACWY-TT subjects: Unsolicited AEs within the reporting window following Day 0 vaccination. o MENACWY-TT/EBO-Z subjects: Unsolicited AEs within the reporting window following Month 6 vaccination.

15.1.2.1. Severity

Severity is classed as mild, moderate or severe (increasing severity) and will be obtained from the Intensity variable recorded on the Adverse Events form in eSource. If there are any missing intensities at the time of the analysis, an unknown category will be used to summarise those SOC/PTs terms.

15.1.2.2. Relationship to Study Vaccine

Relationship, as indicated by the Investigator, is categorised as not related or related (increasing severity of relationship) and will be obtained from the relationship to study vaccine variable on the Adverse Event Relationship form in eSource. Missing relationships should be queried prior to the analysis transfer is made to Biostatistics. If there is any missing relationship to study vaccine at the time of the analysis, an unknown category will be used to summarise those SOC/PTs.

15.1.3. Unsolicited AEs Leading to Premature Study Withdrawal

Unsolicited AEs leading to premature study withdrawal, as indicated by the investigator, will be obtained from the led to study discontinuation variable on the Adverse Events form in eSource. These AEs will be included in the unsolicited AE overview and also indicated in the unsolicited AE listing.

15.1.4. Adverse Events Of Specific Interest (AESIs)

Adverse events of specific interest (AESIs), as indicated by the investigator, will be obtained from the clinical symptoms of thrombocytopenia within 7 days post vaccination Day 0 variable on the Adverse Events form in eSource.

The following tables are planned for presentation for the Total Vaccinated Cohort:

- Overview of AESIs:
  - These will be presented together with the overview of unsolicited AEs (refer to Section 15.1.2: All Unsolicited Adverse Events):
    - Any AESI.
    - Any severe (grade 3) AESI.
    - Any related AESI.
    - Any severe (grade 3) related AESI.
    - Any AESI leading to premature study withdrawal.
- Incidence of AESIs.
- Incidence of AESIs by severity.

- Incidence of related AESIs by severity.
- Incidence of AESIs by relationship.

For all AESIs the SOCs will be sorted by descending frequency of the total number of subjects with at least one AESI in the overall category. Within each SOC, PTs will be sorted by descending frequency of the total number of subjects with at least one AESI in each category. Ties will be sorted alphabetically.

Adverse event of specific interest (AESIs) tables will not be repeated for any pooled AESIs as AESIs are only following Day 0 vaccination and hence the MENACWY-TT/EBO-Z subjects will not have AESIs reported following Month 6 vaccination. Refer to APPENDIX 3: Adverse Events of Specific Interest (AESIs) Terms for a list of AE terms considered as AESIs.

15.1.5. Serious Adverse Events (SAEs)

Serious adverse events (SAEs) as indicated by the investigator, will be obtained from the serious variable on the Adverse Events form in eSource. These AEs will be included in the unsolicited AE overview as well as in the unsolicited AE listing.

The following tables are planned for presentation for the Total Vaccinated Cohort:

- Overview of SAEs by dose:
  - Number and percentage (%) of subjects in each of the following categories:
    Any SAE.
    SAE with outcome of death.
    Severe (grade 3) SAE.
    Related SAE.
    Related SAE with outcome of death. Severe (grade 3) related SAE. o Percentage (%) of subjects will be calculated relative to the total number of subjects in the relevant analysis cohort per treatment group.
  - A 95% confidence interval (CI) for the proportion of subjects with AEs in each category will be obtained by using the exact binomial option.
  - Subjects with multiple events in each category are counted only once in each category.

  The following by dose (Total, EBO-Z, Nimenrix) tables are similar to those described for the unsolicited AEs in Section 15.1: Unsolicited Adverse Events:

- Incidence of SAEs.
- Incidence of SAEs by severity.
- Incidence of related SAEs by severity.
- Incidence of SAEs by relationship.
- Number and percentage of SAEs including the number of events.
- Number and percentage of related SAEs including the number of events.

For all SAEs the SOCs will be sorted by descending frequency of the total number of subjects with at least one SAE in the overall category. Within each SOC, PTs will be sorted by descending frequency of the total number of subjects with at least one SAE in each category. Ties will be sorted alphabetically.

15.1.5.1. Serious Adverse Events (SAEs) with Outcome of Death

Adverse events (AEs) with outcome of death are those events which are recorded as resulting in death on the Adverse Events form in eSource. These AEs will be included in the unsolicited AE overview and also indicated in the SAE listing.

15.1.6. Adverse Event (AE) Post-vaccination Reporting Window

All AE incidence tables will only include AEs (SAEs, AESIs and unsolicited AEs) which occurred within the protocol defined post-vaccination reporting window, as defined in Table 5: Unsolicited Adverse Event (AE) Postvaccination Reporting Windows, below. All AE listings will include all the AEs reported, regardless whether it was reported within the reporting window. All AEs reported outside the reporting window will be indicated in the listing.

Table 5: Unsolicited Adverse Event (AE) Post-vaccination Reporting Windows

Adverse Event Type	Post-vaccination Reporting Window
SAEs	Through data cut-off
AESIs	7-day window following Day 0
Unsolicited AEs	30-day window following each vaccination

15.2. Solicited Adverse Events (AEs)

Solicited AEs will not be coded by data management and as per coding will be assigned based on the information provided in Table 6: Solicited Adverse Events MedDRA Coding.

For a given subject, missing or non-evaluable measurements will not be replaced. Therefore the analysis of the solicited symptoms will include only vaccinated subjects with documented safety data (that is; symptom screen completed after the vaccination). More specifically the following rules will be used:

- Subjects who documented the absence of a solicited symptom after a vaccination will be considered not having that symptom after that vaccination.
- Subjects who documented the presence of a solicited symptom and fully or partially recorded daily measurement over the solicited period will be included in the summaries for that vaccination and classified according to their maximum observed daily recording over the solicited period.
- Subjects who documented the presence of a solicited symptom after a vaccination without having recorded any daily measurement will be assigned to the lowest intensity category for that vaccination (that is; 37.5°C for fever or grade 1 for other symptoms).

- Vaccinations without symptom sheets documented will be excluded.

The following AE variables, as presented in the planned TLF shells, will be collected on the Solicited Adverse Events Local Signs and Symptoms form in eSource:

- Any signs or symptoms between Day 0 and Day 6:
  - Yes. o No.
- Per day (Day 0 to Day 6) presence of each of the following signs or symptoms:
  - Redness:
    Diameter measurement (mm).
  - Swelling:
    Diameter measurement (mm).
  - Pain:
    Intensity (0 to 3).

  Per sign or symptom:
- Ongoing after Day 6:
  - Yes:
    Maximum diameter/intensity after Day 6.
    End date after Day 6. o
    No.
- Did the subject discontinue due to the event:
  - Yes.
  - No.

The following AE variable, as presented on the planned TLFs, will be collected on the Solicited Adverse Events General Signs and Symptoms form in eSource:

- Any signs or symptoms between Day 0 and Day 6:
  - Yes.
  - No.
- Per study day (Day 0 to Day 6) presence of each of the following signs or symptoms for children aged 6 to 17 years of age:
  - Fever:
    Temperature reading (˚C).
  - Headache:
    Intensity (0 to 3).
  - Fatigue:
    Intensity (0 to 3).
  - Gastrointestinal symptoms: Intensity (0 to 3).

- Per study day (Day 0 to Day 6) presence of each of the following signs or symptoms for children aged 1 to 5 years of age:
  - Fever:
    Temperature reading (˚C).
  - Loss of Appetite:
    Intensity (0 to 3).
  - Drowsiness:
    Intensity (0 to 3).
  - Irritability/Fussiness:
    Intensity (0 to 3).

Per sign or symptom:

- Ongoing after Day 6:
  - Yes:
    Maximum reading/intensity after Day 6.
    End date after Day 6. o
    No.
- Did the subject discontinue due to the event:
  - Yes. o No.
- Relationship to study vaccine:
  - Yes.
  - No.

The following diary card variable will be collected on the Diary Card Review form in eSource:

- Did the field worker/site personnel return the diary card:
  - Yes. o No.

15.2.1. DERIVATIONS

Based on the aforementioned variables, the following variables will be derived:

- End date after Day 6 relative day:
  - Calculated relative to the most recent vaccination (refer to Section 6.1: Reference Start Date and Relative Day).
- Duration of solicited sign or symptom (refer to Section 6.7.3: Duration):
  - If ongoing after Day 6:
    End date/day: End date after Day 6 as recorded in eSource.

Start date/day: Start date of sign or symptom (derived from the first study day where sign or symptom is present relative to the study vaccination date). o If not ongoing after Day 6:

End date/day: Last date of sign or symptom (derived from the study day where sign or symptom is present relative to the study vaccination date).

Start date/day: Start date of sign or symptom (derived from the first study day where sign or symptom is present relative to the study vaccination date).

- Relationship to study vaccine for local solicited signs or symptoms:
  - All local signs or symptoms will be regarded as related to study vaccine.
- Intensity for fever, redness and swelling:

Refer to APPENDIX 4: Solicited Adverse Event (AE) Intensity Grading, for the required intensity grade assignment for fever, redness and swelling.

- Dose at onset:
  - Dose at onset will be assigned for all solicited AEs and is defined as the most recent dose prior to the onset of the AE:

EBO-Z:

Day 0.

Month 6.

Nimenrix:

Day 0.

Month 6.

- MedDRA System Organ Class as well as Preferred Term will be assigned based on Table 6: Solicited Adverse Events MedDRA Coding, below.

Table 6: Solicited Adverse Events MedDRA Coding

Solicited AE	MedDRA System Organ Class	MedDRA Preferred Term
Redness	Skin and subcutaneous tissue disorders	Erythema
Swelling	General disorders and administration site conditions	Swelling
Pain	General disorders and administration site conditions	Pain
Fever	General disorders and administration site conditions	Pyrexia
Headache	Nervous system disorders	Headache
Fatigue	General disorders and administration site conditions	Fatigue
Gastrointestinal Symptoms	Gastrointestinal disorders	Gastrointestinal disorder
Loss of Appetite	Metabolism and nutrition disorders	Decreased appetite
Drowsiness	Nervous system disorders	Somnolence
Irritability/Fussiness	Psychiatric disorders	Irritability

15.2.2. ALL SOLICITED ADVERSE EVENTS

The following listing is planned for presentation for the Total Vaccinated Cohort:

- Solicited AEs.

The following tables are planned for presentation for the Total Vaccinated Cohort:

- Overview of Solicited AEs:
  - Number and percentage (%) of subjects in each of the following categories:
    Solicited AE.
    Solicited severe (grade 3) AE.
    Solicited related AE.
    Solicited severe (grade 3) related AE.
    Solicited local AE.

Severe (grade 3) solicited local AE.
Solicited general AE.
Severe (grade 3) solicited general AE.
Related solicited general AE.
Severe (grade 3) related solicited general AE.
Solicited AE leading to premature study withdrawal.
Severe (grade 3) solicited AE leading to premature study withdrawal.
Related solicited AE leading to premature study withdrawal.
Severe (grade 3) related solicited AE leading to premature study withdrawal.

- Percentage (%) of subjects will be calculated relative to the total number of subjects in the relevant analysis cohort, per treatment group with returned diary cards.
- A 95% confidence interval (CI) for the proportion of subjects with AEs in each category will be obtained by using the exact binomial option.
- Subjects with multiple events in each category are counted only once in each category.

- Incidence of solicited AEs:
  - Number and percentage (%) subjects with solicited AEs summarised by category and sign or symptom.
- Incidence of solicited AEs by severity:
  - Number and percentage (%) subjects with solicited AEs summarised by category, sign or symptom and severity.
  - This table will be repeated for related solicited AEs (including general solicited AEs only).
- Incidence of solicited AEs by relationship:
  - Number and percentage (%) subjects with solicited AEs summarised by category, sign or symptom and relationship.
- Duration of fever (days):
  - Descriptive statistics for the duration of fever will be provided, based on all subjects with at least one fever event reported.
- Onset Day of Fever during 7-day Follow-up Period After Vaccination on Day 0
  - Number and percentage (%) subjects with solicited fever summarised by earliest onset day (Day 0 to Day 6) following Day 0 study vaccination.
  - Subjects with multiple events are considered only once at the earliest onset day. o % is based on the number of subject who reported fever in each category.

The following figures are planned for presentation for the Total Vaccinated Cohort:

- Reactogenicity events:
  - Percentage of subjects presenting solicited AEs along with the 95% CI will be presented for all solicited events as well as Grade 3 or 4 events on the same figure (nested bar chart). o The bars will be presented separately for each treatment group. o This figure will be presented separately for

- the local and general solicited AEs. o This figure will be repeated for the pooled data following the EBO-Z vaccination.

- Fever incidences per study day following Day 0 vaccination:
  - Percentage of subjects presenting solicited fever along with the 95% CI will be presented for all solicited fever events as well as Grade 3 or 4 fever on the same figure (nested bar chart).
  - The figure will be presenting the earliest study of fever onset. o The bars will be presented separately for each treatment group. o These figures will only include solicited fever within the reporting period following Day 0 vaccination.

For all solicited AEs the categories and signs or symptoms will be sorted as listed below:

Local:

- Pain. o Redness.
- Swelling.

- General:
  - Fever. o Fatigue (only applicable to age strata: 13 to 17 years of age and 6 to 12 years of age).
  - Gastrointestinal symptoms (only applicable to age strata: 13 to 17 years of age and 6 to 12 years of age).
  - Headache (only applicable to age strata: 13 to 17 years of age and 6 to 12 years of age). o Drowsiness (only applicable to age stratum: 1 to 5 years of age). o Irritability/Fussiness (only applicable to age stratum: 1 to 5 years of age). o Loss of appetite (only applicable to age stratum: 1 to 5 years of age).

All solicited AE incidence tables will include AEs reported during the collection period following the vaccination at Day 0. Therefore, solicited AEs reported during the collection period following the Month 6 vaccination will be excluded from the solicited AE incidence tables, unless otherwise specified.

All solicited AE incidence tables will be repeated for the following pooling of AEs:

- AEs following the active ChAd3-EBO-Z vaccination; hence:
  - EBO-Z/MENACWY-TT subjects: Solicited AEs within the reporting window following Day 0 vaccination.
  - MENACWY-TT/EBO-Z subjects: Solicited AEs within the reporting window following Month 6 vaccination.

15.2.2.1. Severity

Severity will be derived based on the intensity grading:

- Mild: Intensity grade of 1.
- Moderate: Intensity grade of 2.
- Severe: Intensity grade of 3.

In addition, for the intensity it can also be reported as the following:

- Redness:
  - o Unknown. o Uninterpretable.
- Swelling, and fever:
  - o Unknown.

Severity is therefore classed as unknown, uninterpretable, mild, moderate or severe (increasing severity). If there are any missing intensities at the time of the analysis, those will be summarised in the unknown category.

15.2.2.2. Relationship to Study Vaccine

Relationship, as indicated by the Investigator, is classified as not related or related (increasing severity of relationship) and will be obtained from the relationship to study vaccine variable on the Solicited Adverse Events General forms in eSource. Missing relationships should be queried prior to the analysis transfer to Biostatistics. If there are any AEs with a missing relationship to study vaccine at the time of the analysis, an unknown category will be used to summarise those solicited AEs.

15.3. SOLICITED AND UNSOLICITED ADVERSE EVENTS (AES)

The following tables are planned for presentation for the Total Vaccinated Cohort:

- Overview of solicited and unsolicited AEs:
  - o These will be presented together with the overview of unsolicited AEs (refer to Section 15.1.2: All Unsolicited Adverse Events):
    - *Any AE.
    - *Any severe (grade 3) AE.
    - *Any related AE.
    - *Any severe (grade 3) related AE.
    - *Any AE leading to premature study withdrawal.
    - *Any Severe (grade 3) AE leading to premature study withdrawal.
    - *Any Related AE leading to premature study withdrawal.
    - *Any Severe (grade 3) AE related leading to premature study withdrawal.
- Solicited and unsolicited AEs experienced by at least 5% of subjects within the 30 day post-vaccination window, including the number of events:
  - o Multiple events are counted as multiple events for the calculation of the number of events (n*). o AEs will be presented by MedDRA System Organ Class and Preferred Term. o SAEs will be excluded from this table.

15.4. LABORATORY EVALUATIONS

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The list of laboratory assessments to be included in the analysis is provided in APPENDIX 5: Laboratory Assessments.

The following listings are planned for presentation based on the Total Randomised Cohort:

- Clinical laboratory results, including change from Baseline and toxicity grading.
- Clinical laboratory results: Platelets, including an indication of subjects with AESIs.
- Malaria rapid diagnosis test (RDT) results.
- Pregnancy test results:
  - Based on the Total Enrolled Cohort and only includes female subjects with results available.

The following tables are planned for presentation based on the Total Vaccinated Cohort:

- Clinical laboratory results, including change from Baseline:
  - Descriptive statistics, including the interquartile range.

  Out of range clinical laboratory results:
  - Number and percentage (%) of subjects with results above or below the normal range.
  - Percentage (%) is relative to the number of subjects with result available for the specific test and the relevant time point.
- Toxicity grade shift from Baseline to post-baseline, the table will include the following categories:
  - Grade 0. o Grade 1. o Grade 2. o Grade 3.
  - Grade 4.
- Clinical Laboratory Percent Decrease from Baseline to Post-baseline: Platelets (10^9/L):
  - Number and percentage (%) of subjects with decrease in platelets in the derived categories will be summarized.
  - Decrease in platelets from Baseline will be categorised as follows: Any increase

    0 to <10% decrease

    10% to <20% decrease

    >=20% decrease o This table will be repeated for the maximum percent decrease observed between Day 3 and Day 6. o This table will not be repeated as a pooled table.
- Reported pregnancies per most recent vaccination and centre:
  - The number and percentage (%) of reported pregnancies will be presented per most recent vaccination (Day 0 or Month 6) and centre as well as overall.
  - The percentage will be based on the number of female subjects of childbearing potential within each centre.

All laboratory tables (unless otherwise noted) will be repeated for the following pooling of results:

- Results following the active ChAd3-EBO-Z vaccination; hence:
  - EBO-Z/MENACWY-TT subjects: Laboratory results following Day 0 vaccination.
  - MENACWY-TT/EBO-Z subjects: Laboratory results following Month 6 vaccination.

The following figure is planned for presentation based on the Total Vaccinated Cohort:

- Platelet: Quartile Distribution following Day 0 Vaccination:
  - Box and whisker plot presenting the platelet distribution up to Day 30. o The mean, median as well as the Q1 and 3 values will be presented on the figure. o The treatment groups will be presented separately on the same figure.

The following laboratory variables, as presented in the planned TLF shells, will be recorded on the Blood Sampling form in eSource:

- Date and time of sample collection:
  - Haematology samples.
  - Biochemistry samples.

The following laboratory variables, as presented in the planned TLF shells, will be recorded on the Laboratory Results form in eSource:

- Date of sample collection:
  - Haematology samples.
  - Biochemistry samples.
- Result and unit.
- Significance:
  - Not clinically significant (NCS). o Clinically significant (CS).

The following laboratory variables, as presented in the planned TLF shells, will be recorded on the Malaria RDT and Results form in eSource:

- Date and time of assessment.
- Result:
  - Positive.
  - Negative.
- Malaria treatment prescribed per local/national requirements:
  - Yes.
  - No.
- Prescribed malaria treatment completed:

-
    - Yes.
    - No.

The following laboratory variables, as presented in the planned TLF shells, will be recorded on the Pregnancy Test form in eSource:

- Date and time of assessment.
- Result:
    - Positive.
    - Negative.

The following pregnancy variables, as presented in the planned TLF shells, will be recorded on the Pregnancy Report form in eSource:

- Date and time of outcome.
- Outcome:
    - Live infant NO apparent congenital anomaly. o Live infant congenital anomaly. o Elective termination NO apparent congenital anomaly.
    - Elective termination congenital anomaly.
    - Spontaneous abortion NO apparent congenital anomaly.
    - Spontaneous abortion congenital anomaly. o Stillbirth NO apparent congenital anomaly.

- Stillbirth congenital anomaly. o Ectopic pregnancy. o Molar pregnancy. o Lost to follow-up.
- Pregnancy ongoing.

- Relevant family history.

The following laboratory variables, as presented in the planned TLF shells, will be included in the data transfer from Data Management:

- Local laboratory references ranges in reported units.
- Local laboratory reference ranges in SI units.
- Laboratory results in SI units.

15.4.1. DERIVATIONS

Based on the aforementioned variables, the following variables will be derived:

- Relative day:
  - Calculated relative to Day 0 vaccination (refer to Section 6.1: Reference Start Date and Relative Day).
- Change from Baseline for results in System of International (SI) units (refer to Section 6.7.1: Change from Baseline).
- Derived decrease categories (%):
  - Change from Baseline/value at Baseline x 100
- Toxicity grade for selected laboratory tests (refer to APPENDIX 6: Laboratory Toxicity Grading for derivation details).
  - Maximum grade overall will also be derived as the highest post-vaccination toxicity grade across all post-baseline visits and time points.
- Reference range indicator based on the results in SI units.
  - Low: Result < reference range lower limit.
  - Normal: Result >= reference range lower limit AND result <= reference range upper limit. o High: Result > reference range upper limit.

For clinical laboratory results below or above the limit of quantification will be handled as follows:

- Assign as equal to the limit of quantification, for example '<x' will be assigned as x for analysis purposes. SI conversions can be applied to the derived result. In the listings the result will be presented as the SI value (after conversion) with the qualifier symbol concatenated, for example '<y' in SI unit.

15.5. VITAL SIGNS

The list of vital signs assessments to be included in the analysis is provided in APPENDIX 7: Vital Signs Assessments.

The following listing is planned for presentation based on the Total Randomised Cohort:

- Vital signs results.

The following table is planned for presentation based on the Total Vaccinated Cohort:

- Vital signs results.

The following vital signs variables, as presented in the planned TLF shells, will be recorded on the Vital Signs form in eSource:

- Date and time of assessment.
- Result and unit for each of the vital signs assessments.
- Location of temperature assessment:
  - Axillary (preferred).
  - Oral. o Rectal. o Tympanic (not recommended).

The following vital signs variables, as presented in the planned TLF shells, will be recorded on the Pre Vaccination Temperature form in eSource:

- Date and time of assessment.
- Location of temperature assessment.
  - Axillary (preferred). o Oral. o Rectal. o Tympanic (not recommended).
- Pre-vaccination temperature and unit.

No standardisation of temperatures based on the location of assessment will be performed.

15.5.1. DERIVATIONS

Based on the aforementioned variables, the following variable will be derived:

- Relative day:
  - Calculated relative to Day 0 vaccination (refer to Section 6.1: Reference Start Date and Relative Day).

15.6. PHYSICAL EXAMINATION

The list of physical examination assessments to be included in the analysis is provided in APPENDIX 8: Physical Assessments.

The following listing is planned for presentation based on the Total Enrolled Cohort:

- Abnormal physical assessment results.

The following physical assessment variables, as presented in the planned TLF shells, will be recorded on the Physical Assessment form in eSource:

- Date and time of assessment.
- Physical assessment:
  - Normal. o Abnormal.
  - Not done.
- Finding one classification:
  - Clinically significant.
  - Not clinically significant.
- Finding two classification:
  - Clinically significant. o Not clinically significant.

15.6.1. DERIVATIONS

Based on the aforementioned variables, the following variable will be derived:

- Relative day:
  - Calculated relative to Day 0 vaccination (refer to Section 6.1: Reference Start Date and Relative Day).

15.7. SUSPECTED EBOLA VIRUS DISEASE (EVD)

The following listing is planned for presentation based on the Total Randomised Cohort:

- Suspected Ebola virus disease (EVD).

The following EVD variables, as presented in the planned TLF shells, will be recorded on the Management of Suspected EVD form in eSource:

- Subject travelled to a country affected by the EBOV epidemic since last visit:

o Yes: o
Date of
return. o
No.

- Subject in direct contact with a person with EVD within 21 days prior to the study visit:

  o Yes. o No.

16. DATA NOT SUMMARISED OR PRESENTED

The other variables and/or domains not summarised or presented are:

- Pregnancy report (the pregnancy test results will be reported in a listing including selected pregnancy report variable (outcome, date of outcome and relevant family history).

17. REFERENCES

202090 (EBOLA Z CHAD3-004) Protocol:

- Amendment 2 Final version of the protocol, dated 06MAY2015.
- Addendum Ghana, dated 07AUG2015.

GSK-EBOLA-CHAD3-004_Annotated Source PDF_21SEP2015.

ICS Positivity Criteria-CAD3-EBOZ.doc.

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

Refer to the latest version of the relevant TLF shells for additional guidance on the output conventions.

SPELLING FORMAT

English UK.

PRESENTATION OF TREATMENT GROUPS

- Not Randomised.
- EBO-Z/MENAWY-TT.
- MENAWY-TT /EBO-Z.
- Total.

PRESENTATION OF VISITS

All study visits will be included as visit in the relevant outputs (TLFs). The visits will be presented as follows:

- Screening.
- Day x, where x = 0, 3, 6, 30.
- Month x, where x = 3, 6.
- Month 6 + x days, where x = 6, 30.
- Month x, where x = 9, 12.

DECIMAL PRECISION:

All values are to be rounded using the SAS® function ROUND, as the last step prior to presentation. All computed percentages (%) are to be presented using one decimal place. If the original data has N decimal places (as derived from the raw data), then the summary statistics for quantitative data are to contain the following number of decimal places (with a maximum of 4 decimal places):

- Minimum and maximum: N.
- Mean, geometric mean and median: (N+1).
- Standard deviation and geometric standard deviation: (N+2).

APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings and will simply be used to determine whether the within reporting window for AEs as Yes or No.

AE Start Date			Criterion	Action
Day	Month	Year		
Missing	Known	Known	AE start month and year are the same as the month and year of one vaccination (Day 0 or Month 6)	Assign the missing day as the day of the relevant vaccination in the coinciding month and year
			AE start month and year are not the same as the month and year of any of the vaccinations (Day 0 or Month 6) and known to be in between vaccinations	Assign the missing day as the first day of the month
			AE start month and year are not the same as the month and year of any of the vaccinations (Day 0 or Month 6) and known to be prior to all vaccinations	Assign the missing day as the last day of the month
			AE start month and year are not the same as the month and year of any of the vaccinations (Day 0 or Month 6) and known to be after all vaccinations	Assign the missing day as the first day of the month
Missing	Missing	Known	AE start year is the same as the year of one vaccination (Day 0 or Month 6)	Assign the missing day and month as the day and month of the relevant vaccination in the coinciding year
			AE start year is the same as the year of more than one vaccination (Day 0 or Month 6)	Assign the missing day and month as the day and month of the earliest vaccination in the coinciding year

			AE start year is not the same as the year of any of the vaccinations (Day 0 or Month 6) and known to be prior to all vaccinations	Assign the missing day and month as 31 December
			AE start year is not the same as the year of any of the vaccinations (Day 0 or Month 6) and known to be after all vaccinations	Assign the missing day and month as 01 January

AE Start Date			Criterion	Action
Day	Month	Year		
Missing	Missing	Missing	-	Assign the missing date as the date of vaccination at Day 0

APPENDIX 3. ADVERSE EVENTS OF SPECIFIC INTEREST (AESIS) TERMS

MedDRA 17.1 Preferred Term	Preferred Term Code	MedDRA 17.1 Preferred Term	Preferred Term Code
Abdominal wall haematoma	10067383	Iris haemorrhage	10057418
Abdominal wall haemorrhage	10067788	Kidney contusion	10023413
Abnormal withdrawal bleeding	10069195	Lacrimal haemorrhage	10069930
Acute haemorrhagic leukoencephalitis	10058994	Large intestinal haemorrhage	10052534
Administration site haematoma	10075100	Large intestinal ulcer haemorrhage	10061262
Administration site haemorrhage	10075101	Laryngeal haematoma	10070885
Adrenal haematoma	10059194	Laryngeal haemorrhage	10065740
Adrenal haemorrhage	10001361	Lip haematoma	10066304
Anal haemorrhage	10049555	Lip haemorrhage	10049297
Anal ulcer haemorrhage	10063896	Liver contusion	10067266
Anastomotic haemorrhage	10056346	Lower gastrointestinal haemorrhage	10050953
Anastomotic ulcer haemorrhage	10002244	Lymph node haemorrhage	10074270
Aneurysm ruptured	10048380	Mallory-Weiss syndrome	10026712
Anorectal varices haemorrhage	10068925	Mediastinal haematoma	10049941
Aortic aneurysm rupture	10002886	Mediastinal haemorrhage	10056343
Aortic dissection rupture	10068119	Melaena	10027141
Aortic intramural haematoma	10067975	Melaena	10027141
Aortic rupture	10060874	Melaena neonatal	10049777
Aponeurosis contusion	10075330	Meningorrhagia	10052593
Application site bruise	10050114	Menometrorrhagia	10027295
Application site haematoma	10068317	Menorrhagia	10027313
Application site haemorrhage	10072694	Menorrhagia	10027313

MedDRA 17.1 Preferred Term	Preferred Term Code	MedDRA 17.1 Preferred Term	Preferred Term Code
Arterial haemorrhage	10060964	Mesenteric haematoma	10071557
Arterial intramural haematoma	10074971	Mesenteric haemorrhage	10060717
Arterial rupture	10003173	Metrorrhagia	10027514
Arteriovenous fistula site haematoma	10055150	Mouth haemorrhage	10028024
Arteriovenous fistula site haemorrhage	10055123	Mouth haemorrhage	10028024
Arteriovenous graft site haematoma	10055152	Mucosal haemorrhage	10061298
Arteriovenous graft site haemorrhage	10055126	Muscle contusion	10070757
Astringent therapy	10067372	Muscle haemorrhage	10028309
Atrial rupture	10048761	Myocardial haemorrhage	10048849
Auricular haematoma	10003797	Myocardial rupture	10028604
Basal ganglia haemorrhage	10067057	Naevus haemorrhage	10062955
Bladder tamponade	10062656	Nail bed bleeding	10048891
Bleeding time abnormal	10049227	Nasal septum haematoma	10075027
Bleeding time abnormal	10049227	Neonatal gastrointestinal haemorrhage	10074159
Bleeding time prolonged	10005140	Nephritis haemorrhagic	10029132
Bleeding varicose vein	10005144	Nipple exudate bloody	10029418
Blood blister	10005372	Ocular retrobulbar haemorrhage	10057571
Blood urine	10005863	Oesophageal haemorrhage	10030172
Blood urine present	10018870	Oesophageal ulcer haemorrhage	10030202
Bloody discharge	10057687	Oesophageal varices haemorrhage	10030210
Bloody peritoneal effluent	10067442	Oesophagitis haemorrhagic	10030219
Bone contusion	10066251	Optic disc haemorrhage	10030919
Bone marrow haemorrhage	10073581	Optic nerve sheath haemorrhage	10030941

Brain stem haematoma	10073230	Oral mucosa haematoma	10074779

MedDRA 17.1 Preferred Term	Preferred Term Code	MedDRA 17.1 Preferred Term	Preferred Term Code
Brain stem haemorrhage	10006145	Osteorrhagia	10051937
Breast haematoma	10064753	Ovarian haematoma	10033263
Breast haemorrhage	10006254	Ovarian haemorrhage	10065741
Broad ligament haematoma	10006375	Pancreatic haemorrhage	10033625
Bronchial haemorrhage	10065739	Pancreatitis haemorrhagic	10033650
Cardiac contusion	10073356	Papillary muscle haemorrhage	10059164
Carotid aneurysm rupture	10051328	Paranasal sinus haematoma	10069702
Catheter site bruise	10063587	Parathyroid haemorrhage	10059051
Catheter site haematoma	10055662	Parotid gland haemorrhage	10051166
Catheter site haemorrhage	10051099	Pelvic haematoma	10054974
Central nervous system haemorrhage	10072043	Pelvic haematoma obstetric	10034248
Cephalhaematoma	10008014	Pelvic haemorrhage	10063678
Cerebellar haematoma	10061038	Penile contusion	10073352
Cerebellar haemorrhage	10008030	Penile haematoma	10070656
Cerebral aneurysm ruptured syphilitic	10008076	Penile haemorrhage	10034305
Cerebral arteriovenous malformation haemorrhagic	10008086	Peptic ulcer haemorrhage	10034344
Cerebral haematoma	10053942	Pericardial haemorrhage	10034476
Cerebral haemorrhage	10008111	Perineal haematoma	10034520
Cerebral haemorrhage foetal	10050157	Periorbital contusion	10062515
Cerebral haemorrhage neonatal	10008112	Periorbital haematoma	10034544
Cerebral microhaemorrhage	10067277	Peripartum haemorrhage	10072693
Cervix haematoma uterine	10050020	Perirenal haematoma	10049450
Cervix haemorrhage uterine	10050022	Peritoneal haematoma	10058095

MedDRA 17.1 Preferred Term	Preferred Term Code	MedDRA 17.1 Preferred Term	Preferred Term Code
Choroidal haematoma	10068642	Peritoneal haemorrhage	10034666
Choroidal haemorrhage	10008786	Petechiae	10034754
Chronic gastrointestinal bleeding	10050399	Petechiae	10034754
Ciliary body haemorrhage	10057417	Pharyngeal haematoma	10068121
Coital bleeding	10065019	Pharyngeal haemorrhage	10034827
Colonic haematoma	10009996	Pituitary haemorrhage	10049760
Conjunctival haemorrhage	10010719	Placenta praevia haemorrhage	10035121
Conjunctival haemorrhage	10010719	Platelet count decreased	10035528
Contusion	10050584	Polymenorrhagia	10064050
Corneal bleeding	10051558	Post abortion haemorrhage	10036246
Cullen's sign	10059029	Post procedural contusion	10073353
Cystitis haemorrhagic	10011793	Post procedural haematoma	10063188
Deep dissecting haematoma	10074718	Post procedural haematuria	10066225
Diarrhoea haemorrhagic	10012741	Post procedural haemorrhage	10051077
Disseminated intravascular coagulation	10013442	Post transfusion purpura	10072265
Diverticulitis intestinal haemorrhagic	10013541	Postmenopausal haemorrhage	10055870
Diverticulum intestinal haemorrhagic	10013560	Postpartum haemorrhage	10036417
Duodenal ulcer haemorrhage	10013839	Premature separation of placenta	10036608
Duodenitis haemorrhagic	10013865	Procedural haemorrhage	10071229
Dysfunctional uterine bleeding	10013908	Proctitis haemorrhagic	10036778
Ear haemorrhage	10014009	Prostatic haemorrhage	10036960
Ear haemorrhage	10014009	Pulmonary alveolar haemorrhage	10037313
Ecchymosis	10014080	Pulmonary contusion	10037370
Encephalitis haemorrhagic	10014589	Pulmonary haematoma	10054991

MedDRA 17.1 Preferred Term	Preferred Term Code	MedDRA 17.1 Preferred Term	Preferred Term Code
Enterocolitis haemorrhagic	10014896	Pulmonary haemorrhage	10037394
Epidural haemorrhage	10073681	Puncture site haemorrhage	10051101
Epistaxis	10015090	Purpura	10037549
Epistaxis	10015090	Purpura	10037549
Exsanguination	10015719	Purpura neonatal	10037557
Extradural haematoma	10015769	Purpura senile	10037560
Extravasation blood	10015867	Putamen haemorrhage	10058940
Eye contusion	10073354	Radiation associated haemorrhage	10072281
Eye haemorrhage	10015926	Rectal haemorrhage	10038063
Eyelid bleeding	10053196	Rectal ulcer haemorrhage	10038081
Eyelid contusion	10075018	Renal cyst haemorrhage	10059846
Eyelid haematoma	10064976	Renal haematoma	10038459
Foetal-maternal haemorrhage	10016871	Renal haemorrhage	10038460
Gastric haemorrhage	10017788	Respiratory tract haemorrhage	10038727
Gastric ulcer haemorrhage	10017826	Respiratory tract haemorrhage neonatal	10038728
Gastric ulcer haemorrhage, obstructive	10017829	Retinal haemorrhage	10038867
Gastric varices haemorrhage	10057572	Retinopathy haemorrhagic	10051447
Gastritis alcoholic haemorrhagic	10017857	Retroperitoneal haematoma	10058360
Gastritis haemorrhagic	10017866	Retroperitoneal haemorrhage	10038980
Gastroduodenal haemorrhage	10053768	Retroplacental haematoma	10054798
Gastroduodenitis haemorrhagic	10048712	Ruptured cerebral aneurysm	10039330
Gastrointestinal angiodysplasia haemorrhagic	10017929	Scleral haemorrhage	10050508
Gastrointestinal haemorrhage	10017955	Scrotal haematocoele	10061517

MedDRA 17.1 Preferred Term	Preferred Term Code	MedDRA 17.1 Preferred Term	Preferred Term Code
Gastrointestinal haemorrhage	10017955	Scrotal haematoma	10039749
Gastrointestinal polyp haemorrhage	10074437	Shock haemorrhagic	10049771
Gastrointestinal ulcer haemorrhage	10056743	Skin haemorrhage	10064265
Genital contusion	10073355	Skin ulcer haemorrhage	10050377
Genital haemorrhage	10061178	Small intestinal haemorrhage	10052535
Gingival bleeding	10018276	Small intestinal ulcer haemorrhage	10061550
Gingival bleeding	10018276	Soft tissue haemorrhage	10051297
Graft haemorrhage	10063577	Soft tissue haemorrhage	10051297
Grey Turner's sign	10075426	Spermatic cord haemorrhage	10065742
Haemarthrosis	10018829	Spinal cord haemorrhage	10048992
Haematemesis	10018830	Spinal epidural haematoma	10050162
Haematochezia	10018836	Spinal epidural haemorrhage	10049236
Haematochezia	10018836	Spinal haematoma	10048464
Haematoma	10018852	Spinal subarachnoid haemorrhage	10073564
Haematoma evacuation	10060733	Spinal subdural haematoma	10050164
Haematoma infection	10051564	Spinal subdural haemorrhage	10073563
Haematosalpinx	10050468	Spleen contusion	10073533
Haematospermia	10018866	Splenic haematoma	10041646
Haematotympanum	10063013	Splenic haemorrhage	10041647
Haematuria	10018867	Splenic varices haemorrhage	10068662
Haematuria	10018867	Splinter haemorrhages	10041663
Haematuria traumatic	10018871	Spontaneous haematoma	10065304
Haemobilia	10058947	Spontaneous haematoma	10065304
Haemophilic arthropathy	10065057	Spontaneous haemorrhage	10074557

MedDRA 17.1 Preferred Term	Preferred Term Code	MedDRA 17.1 Preferred Term	Preferred Term Code
Haemoptysis	10018964	Spontaneous haemorrhage	10074557
Haemorrhage	10055798	Stoma site haemorrhage	10074508
Haemorrhage coronary artery	10055803	Stomatitis haemorrhagic	10042132
Haemorrhage foetal	10061191	Subarachnoid haemorrhage	10042316
Haemorrhage in pregnancy	10018981	Subarachnoid haemorrhage neonatal	10042317
Haemorrhage intracranial	10018985	Subchorionic haematoma	10072596
Haemorrhage neonatal	10061993	Subcutaneous haematoma	10042345
Haemorrhage subcutaneous	10018999	Subdural haematoma	10042361
Haemorrhage subepidermal	10019001	Subdural haematoma evacuation	10042363
Haemorrhage urinary tract	10055847	Subdural haemorrhage	10042364
Haemorrhagic anaemia	10052293	Subdural haemorrhage neonatal	10042365
Haemorrhagic arteriovenous malformation	10064595	Subgaleal haematoma	10069510
Haemorrhagic ascites	10059766	Subretinal haematoma	10071935
Haemorrhagic cerebral infarction	10019005	Testicular haemorrhage	10051877
Haemorrhagic diathesis	10062713	Thalamus haemorrhage	10058939
Haemorrhagic disease of newborn	10019008	Third stage postpartum haemorrhage	10043449
Haemorrhagic disorder	10019009	Thoracic haemorrhage	10062744
Haemorrhagic erosive gastritis	10067786	Thrombocytopenia	10043554
Haemorrhagic hepatic cyst	10067796	Thrombocytopenia	10043554
Haemorrhagic infarction	10019013	Thrombocytopenic purpura	10043561
Haemorrhagic ovarian cyst	10060781	Thrombocytopenic purpura	10043561
Haemorrhagic stroke	10019016	Thrombotic thrombocytopenic purpura	10043648

MedDRA 17.1 Preferred Term	Preferred Term Code	MedDRA 17.1 Preferred Term	Preferred Term Code
Haemorrhagic thyroid cyst	10072256	Thyroid haemorrhage	10064224
Haemorrhagic transformation stroke	10055677	Tongue haematoma	10043959
Haemorrhagic tumour necrosis	10054096	Tongue haemorrhage	10049870
Haemorrhagic urticaria	10059499	Tonsillar haemorrhage	10057450
Haemorrhagic vasculitis	10071252	Tooth pulp haemorrhage	10072228
Haemorrhoidal haemorrhage	10054787	Tooth socket haemorrhage	10064946
Haemostasis	10067439	Tracheal haemorrhage	10062543
Haemothorax	10019027	Traumatic haematoma	10044522
Henoch-Schonlein purpura	10019617	Traumatic haemorrhage	10053476
Hepatic haemangioma rupture	10054885	Traumatic haemothorax	10074487
Hepatic haematoma	10019676	Traumatic intracranial haemorrhage	10061387
Hepatic haemorrhage	10019677	Tumour haemorrhage	10049750
Hereditary haemorrhagic telangiectasia	10019883	Ulcer haemorrhage	10061577
Hyperfibrinolysis	10074737	Umbilical cord haemorrhage	10064534
Hyphaema	10020923	Umbilical haematoma	10068712
Iliac artery rupture	10072789	Umbilical haemorrhage	10045455
Immune thrombocytopenic purpura	10074667	Upper gastrointestinal haemorrhage	10046274
Implant site bruising	10063850	Ureteric haemorrhage	10065743
Implant site haematoma	10063780	Urethral haemorrhage	10049710
Implant site haemorrhage	10053995	Urinary bladder haemorrhage	10046528
Incision site haematoma	10059241	Urogenital haemorrhage	10050058
Incision site haemorrhage	10051100	Urogenital haemorrhage	10050058

MedDRA 17.1 Preferred Term	Preferred Term Code	MedDRA 17.1 Preferred Term	Preferred Term Code
Increased tendency to bruise	10021688	Uterine haematoma	10063875
Increased tendency to bruise	10021688	Uterine haemorrhage	10046788
Induced abortion haemorrhage	10052844	Vaccination site bruising	10069484
Infusion site bruising	10059203	Vaccination site haematoma	10069472
Infusion site haematoma	10065463	Vaccination site haemorrhage	10069475
Infusion site haemorrhage	10065464	Vaginal haematoma	10046909
Injection site bruising	10022052	Vaginal haemorrhage	10046910
Injection site haematoma	10022066	Varicose vein ruptured	10046999
Injection site haemorrhage	10022067	Vascular pseudoaneurysm ruptured	10053949
Instillation site haematoma	10073609	Vascular purpura	10047097
Instillation site haemorrhage	10073610	Vascular rupture	10053649
Internal haemorrhage	10075192	Venous haemorrhage	10065441
Intestinal haematoma	10069829	Ventricle rupture	10047279
Intestinal haemorrhage	10059175	Vessel puncture site bruise	10063881
Intra-abdominal haematoma	10056457	Vessel puncture site haematoma	10065902
Intra-abdominal haemorrhage	10061249	Vessel puncture site haemorrhage	10054092
Intracerebral haematoma evacuation	10062025	Vitreous haematoma	10071936
Intracranial haematoma	10059491	Vitreous haemorrhage	10047655
Intracranial tumour haemorrhage	10022775	Vulval haematoma	10047756
Intraocular haematoma	10071934	Vulval haematoma evacuation	10047757
Intrapartum haemorrhage	10067703	Vulval haemorrhage	10063816
Intraventricular haemorrhage	10022840	Wound haematoma	10071504
Intraventricular haemorrhage neonatal	10022841	Wound haemorrhage	10051373

APPENDIX 4. SOLICITED ADVERSE EVENT (AE) INTENSITY GRADING

Adverse Event	Age	Intensity Grade	Parameter
Pain at injection site	< 6 years of age	0: None	-
		1: Mild	Minor reaction to touch
		2: Moderate	Cries/protests on touch
		3: Severe	Cries when limb is moved/spontaneously painful
	≥ 6 years of age	0: None	-
		1: Mild	Any pain neither interfering with nor preventing normal every day activities
		2: Moderate	Painful when limb is moved and interferes with every day activities
		3: Severe	Significant pain at rest. Prevents normal every day activities
Redness * at injection site	All		Record greatest surface diameter in mm
Swelling at injection site	All		Record greatest surface diameter in mm
Fever **	All		Record temperature in °C/°F
Fatigue	≥ 6 years of age	0: Normal	-
		1: Mild	Fatigue that is easily tolerated
		2: Moderate	Fatigue that interferes with normal activity
		3: Severe	Fatigue that prevents normal activity
Gastrointestinal symptoms (nausea, vomiting, diarrhoea and/ or abdominal pain)	≥ 6 years of age	0: Normal	-
		1: Mild	Gastrointestinal symptoms that are easily tolerated
		2: Moderate	Gastrointestinal symptoms that interfere with normal activity
		3: Severe	Gastrointestinal symptoms that prevent normal activity
Headache	≥ 6 years of age	0: Normal	-
		1: Mild	Headache that is easily tolerated
		2: Moderate	Headache that interferes with normal activity
		3: Severe	Headache that prevents normal activity
Drowsiness		0: None	Behaviour as usual

	< 6 years of age	1: Mild	Drowsiness easily tolerated
		2: Moderate	Drowsiness that interferes with normal activity
		3: Severe	Drowsiness that prevents normal activity
Irritability/Fussiness	< 6 years of age	0: None	Behaviour as usual
		1: Mild	Crying more than usual/no effect on normal activity
		2: Moderate	Crying more than usual/interferes with normal activity
		3: Severe	Crying that cannot be comforted/prevents normal activity
Loss of appetite	< 6 years of age	0: None	Appetite as usual
		1: Mild	Eating less than usual/no effect on normal activity
		2: Moderate	Eating less than usual/interferes with normal activity
		3: Severe	Not eating at all

* In case it is not possible to determine the extent of redness on darkly pigmented skin, it will be reported as uninterpretable on the Diary Card and in eSource.

** Fever is defined as temperature ≥ 37.5°C / 99.5°F. The preferred route for recording temperature in this study will be axillary.

The intensity of local vaccination site redness/swelling will be scored as follows:

Age	Intensity Grade	Diameter Measurement (mm)
1 to 5 years of age	0: None	-
	1: Mild	> 0 to ≤ 10
	2: Moderate	> 10 to ≤ 30
	3: Severe	> 30
6 to 12 years of age	0: None	-
	1: Mild	> 0 to ≤ 20
	2: Moderate	> 20 to ≤ 50
	3: Severe	> 50

13 to 17 years of age	0: None	≤ 20
	1: Mild	> 20 to ≤ 50
	2: Moderate	> 50 to ≤ 100
	3: Severe	> 100

The intensity of fever will be scored as follows:

Age	Intensity Grade	Temperature Reading (˚C)
All	0: None	< 37.5
	1: Mild	≥ 37.5 to ≤ 38.5
	2: Moderate	> 38.5 to ≤ 39.5
	3: Severe	> 39.5

APPENDIX 5. LABORATORY ASSESSMENTS

Category	Test	Reported Unit	Conversion Factor	SI Unit	Toxicity Grading
Haematology	Basophils	%	1	%	
	Basophils absolute	/mm^3	0.001	10^9/L	
	Eosinophils	%	1	%	
	Eosinophils absolute	/mm^3	0.001	10^9/L	
	Haemoglobin	g/dL	10	g/L	Haemoglobin

	Lymphocytes	%	1	%	
	Lymphocytes absolute	/mm^3	0.001	10^9/L	
	Mean cell volume	fL	1	fL	
	Monocytes	%	1	%	
	Monocytes absolute	/mm^3	0.001	10^9/L	
	Neutrophils	%	1	%	
	Neutrophils absolute	/mm^3	0.001	10^9/L	
	Platelets	/mm^3	0.001	10^9/L	Platelets
	Red blood cells	/mm^3	0.000001	10^12/L	
	White blood cells	$x10^3/\mu L$	0.001	10^9/L	White blood cells - decrease
Biochemistry	Alanine aminotransferase	U/L	1	U/L	Alanine aminotransferase increase by factor
	Creatinine	umol/L	1	umol/L	Creatinine
		mg/dL	88.4	umol/L	

APPENDIX 6. LABORATORY TOXICITY GRADING

Category	Test (Unit)	Age	Gender	Grade			
				1	2	3	4
Haematology	Haemoglobin (g/dL)	≤ 12 years of age	Both	7.5 to 8.49	6.5 to 7.49	5 to 6.49	< 5
		> 12 years of age	Male	10 to 10.9	9 to 9.9	8 to 8.9	< 8
			Female	8.5 to 9.4	7.5 to 8.4	6.5 to 7.4	< 6.5
	Platelets ($x10^3/\mu L$)	≤ 12 years of age	Both	75 to 99.999	50 to 74.999	25 to 49.999	< 25
		> 12 years of age	Both	75 to 100	50 to 74.999	25 to 49.999	< 25
	White blood cells - decrease ($x10^3/\mu L$)	≤ 12 years of age	Both	2.5 to 3.999	1.50 to 2.499	1 to 1.499	< 1
		> 12 years of age	Both	2 to 2.749	1.50 to 1.999	1 to 1.499	< 1
Biochemistry	Creatinine (mg/dL)	≤ 12 years of age	Both	1.2 to 1.7	> 1.7 to 2.1	> 2.1 to 2.5	> 2.5
		> 12 years of age	Both	1.5 to 1.7	> 1.7 to 2	> 2.0 to 2.5	> 2.5
		≤ 12 years of age	Both	1.1 to 2.5xULN	> 2.5 to 5.0xULN	> 5.0 to 10xULN	> 10xULN

	Alanine aminotransferase increase by factor	> 12 years of age	Both	1.1 to 2.5xULN	> 2.5 to 5.0xULN	> 5.0 to 10xULN	> 10xULN

ULN: Upper limit of the normal range.

Note: acceptable limits for eligibility and grading scale adapted from Division of AIDS table for grading severity of adult and pediatric adverse events December 2004; WHO Toxicity Grading Scale for Determining Severity of Adverse Events, February 2003; Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, Guidance for Industry, 2007.

APPENDIX 7. VITAL SIGNS ASSESSMENTS

Assessment	Unit
Temperature	C
Height	cm
Weight	kg
Heart rate	beats per minute
Respiratory rate	breaths per minute

APPENDIX 8. PHYSICAL ASSESSMENTS

Assessment
Abdomen
Anorectal
Breast
Cardiovascular
Eyes/Ears/Nose/Throat
Genitalia
Head/Neck/Thyroid
Lymph nodes
Musculoskeletal
Neurological
Respiratory
Skin