HHS Public Access

Author manuscript

Vaccine. Author manuscript; available in PMC 2015 September 28.

Published in final edited form as:

Vaccine. 2013 November 12; 31(47): 5602–5620. doi:10.1016/j.vaccine.2013.02.041.

Template protocol for clinical trials investigating vaccines—Focus on safety elements☆

Jan Bonhoeffer[a,*], **Egeruan B. Imoukhuede**[b], **Grace Aldrovandi**[c], **Novilia S. Bachtiar**[d], **Eng-Soon Chan**[e], **Soju Chang**[f], **Robert T. Chen**[g], **Rohini Fernandopulle**[h], **Karen L. Goldenthal**[i], **James D. Heffelfinger**[g], **Shah Hossain**[j], **Indira Jevaji**[f], **Ali Khamesipour**[k], **Sonali Kochhar**[l], **Mamodikoe Makhene**[f], **Elissa Malkin**[m], **David Nalin**[n], **Rebecca Prevots**[e], **Ranjan Ramasamy**[o], **Sarah Sellers**[p], **Johan Vekemans**[q], **Kenneth B. Walker**[r], **Pam Wilson**[s], **Virginia Wong**[t], **Khalequz Zaman**[u], and **Ulrich Heininger**[a] **for the Brighton Collaboration Clinical Trial Protocol Working Group**[1]

[a]University Children's Hospital (UKBB), University of Basel, Basel, Switzerland [b]European Vaccine Initiative, Heidelberg, Germany [c]The Saban Research Institute Children's Hospital Los Angeles, USA [d]Bio Farma, Indonesia [e]Sanofipasteur, Canada [f]National Institutes of Health, USA [g]Centers of Disease Control and Prevention, USA [h]University of Colombo, Sri Lanka [i]Independent Consultant, Bethesda, MD, USA [j]National Institute of Communicable Diseases, India [k]Tehran University of Medical Sciences, Iran [l]International AIDS Vaccine Initiative, India [m]MedImmune, LLC, USA [n]Consultant in vaccinology, PA, USA [o]Institute of Health Sciences, Universiti Brunei Darussalam, Brunei Darussalam [p]q-Vigilance, LLC, USA [q]Glaxo Smith Kline, Belgium [r]Health Protection Agency, UK [s]Harvard Clinical Research Institute, Boston MA [t]Department of Paediatrics and Adolescent Medicine, The University of Hong Kong, Hong Kong, China [u]International Centre for Diarrhoeal Disease Research, Bangladesh

Abstract

This document is intended as a guide to the protocol development for trials of prophylactic vaccines. The template may serve phases I–IV clinical trials protocol development to include

☆*Disclaimer*: The findings, opinions, and assertions contained in this consensus document are those of the individual scientific professional members of the working group. They do not necessarily represent the official positions of each participant's organization (e.g., government, university, or corporations). Specifically, the findings and conclusions in this paper are those of the authors and do not necessarily represent the views of the US National Institutes of Health (NIH) and the Centers of Disease Control and Prevention (CDC).

*Corresponding author at: University Children's Hospital (UKBB), University of Basel, Spitalstrasse 33, 4056 Basel, Switzerland. Tel.: +41 61 704 12 12. contact@brightoncollaboration.org (J. Bonhoeffer).

[1]**Further members of the Brighton Collaboration Clinical Trial Protocol Working Group:** Ananda Amarasinghe, Allan M. Arbeter, Immanuel Bath, Steve Black, Kalifa Bojang, Arthur E. Brown, Rana Chakraborty, Elena Chiappini, Christopher T. da Costa, Jaime G. Deville, Glacus de Souza Brito, Fabiana de Freitas, Blaise Genton, Jane Gidudu, Roxana Mansour Ghanaie, Yolanda Guerra-Mendoza, Stephane Guishard, Renald Hennig, Nathalie Imbault, Cassandra N. Josey, Andrea Kulcsár, Xavier Kurz, Noni MacDonald, Denis Macina, Eusebio Macete, Samuel J. McConkey, Zsofia Meszner, Vasee Moorthy, Patricia Nell, Moreshwar Patwardhan, Steven Rosenthal, Andrea Sutherland, Cindy Tamminga, Jelle Thole, Vytautas Usonis, Frederick Varricchio, Beverly A. Warden, Patrick Zuber.

Conflict of interest statement: None of the authors has claimed conflict of interest.

The appendices to this template protocol are available as supplementary online material at http://brightoncollaboration.org *and* http://vaccineorb.com *website.*

safety relevant information as required by the regulatory authorities and as deemed useful by the investigators. This document may also be helpful for future site strengthening efforts.

Keywords

Vaccine; Immunization; Safety; Protocol; Clinical trial

Preamble

Need for developing a template protocol for clinical trials investigating vaccines – with a focus on safety elements

The success of immunization programmes in reducing morbidity and mortality related to vaccine preventable diseases has spurred development of new vaccines and is driving global efforts to accelerate access to vaccines in all countries. However there is an increasing need to globally harmonize approaches to investigating vaccines because of the increasing diversity of target diseases, vaccine constructs, manufacturers, and populations in which vaccines are developed, tested and licensed.

Presently there is no uniformly accepted template protocol for vaccine clinical trials. This is a missed opportunity for several reasons. First, availability of globally accepted templates would facilitate protocol development particularly in Low and Middle Income Countries (LMIC) where vaccine trials will increasingly be conducted and experience is still limited. Second, it might standardize information available for regulatory decision making in an increasing number of countries developing and introducing new vaccines. Third, data comparability across trials would facilitate data interpretation and promote the scientific understanding of the safety profile of vaccines as early as possible in their development.

The safety of trial participants and the safety profile of vaccines are of primary importance in vaccine clinical trials. Safety data are also critical for determining successful candidates early in the process of development. This document is focusing on the safety elements for clinical trials and proposes a standard framework and specific elements for a globally harmonized assessment of vaccine safety in clinical trials.

LMIC suffer the highest public health burden from infectious diseases and are increasingly explored as possible settings for clinical trials. Thus, there is an imperative to conduct well designed and executed clinical trials in LMIC, where such trials could facilitate licensure and availability of safe and effective products for populations in these settings. The standards used to assess safety in LMIC should be as stringent as anywhere else in the world. Therefore, we deviated from the original goal to develop a protocol specific for LMIC and rather propose the template provided below independent of trial setting.

Purpose and guidance for use of the template protocol

This document is intended as a guide to the protocol development for trials of prophylactic vaccines. The template may serve phases I–IV clinical trials protocol development to include safety relevant information as required by the regulatory authorities and as deemed useful by the investigators. This document may also be helpful for future site strengthening

efforts. Other documents are available to guide data collection for immunogenicity and efficacy [1–3]

While the template protocol reflects scientific considerations and should be independent of setting, local implementation of the protocol should be addressed in the respective Investigator's Manual and (site specific) standard operating procedures. In addition, local application of the protocol should give special consideration to and be in compliance with regional/national regulations, customs, and laws. Further, template protocols may provide a general guidance and framework for protocol development. However, they do not replace individual careful planning and decision making on the protocol related to each specific trial question. Further, they are a necessary but insufficient means towards data comparability. Additional training and support of local investigators and strengthening of health system aspects in LMIC are required to ensure the collection of high quality data and that the clinical trials are in compliance with international regulatory and ethics guidelines.

Further, the group recognizes that implementation of all guidelines might not be possible in all settings. The availability of information may vary depending upon resources, geographical region, and study design. Thus the template protocol has been developed for guidance only. It is not considered a mandatory requirement, and is not intended to replace established or mandated procedures nor regulations.

In recognition of different trial settings, professional backgrounds, and clinical trial experience, the working group decided to use a standard format to promote a shared understanding and to facilitate implementation of the template. For each section we first outline the content to be specified in the protocol. This is followed by a comment or example (in italics) to provide specific guidance to investigators by highlighting the importance, providing background and stimulating safety considerations relevant to the pertinent section.

Methods for developing the template protocol

INYVAX is a European Commission funded project (www.inyvax.eu) led by the European Vaccine Initiative, Heidelberg, Germany (www.euvaccine.eu) aiming at optimized development of vaccines in resource-limited environments. One of the INYVAX activities aims at implementation of safety standards in phases I–IV clinical trials. This task has been taken on by the Brighton Collaboration (www.brightoncollaboration.org). Following the process described previously [4], a Brighton Collaboration *INYVAX* working group was formed in February 2009 with 67 inter-disciplinary members with public health, regulatory, clinical, academic, and vaccine manufacturer backgrounds, as well as expertise in protocol development for vaccine clinical trials in different settings including LMIC.

To guide the decision-making for the template protocol and its amendments, a literature search was conducted in MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews, and the Database of Reviews and Effects (DARE) from 1 January 2000 and 1 July 2009 (Manuscript in preparation). This was done for the identification of trials conducted in resource limited countries to optimize development of vaccines in these settings. Our review was then expanded to published and unpublished trial protocols from these and additional

studies developed by pharmaceutical industry, public health agencies, or academic institutes independently of setting. Although the review was limited to the English language due to practicability, the working group consists of experts from different culture and language backgrounds worldwide. The template protocol was further developed to be in line with the International Conference on Harmonization (ICH) guidance document E6 (Good Clinical Practice) Section.

Finally, similar to all Brighton Collaboration case standardized case definitions and guidelines, review and update of the template protocol is planned on a regular basis (i.e., every 3–5 years), or more often, if needed.

Template Protocol – focus on safety elements

TITLE PAGE[a]	
Full Title	Title including type[b] of trial
Short Title	An abbreviated title and acronym, if applicable
Trial ID	Trial identifying number
Registration number	Clinical trial registration number[c]
Primary study Vaccine(s)	International Nonproprietary Name (INN) and number
Version	Version number of protocol
Date	Date of protocol version (e.g. DD/MM/YYYY)
Sponsor(s)	Name of Sponsor(s)
Manufacturer	Name of manufacturer
Principal Investigator	Name of Principal Investigator
Conducted by	Name of network, consortium, or programme, if applicable
Main Co-Investigators	Name of Major Co-Investigators, if applicable
Version log:	Log of specific amendments by version
Confidentiality statement	Statement outlining the distribution of the document

[a] *Note:* If any of the fields listed is not appropriate for a specific trial, please leave it empty.

[b] E.g., randomized, double-blinded, controlled.

[c] E.g., number of Investigational New Drug (IND), or Clinical Trial Authorization (CTA), or European Union Drug Regulating Authorities Clinical Trials (EudraCT).

LIST OF ABBREVIATIONS

This section should list all abbreviations used in the protocol. The example list below should be modified according to specific protocol.

For example,

Abbreviations	
AEFI	Adverse Event Following Immunization
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials

Abbreviations	
CRF	Case Report Form
CSP	Central Safety Physician
DSMB	Data and Safety Monitoring Board
US FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent/Institutional Ethics Committee
IDMC	Independent Data Monitoring Committee
IRB	Institutional Review Board
LMIC	Low and Middle Income Country
LSM	Local Safety Monitor
MedDRA	Medical Dictionary for Regulatory Activities
N	Number
US NCI	United States National Cancer Institute, NIH
US NIH	United States National Institutes of Health
OHRP	Office for Human Research Protections
OHSR	Office for Human Subjects Research
PHI	Protected Health Information
PI	Principal Investigator
RCT	Randomized Controlled Trial
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
WHO	World Health Organization

PROTOCOL SUMMARY

This section should provide an executive summary of the protocol with a dedicated section to outline the approach to safety assessment of the trial. The summary may be presented in narrative or tabular format.

Below is a template protocol summary in tabular format:

Full Title	Provide the title including the type of trial
Short Title	An abbreviated title or acronym
Trial code	
Trial Phase	I, II (IIa, IIb), III, or IV
Objectives	Objectives of the trial • Primary Objective • Secondary Objectives • Exploratory Objectives (if applicable)

Study Design	Outline study type, study arms, type of control, trial blinding, randomization ratio
Sample Size	Provide sample size in total and by study arm
Study Population	Describe briefly main characteristics of the study population including health status (e.g., healthy volunteers or HIV-positive), gender, age, ethnicity, etc.
Immunization(s)	Outline name of primary and concomitant vaccine(s), dose, route of administration, schedule
Trial Duration	State trial duration, time of participants on trial (intervention and follow-up) and total accrual time
Safety Evaluation	Summarize methods, measures, and timeline for safety assessment
Endpoints	Specify the endpoints with specific focus on safety • Primary endpoints: Include measures and methods to determine each endpoint • Secondary endpoints: Include measures and methods to determine each endpoint • Exploratory endpoints (if applicable): Include exploratory outcome measure(s) that may ask separate research questions from the parent protocol.

LIST OF KEY ROLES

This section should list all key roles and responsible individuals of the trial, particularly those pertinent to safety assessment including the Central Safety Physician (CSP), for multi-centre trials, the chair of the Independent Data Monitoring Committee (IDMC). Below is a template with **required elements for a table of key roles**:

Key Roles*	Responsible Individual	Organization
Sponsor(s)	Name, Title, Position of Individual authorized to sign the protocol and protocol amendments for the Sponsor and the Sponsor's medical expert for the trial	Institution Address Phone Number Fax Number E-mail
Medical Monitor (if other than Sponsor)	Name, Title, Position of the medical monitor	Institution Address Phone Number Fax Number E-mail
Principal Investigator	Name, Title, Position of the Lead investigator(s) responsible for conducting the trial in all trial sites	Institution Address Phone Number Fax Number E-mail
Central Safety Physician	Name, Title, Position of the qualified physician who is responsible for management of all safety related medical decisions	Address Phone Number Fax Number E-mail
Chair of IDMC	Name, Title, Position of the IDMC chair. Detailed names and contacts of the IDMC members may be listed in a specified separate document.	Institution Address Phone Number Fax Number E-mail
Contact for questions regarding the protocol	Name, Title, Position of the central person to be contacted for protocol related questions	Address Phone Number Fax Number E-mail

* *Note:* If any of the roles listed are not part of the trial, please say so under "Responsible Individual".

Optional elements to be added to the above table include (consider listing in this section, for example): Trial sites and Investigators, Major International Collaborators, if not included

as site investigators, Clinical laboratory/ies and other medical or technical departments and/or institutions, Vaccine Manufacturer Representative(s), Local Safety Monitor, Protocol Data Manager, Protocol Epidemiologist, Protocol Pharmacologist, Protocol Statistician(s).

Any other roles should be listed in a separate document (e.g., the Standard Operation Procedure (SOP)) with names and contacts per site.

1. Background information and rationale

1.1. Summary of target disease pathogenesis and the study vaccine(s)

The background section should outline the relevant information about the pathogen/pathogenesis causing the disease.

The characteristics of the candidate vaccine(s) and all relevant safety information of the candidate and control vaccines used in the trial should be outlined. Relevant safety information of adjuvant(s) should be provided, when applicable. A rationale for the use of the different components of the vaccine should also be given.

> Comment: It would be relevant to briefly outline, for example, safety information of existing vaccines targeting the same disease.

The known reactogenicity of all components present in the vaccine and other characteristics of the vaccine that can affect safety of the vaccinees should be provided. The known interactions of components in the vaccine(s) should be provided. Wherever possible, attention should also be given to the components of the vaccines in view of the local, ethnic, cultural, and religious context of the study and target population.

> Comment: Religious rules regarding injunctions on use of animal derivatives should be weighted. In cases of lifesaving medications or vaccines, exemptions to religious rules are possible with reference to religious authorities.

1.2. Summary of the study population characteristics and site-specific information

This section should provide the rationale for the selection of the study population (i.e., the defined subgroup of the source population from which the sample is drawn) and trial sites.

The rationale should include the target disease incidence, prevalence and mortality rates, potential safety impact of nutritional status, underlying or concurrent diseases, prior or subsequent exposure to vectors and diseases should be outlined. It should further specify the impact on the collection and evaluation of safety data, as well as trial implementation, if the trial is conducted in an endemic area. State that the minimum requirements of a qualified trial site, particularly in terms of capacity to conduct the trial are provided in the site specific information document.

A brief summary of other factors such as access to health care, infrastructure and availability of resources to detect safety outcomes particularly in the LMIC where the trial is being conducted should be specified. Their impact on the collection of safety data, the potential introduction of bias and its control in the frame of the local setting should be discussed in

detail in a dedicated subsection. Finally, the general approach to safety assessment of the candidate vaccine reflecting the considerations mentioned above should be outlined.

Comment: It would be relevant to discuss, for example, that limited access to health care may lead to delayed or missed diagnosis such as sudden death. The possibility to identify and document causes of health events may also be limited. For example, the complete investigation of acute paralysis may require facilities not locally available. Both scenarios exemplify how the lack of diagnostic capacity may impact safety evaluation. This is particularly true if a cluster of similar health outcomes is observed and possible alternative explanations to the vaccine cannot be identified.

1.3. Rationale for trial design

Justify the trial design with particular reference to the safety aspects of the trial. Justify any aspects of the trial that are modified according to local regulatory authorities or practicability, if feasible. Justify any aspects of the trial that are modified according to available data from preclinical and clinical trials and epidemiological studies.

Comment: Justify trial aspects such as route of administration, modified dosage and dosing schedule, and modified study population. Justify the reason why a trial with multiple sites over world is needed, and relevant safety. Data from literature review should be referenced.

Provide a rationale for the control group/arm(s), e.g., placebo control; no treatment control; active treatment control; dose comparison control.

1.4. Risks and benefits

Provide a brief profile of available information on risks and benefits of the investigational vaccine(s) and trial design based on literature review including data from available preclinical and clinical trials at the time of writing. Briefly summarize known risks and benefits and relevant safety experience of the investigational vaccine(s) to human subjects, particularly the specific study population, in the context of individual versus society impact as far as known. State that detailed discussion and emerging information is provided in the site specific information document.

2. Trial objectives

Comment: Depending on the trial phase, reactogenicity or safety may be either a primary or secondary objective. Typically, phase I studies focus on safety as the primary objective. Phases II and III studies increasingly address safety concerns in parallel to expanded dose ranging and efficacy testing, while phase IV studies focusing on safety as the primary or co-primary objective are typically observational epidemiological studies.

PRIMARY OBJECTIVE

- If safety or reactogenicity are the primary objectives of the trial, details should be outlined here.

Example: “The primary objective of this trial is to describe the tolerability of 3 doses of vaccine candidate X in healthy adults at dosages of 0.5, 1.0 and 3 mg”

- The primary endpoints to be measured should also be highlighted here.

SECONDARY OBJECTIVES

- If safety or reactogenicity are secondary objectives, details should be outlined here.

  Example: “1. To assess safety profile of the study vaccine during the entire study period; 2. To assess Serious Adverse Events (SAE) profile of the study vaccine during the entire study period; 3. To assess incidence of concurrent wild type dengue infection in vaccinated subjects who developed haemorrhagic fever following immunization from Day 1 to the end of the trial.

- The secondary endpoints to be measured should also be highlighted here.

  Example: “1. Solicited “reactogenicity” events (injection site and systemic) from Day 1 to Day 7.; 2. Unsolicited events (injection site and systemic) from Day 1 to the end of the trial.

EXPLORATORY OBJECTIVES

- If applicable, details and outcome measures should be outlined for separate research questions from the parent protocol.
- The exploratory endpoints to be measured should also be highlighted here.

3. Trial design

Comment: Later stage trials (usually starting with proof of concept) tend to be powered for immunogenicity or efficacy - but typically phase 1 trials are not powered. All have limited sample size from a safety perspective. Thus, comparability of data across trials throughout vaccine development is critical for pooling or meta-analysis. Therefore, special attention should be paid to trial design and data collection to ensure data comparability across trials throughout the development of a candidate. This section should provide a short overview of the study structure and should be consistent with the study title and objectives.

This section of the protocol should briefly highlight the following elements:

- The experimental design including the phase of trial, type of trial, trial configurations (labelling, blinding, controlling, randomizing, etc.).
- Brief description (details should be provided in Section 10) of statistical considerations relevant to trial design (e.g., power calculation, estimated drop-out rate) and the size and kind of study groups/arms.

Example:

SUMMARY OF TRIAL BY GROUPS/ARMS			
	Group/arm 1	**Group/arm 2**	**Group/arm 3**
N vaccinees	1000	2000	2000
N controls	1000	2000	2000
Total *N* by dose cohort	2000	4000	4000
Total *N*		10,000	

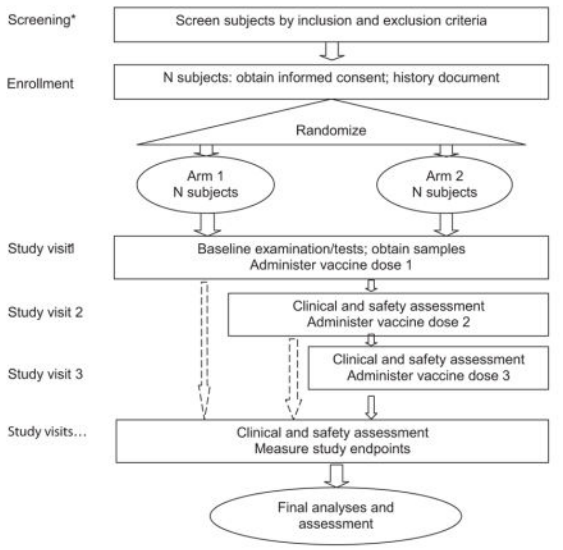
- The kind, number of doses, and schedule of the investigational vaccine(s).

  Comment: special safety consideration should be given to concomitant vaccinations.

- The kind, number of doses, and schedule of the comparator/placebo.
- All study endpoints should be listed again with the respective follow-up period for both solicited and unsolicited outcomes.
- Duration of the trial for individual participants.
- The proactive plan in recruitment and data evaluation and analyses in case the expected sample size is not reached.
- Pre-determined sub-cohort studies should also be briefly outlined when applicable.

This description should be complimented by an overview schematic illustrating the trial flow.

Template Schematic of trial design (modified from the National Institute of Allergy and Infectious Diseases (NIAID) Protocol Template version 2.0)



Timelines of the main phases and milestones of the trial and trial individual participants should be outlined in a summary table in the Investigator's Manual.

4. Study population

Comment: The study population is defined as the subgroup of the source population from which the study sample is drawn.

4.1. Description of study population

- Characterize the source population covered by the respective trial sites.
- Brief main characteristics of the study population specific for the trial objectives (e.g., healthy or sick or special groups).
- Brief outline of the main characteristics of each trial setting including location and disease endemicity.

4.2. Inclusion and exclusion criteria

Comment: Inclusion criteria describe primarily eligible subjects. Exclusion criteria limit the number of primarily eligible subjects to a subgroup. Both are important in terms of safety consideration.

This sub-section should clearly specify:

- Inclusion criteria:
  - State that participants should meet all inclusion criteria.
  - Clearly describe all eligibility criteria (e.g., parent/guardian suitability for enrolment, clinical, laboratory, imaging, informed consent) for participant inclusion and provide the respective rationale.
  - Describe how inclusion criteria will be assessed and decided on.
- Exclusion criteria:
  - State that participants should not meet any of the exclusion criteria.
  - Clearly provide exclusion criteria (e.g., clinical, laboratory, imaging, pregnancy, and particular life circumstances such as distance to responsible physician/investigator site).

    Example: Exclude from the study any participant who has experienced a hypersensitivity reaction to any component of the vaccine.
  - How exclusion criteria will be assessed and decided.
  - A rationale is needed particularly for excluding women, children, or ethnic groups, if applicable.

4.3. Withdrawal

Comment: The investigator may decide to discontinue administration of further doses. This may be either for medical reasons (for trial participant's safety), for protocol violation, or because new data becomes available suggesting inappropriateness of the immunization to a specific category of trial participants.

Meanwhile, a trial participant may decide to withdraw from the trial or any part of the trial (e.g., specific sample collection or genetic test) at any time. A trial participant included in the clinical trial is said to have dropped out after deciding, on his/her own volition, to terminate his participation in the trial.

It should be stated

- that at any time trial participants may withdraw voluntarily from the trial or from receiving any of the study interventions
- that trial participants may also be withdrawn from receiving further doses, but not from the follow-up procedure, by the investigators for safety reasons

In this subsection one should also

- specify the criteria for contraindications of individual trial participant from the trial including the subsequent immunizations
- provide instruction on how the investigators should document the time and reason for all withdrawals

  Comment: The time and reason for withdrawal should be noted in the space provided for this purpose in the Case Report Form (CRF). Participants who are withdrawn because of occurrence of AEFI should be clearly distinguished from participants who are withdrawn for other reasons.

- Specify follow-up procedure for all withdrawals.

  Comment: Investigators should follow participants who are withdrawn for an AEFI until the event resolves or stabilizes as part of long-term follow-up.

- Describe the replacement procedure for the withdrawals if replacement will be planned.

4.4. Lost to follow-up procedures

- Specify the procedure to limit lost to follow-up.
- Outline the plan to locate the trial participant for health status.

  Comment: If a trial participant fails to appear for a follow-up examination, extensive effort (i.e., documented phone calls and certified mail and home visits, to be adapted to the trial setting) should be undertaken to locate or recall him/her or at least to determine his/her health status.

- Determine the documentation plan of these efforts.

For example: These efforts should be documented in the trial participant's CRF and other pertinent source documents.

- Provide guidance for classification of the reasons for "lost to follow-up".

  Comment: Any trial participant who is not available for the final follow-up should be classified as "lost to follow-up" and the classification noted on the CRF together with the reason, if known.

- Outline the conditions and plans for replacement of "lost to follow-up".

4.5. Trial participants in sub-cohorts

This section should specify predetermined sub-cohorts of trial participants for detailed analysis. This may include cohorts with simultaneous treatments or with special investigations. For each sub-cohort, details of inclusion and exclusion criteria, specific immunization or treatment procedures, specific outcome measurements and specific data collections should be provided.

5. Investigational vaccine and immunization procedures

5.1. Investigational vaccine and administration

The following subsections (5.1.1–5.1.3) should be provided for each investigational or control vaccine.

5.1.1. Vaccine description and acquisition—Describe:

- The investigational and control vaccine(s) including name of vaccine, manufacturer, multi- or mono-dose vial, pre-filled syringe, volume (e.g., 0.25 ml, 0.5 ml, etc.), adjuvants, diluents and the need for reconstitution, if applicable.
- Requirements on transportation and storage conditions for keeping the stability of the vaccine(s)

  Comment: This is a major challenge in LMIC.

- State that other characteristics of all components of the vaccine relevant for safety assessment should be described in sufficient detail in the Investigator's Manual. These include requirements and plans of packaging, labelling, and distribution and expiration time.

State that the stability of vaccine(s) should be monitored throughout the trial. The respective manufacturer's or the sponsor's manuals should be referenced for detailed plan in monitoring the stability (e.g., a sampling plan).

5.1.2. Accountability of the vaccine—State here that the study procedures manual should be referenced for:

- The procedure in place for accounting for investigational and control vaccines received in the trial centre and their use during the trial including the planned

logistics and documentation of stocks and their distribution from and to central and peripheral sites.

5.1.3. Immunization safety precautions and instructions—Highlight the safety precautions and instructions including:

- Safety aspects of the device (if any) used for delivering the vaccine.
- The safety aspects of the location where the vaccine is administered in each vaccine trial centre (e.g., hygiene, disposals, etc.).
- The required training and minimal requirement of the vaccine administrator. State that more detailed training is described in Section 6.1.
- Required availability and qualifications of medical personnel present during and following immunization.
- Potential medication errors could also be described in the Investigator's Manual.

5.1.4. Vaccine administration—Briefly highlight the procedure for administering the vaccine in sufficient detail for assessment of safety including

- Preparation before administration: include preparation of the study vaccine and temporary storage requirement before administration (e.g., temperature, container, maximum hold time and conditions).
- Administration site and route (e.g., intramuscular, subcutaneous, or intradermal for injectable vaccines).

State that detailed instruction on vaccine administration including instructions for managing administration of wrong route, dose, etc. is provided in the Investigator's Manual.

5.2. Prior and concomitant medications/treatments

State that

- Any concomitant medications or treatments administered *three* months prior to, during, or within *three* months after immunization should be recorded in the Case Report Form (CRF) (refer to Section 7.2).
- Any new medication or change of treatment should lead to a review of the medicine/treatment list under "concomitant medicines" in the study procedures manual.

The study procedures manual should be referenced for

- permitted medications/treatments and those leading to elimination of a subject from certain analyses
- precautionary medications/treatments and strategies
- prophylactic medications/treatments (see Glossary) and plans
- rescue treatments (see Glossary)

Comment: In the referenced study procedures manual, consideration should be given to guidance for how to properly document prophylactic medications versus therapeutic medications (e.g., antipyretic medication).

6. Trial methods and procedures

In this section of the protocol the activities that are to be completed for the clinical trial should be described. This includes trial preparations, a schedule of all procedures, and evaluations that are to be performed throughout the duration of the trial.

6.1. Training, communication, and registration

This part of the protocol should briefly outline preparations for the clinical trial. This includes:

- A summary of the mechanism for monitoring safety including staff requirements, instruments to be used, frequency of monitoring, and data documentation and management.
- Brief plan of staff training to ensure that the trial is conducted appropriately. Details should be provided in the Investigator's Manual.

  For example: protocol and GCP training; trial-specific training, such as types of AEFI experienced by the mother and experienced by the baby for management of new pregnancy; Standard case definitions of AEFI (refer to Section 7.1).
- Strategies to optimize communication between investigators and participants including
  - provision of informed consent in the appropriate local language or dialects where the trial is being conducted

    Comment: The translations of the informed consent should be included in the study procedures manual. Translation may also be considered for other documents such as the training curriculum and materials[5].
  - the approach to addressing the informed consent process taking into consideration the culture of the location where the clinical trial is being conducted

    Comment: There may be differences in the relationship between the physician and the trial participant in various countries.
  - utilization of additional tools or strategies (if applicable) to support the informed consent process or to educate the trial participant in the various trial activities
  - assessment of cultural perspectives on specific Adverse Event Following Immunization (AEFI)

Comment: Some AEFI may not be reported as they are subject to traditional belief rather than perceived as medical events. For example: Convulsions may be interpreted as caused by evil spirits rather than neuronal hyperexcitability.

- the approach to addressing various education and literacy levels of the trial participants and caregivers

  Comment: Describe the development and use of pictures and graphics that may reinforce the trial participant's understanding of the trial in some cases

- the aim of developing a glossary of common trial terminology in different languages to avoid misunderstandings or confusion

- State that detailed training and communication plans such as site-specific plan should be provided in site specific information document or site-specific SOP.
- Briefly highlight the plan for trial registration in a web-based register.

6.2. Assignment, randomization and blinding

Clearly describe the methods and documentation of the procedure assigning participants to study groups/arms.

- Randomization methods should be described. It should also be mentioned that the investigator should follow the trial's randomization plan and document the procedures, if applicable.
- Stratification or minimization factors should also be described (e.g., a weight of each factor in minimization algorithm)
- Blinding methods should be described in detail, if applicable
  - description of blinding methods during intervention

    Comment: Blinding methods may be different for the various persons involved in handling the vaccine. For example, the investigational vaccine and placebo may be prepared by an unblinded pharmacist. Coloured plastic sheaths may be placed over vaccine and placebo by the pharmacist, if the vaccine/placebo is identical in appearance. Administration will be implemented by investigators not involved in endpoint assessment.

  - a statement that the investigator should ensure that emergency unblinding only occur in accordance with the protocol
  - the timing and procedures for planned unblinding or breaking of randomization codes, if applicable
  - instructions for managing emergency unplanned unblinding (refer to Section 7.7)
  - the mode of documentation and reporting

Comment: If the trial is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious AEFI).

- statement that emergency unblinding should be discussed with the CSP, if deemed necessary by the investigator, or other physician managing the participant. Alternatively the investigator may contact the Local Safety Monitor (LSM) who will contact the CSP.

  Comment: An investigator should request participant's treatment code be unblinded only in the case of a medical emergency or in the event of a serious medical condition, and this information is necessary to treat the participant and/or would influence future trial activities. The code for the specific participant can be broken by the CSP.

- statement that the investigator should instruct trial participants or their legally authorized representatives to carry a card (or equivalent) at all times during the trial in order to facilitate unblinding in the event of a medical emergency managed by a physician other than the investigator/ investigational site staff.

- statement that any information regarding emergency unblinding will be shared with the LSM and the medical monitor.

6.3. Trial schedule

Provide a detailed schedule of all the procedures and evaluations. All planned clinic visits and participant contacts should be included in the schedule. The schedule should include allowable windows for all visits. Information outlined in this section should be consistent with information in the schedule table/trial calendar.

Trial calendar: A trial calendar should be provided to list all the procedures and evaluations by the time points/study visits in addition to the following narrative description. It can be attached as an appendix of the protocol (see template trial calendar in Appendix A).

6.3.1. Screening—Include

- whether separate informed consent, if not part of the informed consent for trial participation, is required for screening tests
- clinical, laboratory or other evaluations that are needed to assess, if a trial participant meets the criteria for enrolment
- the actions that should occur during screening and any specified timeframes prior to enrolment
- documentation of the procedure including eligibility evaluation

  Comment: An eligibility screening worksheet should be included in the study procedures manual, including copies of required clinical or

laboratory tests. If mathematical calculations are needed (such as creatinine clearance, or body mass index) then consideration should be given to worksheets or other tools to properly document that and how it was done and for consistency.

- specifics of possibly different approaches to screening at the various trial sites

6.3.2. Enrolment/baseline—In this section, briefly specify

- Recruitment strategies and procedures
  - general strategies should be specified here
  - site-specific strategies should be included in site-specific SOP
- Retention strategies (i.e., strategies to pause or discontinue trial participation)
- Guidelines of co-enrolment of participants to other studies while participating in this trial

  Comment: Generally co-enrolment is discouraged.

It should be emphasized here that informed consent should be signed by the trial participant and be submitted for participant registration prior to trial-related interventions (refer to Section 12.2 for more description).

Provide

- a description of the approach addressing potential variability of site-specific consent forms

  Comment: Depending on local regulations and the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) requirements, the actual informed consent used at each trial site may vary. Site specific requirements should be explored at the time of protocol writing to account for variability and aim for harmonization across sites
- clinical, laboratory, or other assessments that are required at baseline for comparison with outcome measurements

  Comment: If enrolment and baseline investigations are at different time points, further assessments to evaluate or confirm if a trial participant still meets the eligibility criteria may be needed prior to intervention
- description of methods and planned events that should occur during enrolment. This includes participant registration and assignment of participant number and study group/arm
- plan on how this will be documented

6.3.3. Scheduled follow-up visits

- List, sequentially, procedures required to assess trial outcome measures and trial evaluations.

- Discuss methods to be used (e.g., home visits or phone calls where applicable).
- Discuss the events that should occur during each visit. Describe how this will be documented.

6.3.4. Unscheduled follow-up visits

- Define what is considered an unscheduled visit.

  Comment: Unscheduled visits may include self-presentation to a health-care facility, and need for laboratory/clinical evaluations generated during the trial.

- Criteria for a subject/parent to come in for an unscheduled visit should be listed.
- Describe operation procedures for unscheduled visits.
- Describe how the visits will be documented.

6.3.5. Final study visit

- Provide the time point of the final study visit.

  Comment: A clinic visit or other contact should be required at least six months after the last dose of study vaccine to ascertain additional SAE and new onset of chronic illnesses[6].

- Describe any special procedures or clinical laboratory evaluations that should be performed.
- Describe any final instructions the trial participant should be given and how they will be informed about the results of the trial.
- Briefly outline follow-up procedures for any ongoing AEFI or SAE.

6.3.6. Early termination visit

- State the procedure for an early termination visit in case of participant withdrawal.
- Define the evaluations required in such circumstances during an “early termination visit”

  Comment: Any participant receiving at least 1 study dose should be followed for safety for the planned trial duration, if the participant agrees, regardless of the reason for discontinuing vaccinations. If there are signs and symptoms of an AEFI at the time of early termination, the trial participant should be followed-up until the end of the trial, or the signs/symptoms resolve or the participant’s condition becomes stable for SAE.

Detailed instructions for management of withdrawals and contraindications are described in Section 7.8 “Withdrawal procedures”.

6.4. Management of birth control and new pregnancy of trial participants

Comment: Wherever possible, attention should be given to the management of birth in view of the local, ethnic, cultural, and religious context of the study and target population.

This section should specify the birth control policy as well as the procedures of reporting and management of new pregnancy amongst trial participants. It includes:

- Detail of birth control measures and potential consequences of pregnancy during the trial and related participant information and guidance.
- Detailed reporting procedure: which information should be collected and reported, time frame of reporting, responsible reporter, and to whom it should be reported.

  For example, a Pregnancy Report Form with specified information (e.g., Estimated Date of Conception (EDC), date of last study dose) should be completed and sent to the sponsor. Reporting elements should also include time period and details of the outcome of the pregnancy i.e., details of the delivery, gestational age, neonate status including presence or absence of congenital anomalies and pregnancy termination, as applicable.
- Guidance/algorithm should be provided for determining the conception date with respect to vaccination date.
- Specific follow-up plan including predetermined follow-up period and endpoint measurements, (e.g., trial staff maintains contact with the pregnant trial participant to obtain information about the outcome of the pregnancy).
- Plan of data collection and documentation.
- Rule of retention (i.e., pause or discontinue trial participation) with the investigational and placebo vaccination and with other trial procedures.

  Comment: the investigator may decide to discontinue administration of further doses, and the participant may voluntarily withdrawal from the trial. Provide detailed withdrawal procedures and management of withdraw in Section 7.8.
- State that AEFI in pregnant trial participants should be reported and managed following the guidance relevant to pregnancy as well as management of AEFI (Section 7).

6.5. Management of specimens

- State that detailed specimens management and biobanking procedures, including preparation, storage, shipment and transportation, should be provided in the sample management manual.

  Comment: all steps of specimen management should be in line with local and any other applied legal policies and ethical requirement.
- Specify the scope of possible future use of samples during this time.

For example: These specimens are needed for (a) future clinical bridging studies, and (b) testing to assess possible contamination by adventitious or other agents that might not be known at time of initial use in the trial.

Comment: Guidance in development is available from (a) US National Vaccine Program Office (NVPO), (b) Brighton Collaboration Viral Vector Vaccine Safety Workgrouphttps://brightoncollaboration.org/public/resources/Library/viralvectorlibrary.html, and (c)http://biospecimens.cancer.gov/default.asp. Websites accessed in September 2012.

- Provide a brief overview of the procedures of specimen management outlined in the subsections below.

6.5.1. Specimen preparation, handling, and storage

- Clearly outline the preparation, handling, and storage of the specimens, e.g., required temperatures, location of storage, how the specimens will be labelled.
- Discuss procedures of specimen management in emergency situation, e.g., power back up in case of electricity cut offs. Also discuss long-term plan including accessibility and future use of stored specimens.
- State the individuals and agencies responsible for sample taking and storage as well as location and duration of storage are defined in the sample management manual.

  For example, at the end of the clinical trial, all remaining samples will be sent to the sponsor or designee to be stored for 10 years (or as long as appropriate).

6.5.2. Specimen shipment or transportation

- State the frequency (including the days and times), requirements, and conditions of specimen transportation. Reference the Investigator's Manual for the person and institution responsible for coordination of specimen shipment, the shipping address, contact information for the laboratory personnel, and the labelling requirements for specimen shipping.
- State that all specimens should be properly packaged and labelled to indicate the general nature of the materials being transported.
- State in the protocol that all specimen shipments received should comply with all applicable laws governing packing, labelling and transportation, particularly for infectious or diagnostic or toxic or hazardous materials.
- Discuss procedures in case of emergency. Include details in the trial policy manual on Specimen Transportation.

6.6. Data handling and record keeping

In this section, the following items should be mentioned and detailed:

6.6.1. Confidentiality

- Briefly state how all trial participant information will be kept confidential and handled according to regulatory, institutional, or the trial sponsor's requirements. Provide detailed descriptions in Section 12.3.

6.6.2. Source documents

- Describe eligible source documents, which are where information is first recorded and to be recorded directly on the CRF to be utilized. This includes all information, observations, original records and certified copies of clinical findings or other activities in a clinical trial necessary for the evaluation and reconstruction of the trial

  Comment: Acceptable source documents include hospital records, clinical and office charts, laboratory notes, memoranda, trial participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, (reports of) x-rays or other radiographic tests, participant files, and records kept at pharmacies, laboratories and medico-technical departments involved in the clinical trial. There should be consideration of literacy of participants or their parent guardians. For example, special symbols or other mechanisms can be used for recording information on diary cards.

- Explain how source validation will be facilitated and carried out.
- Give details about how all AEFI information, including any related signs, symptoms and abnormal diagnostic results, should be recorded in the source document.

6.6.3. Case Report Forms

- State that the Case Report Form (CRF) is the primary data collection instrument for the trial as it is used to record the required data for each trial participant, and it should include the identity and contact information of all recorders.
- Emphasize here that the investigator is responsible for the accuracy, completeness and the timeliness of the information that is collected in the CRF. Specify that an explanation should be provided for any missing or incomplete data by the investigator who also should sign the CRF when it is considered complete.
- Give details how all AEFI information, including any related signs, symptoms and abnormal diagnostic results, should be recorded in the designated AEFI module of the CRF (refer to Section 7.2 and Appendix B-2). Ensure that all information required for documentation of AEFI as specified in Section 7.2 is captured in the CRF. Provide a plan for CRF management including a plan of regular evaluation of CRF's completeness by the sponsor.

Comments: the CRF does not have to be a paper/traditional form, but may be a virtual document, e.g., fully electronic or multiple-source document comprising traditional and e-diary and other data capture devices.

6.6.4. Record retention

- Describe the detailed plan of record keeping and reference pertinent regulations.

  Comments: Record keeping requirements vary depending upon the funding source of the trial and under what specific regulations the protocol will be conducted.

  Common regulations that should be referred to are:

  – Data Handling and Record Keeping: ICH E6 5.5 – Trial Management, Data Handling and Record keeping. CPMP/ICH/135/95 July 2002

  – For studies conducted under EMA regulation, Article 58 EC Regulatory No 726/2004. EMEA/CHMP/5579/04 23 May 2005

  – For studies conducted under US IND, refer to 21 CFR 312.62(c) for investigator record retention http://www.gpo.gov/fdsys/browse/collectionCfr.action?collectionCode=CFR Website accessed in March 2013.

- The protocol should specify the period of record retention.

  For example, “trial documents will be maintained a minimum of 2 years following the last approval of the marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product.”

- Also, the protocol should indicate whether permission is required and from whom such permission is to be obtained prior to the destruction of any records.

  For example, “the sponsor will inform the investigator(s)/institution(s) in writing when the trial related records do not need to be retained any longer.”

7. Adverse event assessment and management

It should be mentioned that the respective site SOP should be in accordance with the protocol and describe which member(s) of the trial staff is/are responsible for AEFI assessment and management.

7.1. Definitions

- Clearly define the terms used in the clinical trial protocol and provide a glossary for a shared understanding of concepts in English and, ideally, in other languages, for a shared understanding of terms and languages and cultures.
- Clearly define solicited AEFI and SAE.

Comment: It is important that for all solicited AEFI and other specific AEFI that are potentially associated with the vaccine being studied, the investigator should use standardized case definitions (Brighton Collaboration case definitions, if available) for case classification[10–31]The most up-to date and complete case definitions are available together with guidelines for collection, analysis and presentation of vaccine safety data at:https://brightoncollaboration.org/public/what-we-do/standards.html

Adverse Event Following Immunization (AEFI)

Any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease.

Adverse reaction to immunization (ARI)

Any untoward medical occurrence in a study participant with an established causal relationship to immunization.

CIOMS/WHO Classification of cause specific reactions:

1. Vaccine product-related reaction: An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product.
2. Vaccine quality defect-related reaction: An AEFI that is caused or precipitated by a vaccine that is due to one or more quality defects of the vaccine product including its administration device as provided by the manufacturer.
3. Immunization error-related reaction: An AEFI that is caused by inappropriate vaccine handling, prescribing or administration and thus by its nature is preventable.
4. Immunization anxiety-related reaction: An AEFI arising from anxiety about the immunization.
5. Coincidental event: An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety.

Serious AEFI (SAE)—A serious AEFI (SAE) is defined as any event which

- results in death,
- is life-threatening (i.e., there is risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe),
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,

- is a congenital anomaly/birth defect

Solicited AEFI—Solicited AEFI are pre-specified and actively monitored for during the trial.

Unsolicited AEFI—Unsolicited AEFI are not specified for active monitoring, but spontaneously reported as untoward events occurring in a participant.

Adverse events of special interest—Adverse events of special interest are a specific subgroup of solicited AEFI which may be specific to the vaccine or study population and may be monitored for specifically.

7.2. Safety data collection

Comments: The procedure of safety data collection can typically be classified into three stages. The table below outlines appropriate tools and the type of information to be collected by stage.

Stage	Tool	Kind of information
I. Baseline assessment	*CRF base line assessment form*	*Background and risk factor information including elements relevant for safety*
II. AEFI assessment	*CRF for prescheduled visits, AEFI report form, participant diary card,*	*Event specific information*
III. Follow-up	*Follow-up form*	*Event outcome monitoring*

Stage I: Baseline assessment

- State that the following standard set of data relevant for safety assessment should be collected at the base line assessment and append a data collection/report form such as Appendix B-I to this document
  - Demographics (i.e., name, date of birth, gender, ethnicity/race, weight (kg), height (cm), head circumference (cm); for infants include birth weight (g) and gestational age (weeks/days)).
  - Pre-vaccination signs or symptoms.
  - Underlying or concomitant disease(s).
  - Other significant medical history including treatment.
  - Previous exposure to the vaccine-specific infectious agent or the vector.
  - Any medication taken 3 months prior to and during the baseline assessment.
  - Relevant family history.
  - Any relevant local disease outbreaks.

Stage II: Case identification

Comment: While the case-based evaluation of a potential causal relation with the vaccine may be done, all AEFI should be recorded independently of their case-based causality assessment. When possible, negative information should be captured and differentiated from the absence of information.

- State that the following standard set of data relevant for safety assessment should be collected for every identified AEFI and append a data collection/report form such as Appendix B-II to this document
  - Source of information/reporter
  - Most recent immunization(s) prior to AEFI
  - AEFI(s)
    - Initial diagnosis
    - Date of diagnosis (DD/MM/YYYY)
    - Contact information for the physician who made the diagnosis
    - Contact of hospital and admission date if hospitalized
    - Date and time of first onset/first observation
    - Detailed history of present complaint including recent illness since baseline investigation
    - Concomitant diseases (e.g., new onset chronic illness)
    - Findings from physical examination
    - Findings from further investigations (e.g., laboratory, surgical, pathological findings)
    - Treatment(s) for the AEFI
    - History of recurrence
    - Seriousness of the AEFI

Stage III: Follow-up

- State that the following standard set of data relevant for safety assessment should be collected to document the outcome of each AEFI identified and append a data collection/report form such as Appendix B-III to this document
  - Final diagnosis
  - Date of final diagnosis (DD/MM/YYYY)
  - Participant’s condition compared to pre-vaccination health status
  - Seriousness of the AEFI
  - Vaccination after the start of the AEFI

– Outcome of AEFI

7.2.1. Types of events

Solicited AEFI: Specify any anticipated local and systemic events and parameters that will be assessed. Describe how safety assessments will be obtained and recorded (e.g., diary card, clinical visits).

Comment: Generally, local and systemic reactions (reactogenicity) to killed vaccines are expected within 48 hours and monitored for 7 days post vaccination. Reactions to live attenuated vaccines are expected to occur at the end of the incubation period (e.g., 8–12 days following immunization). They are typically monitored for up to 4 weeks following immunization. Adverse events of special interest may fall within these observation periods. However, longer observation and data collection periods may be specified depending on the assumed pathophysiology (e.g., autoimmune diseases should be monitored for during the entire trial period). Data collection of SAE in First in Human (FiH) studies should be at least 6 months following immunization.

The following information should be described in detail here:

- Time period and frequency of data collection

  Comment: Duration and frequency of data collection may vary depending on the vaccine, the event and the assumed pathogenesis of the adverse event.

- Method of data collection and assessment/measurement
- List of pre-specified local AEFI (e.g., erythema, swelling, etc.)
- List of pre-specified systemic AEFI (e.g., fever, anorexia, vomiting, etc.)
- List of pre-specified non-serious AEFI
- List of pre-specified Serious Adverse Event (SAE)

  Comment: The term “serious” is based on patient/event outcome or action criteria usually associated with events that pose a threat to a participant’s life or functioning. Seriousness serves as a guide for defining regulatory reporting obligations. This is to be clearly differentiated from the term “severe”, describing the intensity (e.g., local swelling <2 cm, >2 cm, >5 cm, whole limb swelling) of a specific event.

- Severity assessment

  Comment:

  For trials where AEFI were coded or graded by numerical scores of severity a complete description of this grading system, with definitions should be provided. [Example: Symptoms will be ranked as (1) mild, (2) moderate, or (3) severe]. Mild is an awareness of symptoms that are easily tolerated and do not interfere with usual daily activity. Moderate is

discomfort that interferes with or limits usual daily activity. Severe is disabling, inability to perform usual daily activity, resulting in absenteeism or required bed rest. Reports of moderate and severe reactions will be investigated and documented in the source record.

It is important that for each AEFI, that the investigator assesses the severity. In general, severity should not be graded by terms like “mild”, “moderate”, “severe”, unless these terms are well defined. Therefore, definitions should be based on objective, measurable criteria specific for the event. The severity of local AEFI is generally based on site, size, shape, surface, surround, and number of lesions. The severity of systemic events is generally based on the kind and number of organ systems affected, and the extent of measurable, event-specific, pathological parameters (e.g., body temperature, haemoglobin concentration).

- For formal toxicity grading scales of laboratory values for healthy adults and adolescents, we recommend to refer to the FDA Guidance for Industry (September 2007) Ref: http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074775.htm website accessed in September 2012.
- For grading of adverse event, we recommend to refer to the format of “Common Terminology Criteria for Adverse Events (CTCAE) and Common Toxicity Criteria (CTC)”: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40 website accessed in September 2012.

    An alternative or complementary approach to severity grading based on pathological values is intensity grading based on functional impact of the event on a participants life (e.g., no/minimal interference with daily activity, incapacitating).

    Unless standardized severity grades are available for a specific event, de novo creation of severity grading for the protocol may be guided by intensity grading. For example, the cut offs used for pathological parameters are based on the assumed level of impact on a participant’s life. For each level objective criteria and the increments of measurement should be determined prior to data collection.

Unsolicited AEFI

- The following should be specified in this section:
- Method of data collection and assessment/measurement
- Time period of data collection from the time of first immunization through a specified time period post immunization
- Guidance on intensity scale for severity assessment, if different from the solicited AEFI

- Likely clinical events that are pre-dosing/non-treatment emergent which can modify the actual safety profile

7.2.2. Outcome of events

- State that outcome at last observation of each AEFI should be clearly described (e.g., resolved to pre-immunization health status, spontaneous resolution, persistence of the event, resolved with sequelae, death, or description of any other outcome).

  Comment: In the case of death, post mortem findings should be specified, if available. See also Brighton Collaboration case definition for "Unexplained Sudden Death, including Sudden Infant Death Syndrome (SIDS), in the first and second years of life" [7].

7.2.3. Data collection instruments

- Describe the instrument to be used for routine data collection.

  For example: "trial participants will keep an observation record (diary card) to assess and record information concerning solicited local/systemic events for 14 days following immunization. The solicited local reaction assessment will involve assessment of the injection site. The solicited systemic reaction assessment will involve daily oral temperature readings (each trial participant will be supplied with a digital thermometer and instructed how to use it), and recording any systemic complaints such as headache, muscle aches, etc. on a diary card. An interim health history will be collected at each trial visit. Any medical office visits, emergency room visits or hospitalizations for any reason will be recorded throughout the trial design, implementation, and administration of other instruments, such as questionnaires, etc."

  Comment: For the design and implementation of the instruments it is important to avoid leading or biased questions. All information apart from participant diaries should be recorded by the investigator or a designated person in the respective form. Instructions on the proper way to administer instruments, questionnaires and report cards should be provided in the study procedures manual. For design and implementation of the instruments: it is also important to consider literacy of participants or their parent guardians. E.g. which mechanism can be used for recording on diary cards. Electronic Collection Instrument (ECI) or multiple-source document comprising traditional and electronic or other data capture devices may also be considered.

- State whether the instruments used for data collection constitute source data or not.

7.2.4. Documentation

- State that all AEFI occurring within (for example) four weeks following immunization should be recorded in the patient diary (if applicable), in the AEFI

report form filed in the participant dossier, and entered in an AEFI log book irrespective of severity and whether or not they are considered immunization-related.

- State all SAE occurring during the entire trial period starting from the time that each trial participant signs the Informed Consent Form and ending at the last follow-up visit, early termination visit or death, whichever comes first, should be recorded.
- State the time frame for completion and submission of the AEFI report and follow-up form after onset of AEFI is discussed in Section 7.4, and detailed in the study procedures manual.
- Define the time frame for entry into the AEFI log book after submission.

7.3. Management of participants with AEFI

- Specify procedure and timeline of validating AEFI including SAE: e.g., reviewed by local and Central Safety Physicians.
- Specify access to health care and necessary treatments offered for AEFI of interest including all SAE (refer to Section 5.2 in terms of the list of rescue treatments).
- State that compensation criteria and mechanisms are provided in a separate compensation guidance.
- Specify procedure and timeline of communication with the participants of safety-relevant information from this trial and other studies.

7.4. AEFI reporting

Comment: The investigator should

- accurately document the event
- follow-up to ensure completeness of the information related to the event
- respect notification deadlines
- provide the sponsor with all necessary information
- give access to source documents, if requested by the sponsor

Local and central contacts providing guidance on AEFI reporting and management (e.g., AEFI/SAE) hotline should be provided in the Investigators Manual.

7.4.1. Investigator reporting to sponsor

- Specify the investigator’s reporting requirements to the trial sponsors including the responsible individual reporters, the methods of reporting, minimal required information, time frame, data privacy regulations pertinent for sponsor reports and append the report form to the protocol.
- Specify AEFI not classified as SAE, but meeting requirements for expedite reporting within 72 h.

- Outline a specific plan and requirements for SAE reporting and state that SAE occurring throughout the trial should be reported to the sponsor by the investigator on a specific SAE report form as soon as he/she is alerted of it (e.g., within 24 h), even if the investigator considers that the AEFI is not related to trial vaccination.

  Comment: Emphasize that a preliminary notification should be made by phone or another immediate reporting method to the sponsor or agency responsible for reporting and contain the minimal required information:

  - Reporter information
  - Trial participant's number
  - Study vaccine and date of immunization
  - Description of the event (with onset or observation date of the event)
  - Severity
  - Investigator's causality assessment

- SAE in pregnant trial participants should be reported following the recommendations for SAE as well as Management of pregnancy (Section 6.5).
- Describe here that the preliminary notification should be followed by submission of full regular AEFI report form providing all details of the event (Appendix B-II).

7.4.2. Sponsor reporting to regulatory authorities

Comment: If the product under investigation is registered in different countries, the specific reporting requirements for each authority should be identified. The process of reporting, and the method of reporting by mail, courier, fax, or electronic data transfer may vary with different authorities and should be identified. For example, it is now mandatory to post all approved clinical trial protocols and data updates on the web for FDA (http://prsinfo.clinicaltrials.gov/fdaaa.html website accessed in September 2012).

- State that reporting should be in compliance with all appropriate authorities and regulations.
- State the method (fax, mail, email or other means) of reporting; the address, phone and fax numbers or to which the principal investigator or co-investigator or sponsor should send the adverse reports should be provided in the study procedures manual.
- If pharmacovigilance or safety matters are to be handled by a third party such as a contract research organization, the method (fax, mail, email or other means) of reporting, and the address, phone and fax numbers or of the contractor should be clearly mentioned in the study procedures manual.
- State that the study procedures manual should be referenced for the detailed timeframe for reporting and providing supporting documents.
- Specify reporting requirements for serious unsolicited AEFI especially in special groups such as pregnant participants.

Comment: Most regulatory authorities typically require expedited reporting of serious and unexpected events within 15 calendar days. Deaths and life-threatening events should be reported within 7 days. SAE in pregnant trial participants should be reported following the recommendations for SAE as well as Management of pregnancy (Section 6.5).

Supporting documentation may be requested and should be provided as soon as possible. SAE designated as “not related” to the trial product should be reported to the authority at least annually in a summary format or line listings. ICH provides important guidance for Development Safety Update Reports (DSUR) for periodic reporting on drugs under development: http://www.ema.europa.eu/docs/enGB/document_library/Scientific_guideline/2010/09/WC500097061.pdf website accessed in September 2012.

7.4.3. Sponsor reporting to IDMC

Comment: An IDMC may not be necessary for every clinical trial, depending on local infrastructure, clinical trial phase, and etc. This section is applicable only in case of established IDMC.

- State that the sponsor is responsible for informing the IDMC of the occurrence of any SAE observed in a trial participant.
- Briefly highlight here the planned reporting procedure. State that detailed description including required information, methods, and specific timeframe should be provided in IDMC charter in the study procedures manual.

7.4.4. Reporting of follow-up information

- Any relevant information concerning a SAE that becomes available after the initial SAE report form has been sent should be forwarded to the sponsor within 24 h.
- Describe the reporting procedure of follow-up information for AEFI including the time and duration.
- Emphasize that the anonymity of the trial participants shall be respected when forwarding this information.
- State that any post-trial event may also be reported by the investigator to the sponsor. Such a report should be regarded as a trial report and will require causality assessment by the investigator.

7.5. Specimen management and biobanking for future investigations

Comment: In case of an AEFI, collection and biobanking of samples for future investigation should be performed whenever, indicated or appropriately justified and possible.

- State that the general specimen management is described in Section 6.6

- Describe here how specific samples, if different from the management outlined in Section 6.6, will generally be processed, labelled, handled, shipped, stored and documented.

7.6. Assessment of causal relationship

Case based causality assessment

Comment:

Case based causality assessment should aim at a comprehensive evaluation of possible alternative causes of the AEFI in the trial participant.

- Highlight how case bases causal relationship between the investigational vaccine and AEFI will be assessed, including a brief description of responsible individuals or agencies, methods (e.g., specimen collection, causality assessment algorithm), and timelines.

  Comment:

  The investigator should review the AEFI information and offer an educated opinion about the likelihood of the AEFI being related to a given immunization. Careful medical judgement should be exercised to determine the level of causal relationship between an AEFI and the investigational product. An example for classification in assessing causal relationship is provided in Appendix C.

- For solicited AEFI considered to be routine reactogenicity captured in diaries (e.g., solicited injection site reactions within 7 days post-vaccination, fever within 7 days post-vaccination, etc.) specific causality assessments are not usually performed.

Population based assessment of association

- State that the strength of association will be investigated based on analysis of the entire dataset including all unsolicited AEFI and where applicable solicited AEFI (e.g., adverse events of special interest) independent from the investigator's causal assessment.
- State that the plan of interim and final analyses is described in Section 10.

7.7. Safety criteria for modifying protocol or halting trial

- Specify the criteria that are necessary for modifying, halting or discontinuing of the trial.

  Comment: This includes dose/schedule modification of individual participants and entire study group. Modification of the protocol for safety reasons should be considered if changes do not affect the internal or external validity of the trial but improve participant safety. This may include stopping an entire study group (e.g., in adaptive designs). Of note, "stopping rules" may be relatively detailed and restrictive, particularly in early trials in the absence of prior clinical experience with the vaccine. In

such cases, it is not unusual to have one or more pauses in the trial with an IDMC safety data review because of compliance with stopping rules.

- State that the procedure between the sponsor, the IDMC and the lead investigators, for modifying or discontinuing the trial should be outlined in Section 11.3 and detailed in Investigator's Manual.
- It should be determined, if the informed consent form and/or risk benefit has changed based on a protocol stop.
- State clearly who is ultimately responsible for decision making for modifying the protocol or halting the trial and procedures before and after these decisions are made.

  Comment: The IDMC is responsible for monitoring and/or identifying safety issues and they should recommend continuation, modification or stopping the trial. However, the responsibility ultimately lies with the sponsor. The sponsor should inform the regulatory authorities of any trial discontinuation and specify the reason and processes leading to discontinuation.
- Describe the communication strategy with trial stakeholders, investigators, and participants after modification of the protocol or trial.
- Provide applicable regulatory requirements and plans for communications between stakeholders when the trial is halted or suspended.

  Comment: The trial may be halted or discontinued if new safety data about the investigational product resulting from this or any other trials become available (as part of an interim analysis), and/or on advice of the sponsor, the investigators, the IEC/IRB, or IDMC. If the trial is prematurely terminated or suspended, the sponsor shall inform the investigators, the Regulatory Authorities and the IRB/IEC of the reason for termination or suspension (as specified by the applicable requirements and the protocol). The timing and format of information reporting depends on the phase of the trial. The suspension of a Phase 3 trial is generally reported immediately to all authorities. However, not every stop/restart in earlier development is automatically reviewed in "real time" by a regulatory agency. It depends on the "stopping rules" in the protocol as well as whether the event(s) qualify(ies) for expedited safety reporting.
- Specify potential unblinding procedures for the individual or all study codes to allow adequate safety evaluation (refer to Section 6.2).

7.8. Regulations and guidelines applicable to AEFI management

- State specific legislation or regulations followed. This may vary with each country where the clinical trial site is located.

Comment: An overview of major organizations providing research regulations is available fromhttp://www.nichd.nih.gov/health/clinicalresearch/regulations/ Website accessed in September 2012.

For a trial under ICH or US NIH guidance, the applicable regulations are provided in Appendix D.

8. Trial monitoring

8.1. Overall monitoring plan

- Specify roles and responsibilities for
  - overall safety monitoring (e.g., IDMC)
  - overall trial monitoring (e.g., sponsors, appropriate third party)
  - trial site monitoring
  - review of data collected during monitoring
  - ensuring the monitoring findings are addressed (e.g., protocol modification)

    Comment: The responsible persons/departments should be specified in the site specific information document.
- State that monitoring details should be specified in a separate monitoring manual.
- Briefly highlight how monitoring will be conducted.

  For example, it should include the duration and frequency of monitoring visits and the number of participant source documents to be reviewed at each site.

8.2. Independent Data Monitoring Committee (IDMC)

Comment: The IDMC (also referred to as the “Data and Safety Monitoring Board”, DSMB, or “Data and Safety Monitoring Committee”, DSMC) has a critical role in monitoring the safety aspects and other data of the trial.

- Specify the role and responsibilities of the IDMC in the trial and reference pertinent guidance documents.

  For example, FDA Guidance for Clinical Trial Sponsors, Establishment and Operation of Clinical Trial Data Monitoring Committees (March 2006): http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf EMA Guidance on Data Monitoring Committees: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003635.pdf (websites accessed in September 2012).
- The IDMC charter should be referenced for all details regarding the specific composition and tasks of the IDMC.

  Comment: The IDMC typically operates under a written charter (separate from the protocol) that includes well-defined standard operating

procedures. Ideally, the IDMC should include one or more individuals from the countries where the trial is to be conducted. They have specific local knowledge of the relevant health and safety aspects of the trial setting. The IDMC should be independent of the trial sponsor, investigators and their organizations, and persons or organizations with competing interests.

- State that data from the trial should be reviewed as frequently as deemed necessary by the IDMC.
- State that there should be no direct interaction between the IDMC and the investigators.
- State that the IDMC could request am adjudication committee for case ascertainment of specific AEFI.

9. Data management and data quality control

Comment: Separate data management documents may be referred to for details requested in this section.

Describe the data management plan and data quality control strategy, including:

- State that the study procedures manual should specify the responsible department/ partner and the place where the management will be performed.
- How data from regular data collection and monitoring will be integrated into the data management system (e.g., the standard data dictionary to be used).

  Comment: MedDRA dictionary is typically used for coding safety-relevant data. The only common exception is solicited routine reactogenicity events (e.g., injection site reactions, fever, malaise) captured on diaries for a fixed period of time in the early post-vaccination period.
- Plan on systematic prevention and detection of errors or omissions in data management.

  Comment: This includes

  – double data entry
  – logic or consistency checks at site, region, and trial level as well as for different data batches (e.g., laboratory data vs. clinical data)
  – data queries
  – data cleaning
  – data pooling
- Plan for completing missing information, verifying questionable information, and clarify conflicting information.

- Locking and saving the database after integration of all corrections in the complete set before releasing for statistical analysis.
- Plan on monitoring each step of the data-management process.

  For example, each step of this process will be monitored through the implementation of individual passwords and/or regular backups in order to maintain appropriate database access and to guarantee database integrity.

  Comment: if an electronic web-based data entry system is used, there should be consideration on planning offline backup data entry.

10. Statistical analysis

The following recommendations should be considered for the statistical analysis plan (SAP) of the protocol:

- Clearly indicate the definition of the population (e.g., intention to treat (ITT), per protocol (PP), all participants as treated (APAT)) used for safety analysis including sample size and power considerations.

  For example: The per protocol immunogenicity population includes all eligible participants, participants with no other major protocol violations, all participants who received study vaccines according to their assigned schedule, and who had at least 1 valid pair of pre- and post-vaccination assay results for the comparison of interest. The intent to treat population includes all participants who had 1 or more valid and determinate assay result. The safety population includes all subjects that received at least one dose of vaccine.
- Specify the primary and secondary statistical hypotheses to be tested (e.g., one-sided or two-sided, equivalence, superiority, non-inferiority, etc.).
- Determine the statistical criteria of success (e.g., within 10% of non-inferiority margin).
- Formulate the null and alternative hypotheses in terms of both the clinical and statistical aspect.
- State, how potential bias introduced by multiple comparison is controlled for.
- Outline sample size calculation and make power statements for each hypothesis, including sample size calculation by each end-point.
- Consider the impact of concomitant vaccinations on the safety analysis (especially when regionally variable).
- Specify the rules of data inclusion or exclusion for specified analyses for which data transformation (e.g., logarithmic, root square, etc.) are done.
- Give a description of the methodology that takes into account the data of non-completers.

- Describe the statistical methods used (and provide references for non classical methods).
- Specify any planned adjustments of baseline covariates.
- Specify any planned stratification analyses of safety data.

  For example: solicited local and systemic AEFI by dose; all unsolicited AEFI as well as SAE by dose.
- Analysis of safety data should be done according to Brighton Collaboration guidance for analysis and presentation specifying time periods and stratification of safety data for AEFI [8].
- Specify interim data analyses and time lines, supporting dose to dose progression or trial continuation.

  Comment: Interim analyses are more appropriate for safety analyses. Special consideration should be given to avoid unplanned interim data analyses which may jeopardize interpretation of data.
- State the intention to conduct a separate limited analysis of lost to follow-up cases and briefly outline the plan.
- Describe the timelines for the final analysis.

11. Quality assurance

Comment: Quality assurance of clinical trials involves systematic and independent examination of trial-related activities and documents to ensure the quality of the trial design, conduct, analysis and reporting according to protocol, SOP, and GCP. (ICH E6 1.46) Assessing quality is an activity that is external to the system and should be done by entities that are independent and do not have a stake or conflict of interest in the trial or its stakeholders.

11.1. Site monitoring

- Specify that at least an initiation visit and close-out visit will be done.

  Comment: Typically a follow-up visit will also be arranged between the initiation and close-out visits.
- State that the respective site SOP will have to be in accordance with the protocol.
- For the initiation visit, specify that
  - it will be performed before the inclusion of the first participant in the centre
  - the Monitor will verify and document that the material to be used during the trial has been received and that the investigational team has been properly informed about the trial, regulatory requirements, and all applicable SOPs.
- For the follow-up visit, specify that the monitors will carry out a document review of the trial progress and assess

- compliance with the protocol and SOPs, data collection, signature of consent forms, completion of document and appearance of SAE
- the monitor will discuss issues with the investigator and define actions to be taken
- unless site specific SOP's are issued, it is understood that SOPs may not be possible to implement fully in all resource limited sites. Respective GCP-conform documentation will constitute the basis for acceptance of 3rd country clinical trial data submitted in, e.g., EU marketing authorization.

  Comment: Please refer to EMA Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted in third countries and submitted in marketing authorization applications to the EMA. http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/06/WC500091530.pdf (websites accessed in September 2012).

- For the close-out visit, specify that
  - it will be performed at the end of the trial
  - the centre has all the documents necessary for archiving and submission to the IEC/IRB and other regulatory entity as appropriate
  - all samples have been shipped
  - all unused material has been recovered
  - all products have been returned to the sponsor or destroyed per sponsor instructions.
- State that an SOP should be developed and used at all clinical and laboratory sites. They will be utilized for document review by monitors.

  Comment: The SOPs and standardized quality control guideline for local site should be detailed in a separate monitoring plan that will be included in the Investigator's Manual.

- Specify that the details of the monitoring process will be specified in a separate Monitoring Manual.
- State that auditing report will be shared with all investigators and trial sites.

11.2. Trial/data auditing

Comment: Auditing clinical data focuses on whether the data leading to a trial report were collected and analyzed consistently, comprehensively and accurately and allows an assessment of the outcomes and inference of the conclusions of the clinical trial.

- State that regular independent auditing (e.g., data auditing/ monitoring) should be performed.

- Provide trial-related requirements on data auditing and a brief plan of auditing conduct including responsibilities, data to be audited, frequency, and timeframe.
- State that the auditing report will be shared with all investigators and trial sites

11.3. Procedure for protocol modification

- Outline briefly the procedure for protocol modification. It includes the process of involving and obtaining approval from all parties taking part in the trial.
- State that per the applicable regulations, any protocol modifications should be based on mutual agreement between the sponsor and the investigator.
- For safety criteria of modifying or halting the trial, refer to Section 7.7.
- State that the study procedures manual should describe the details of the procedure, including how protocol modifications will be fully communicated with all trial sites.

  Comments: Modification of the protocol should be kept to a minimum. Wherever modifications are undertaken they should comply with ICH-GCP. If agreement between the sponsors and investigator is reached concerning the need for an amendment, it will be produced in writing by the sponsor and/or the investigator and will be made a formal part of the protocol.

  Modifications need be reported to the IEC/RB and should become part of the dossier submitted to regulatory authorities. All amendments should be transmitted to Regulatory Authorities, if applicable. If the amendment is related to administrative changes to the protocol (e.g., administrative and logistical modifications of a protocol) but does not affect the trial participants' safety, the objectives of the trial or its progress, it does not require IRB/Ethics Committee approval. However, the IEC/IRB should be notified whenever an administrative change is made.

  The investigator is responsible for ensuring that changes to an approved trial during the period for which IEC/IRB approval has been given, are not initiated without IEC/IRB approval except to eliminate apparent immediate hazards to the trial participants.

12. Ethical considerations

- Justify the suitability of the trial site(s) in terms of disease endemicity and ability to perform the trial, and in terms of ability to safeguard the trial participants (e.g., health care provider infrastructure, standard of care, accessibility and payment of care).
- Discuss the potential risks (e.g., expected reactions, etc.) and specify how participants will be protected (e.g., treatment available) – in particular with regard to special populations such as pregnant women, children, and minorities.

- Explain the benefits of participating in the trial, e.g., screening laboratory assays and physical examination (potential benefit from immunization with the trial or control product).
- Specify the remuneration for trial participation, if applicable.
- State that the potential benefits of conducting the trial outweigh the potential risks of the trial and why.
- State that the results of trial auditing and data analysis will be shared with the participants in a lay description.
- Provide ethical statements addressing the ethical justification and scientific validity of the trial.

  Comment: Particular attention should be given to trials conducted in LMIC [9].
- State that the trial will be conducted in accordance with the latest versions of all pertinent guiding documents including GCP.
- Provide a list of the ethical guidance documents or regulation followed including the Declaration of Helsinki (http://www.wma.net/en/30publications/10policies/b3/), ICH Good Clinical Practice (http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002874.pdf), local regulatory requirements, and the four principles framework (http://www.ukcen.net/index.php/ethical_issues/ethical_frameworks/the_four_quadrant_approach). Websites accessed in September 2012.

  Comment: Investigators may also refer to the following considerations:http://www.iom.edu/~/media/Files/Activity%20Files/PublicHealth/ChildhoodImmunization/Nelson%20Presentation.pdf(websites accessed in September 2012).

12.1. Ethical review

Comment: Specific IEC/IRB requirements:

Submission to an IEC/IRB is required for approval of studies involving human trial participants. Specific submission requirements may vary with different countries. Declaration of Helsinki is widely incorporated or referenced in countries' regulations. International Ethical Guidelines for Biomedical Research Involving Human Trial participants CIOMS 2002 also provides guidance on ethical requirements. According to the guidelines, all research involving human trial participants should be conducted with four basic ethical principles, namely respect for persons, beneficence, non-malfeasance, and justice. Per the guidelines, the ethical review committee should be independent of the research team and free from financial or other material benefit.

- List all the requirements/procedures related to ethical review of the trial and their timeframes.

Comment: The protocol including any amendments and consent documents should be signed by the sponsor and investigator(s) or designee(s) of the protocol prior to the start of the trial. A contract (including financial agreement) between the clinical trial sites and the sponsor or designee should be signed prior to the start of the trial. For multi-centre trials, different legislation or regulations that pertain to different sites should be mentioned and ethical review should be obtained from all relevant local boards. Copies of these approvals should be forwarded by the investigator to the sponsor including the following information:

- Approval of ethical committees and specification of the names and locations of the committees
- Risks to trial participant
- Informed consent procedures
- Recruitment procedures
- Monitoring, audits and inspections

- Outline plan of relevant safety reporting to the IEC/IRB.

12.2. Informed consent

- The ICH-GCP Informed Consent Checklist should be used to ensure the Informed Consent Forms (ICF) meet these requirements (http://ichgcp.net/48-informed-consent-of-trial-subjects (websites accessed in September 2012)).
- Indicate all ICF that will be used for the trial, if different ICF are needed.

  Comment: the informed consent may be modified taking into consideration local culture of some trial sites.

- State here that the ICF should specify in lay and culturally appropriate language all expectations from the participant including duration of involvement, number of doses, and visits, procedures at each visit, safety documentation including patient diary, explanation on birth control-relevant expectations (if applicable), sampling and biobanking plan, potential risks, and relevant research scope.
- Reemphasize (in addition to the statement made in Section 6.3.2) that, informed consent should be fully understood and signed by the trial participant, or assent should be obtained as applicable.

  Comment: The trial participant or the trial participant's legal representative should give written informed consent before being included in the trial after having been informed of the nature of the trial, the potential risks, possible benefits, and their obligations. If the trial participant or the trial participant's legal representative is not able to read and sign the form (to be adapted for infants and children), the informed consent must be signed by an impartial witness who is independent from

the investigator and sponsor and is not specified on the list of trial contributors. By signing the consent form, the witness will attest that the information in the consent form and any other written information were accurately explained to the trial participant, or to his/her legally acceptable representative, and apparently understood. Informed Consent Forms will be provided in duplicate (the original will be kept by the investigator and a copy given to the trial participant).

- State that the study procedures manual should be referenced for the detailed approach and time frame of obtaining informed consent from all trial participants and plan for documentation.

12.3. Confidentiality

Detail the requirements and procedures for protecting participant confidentiality and include

- What protected health information (PHI) will be collected from participants in this trial?
- How will the PHI information be de-identified and protected?
- Who will use the PHI information? Explain why.
- Who will have access to the information? Explain why.
- What will be the situation and approach to disclose the information?
- What will the strategy be to manage disclosure of emergent information?

Example: Trial participant confidentiality will be strictly protected by the trial investigators, involved staff, the sponsor(s) and associates following the protocol. This pertains to all personal information relating to participants including clinical information and results of laboratory testing of biological samples. A unique trial participant ID number will be assigned to participant to be used through the trial. Identifiable information of trial participants will not be disclosed without prior written consent of the participant. However, in the case of safety and quality monitoring, the trial monitor or other authorized representatives of the sponsors may access all documents and records maintained by the investigator including these at the trial sites.

The trial protocol, records and documents, data, and all other information generated as part of the trial will also be strictly protected. Any trial-related information will not be disclosed to any unauthorized third party without prior written approval of the sponsor(s). All trial-related information will be stored securely at the trial site. All trial participant information will be stored in locked file cabinets in areas with access limited to trial staff. All laboratory specimens, reports, trial data collection, process and administrative forms will be identified by the coded number to maintain the confidentiality of the trial participants. All computer entry will be done using coded number only, and all local

databases will be secured with password-protected access systems. Forms, lists, log-books, appointment books and any other listings that may link trial participant ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access.

- Indicate that the research trial participant has the right to revoke his/her authorization for use of PHI and what the consequences would be in this event.
- Approaches to address special confidentiality-related requests from participants should also be mentioned.

12.4. Conflict of interest of investigator

- Outline the plan for declaration of conflict of interest of involved investigators, if applicable.

13. Publication policy

- Outline the main aspects for the authorship and publication policy by specifying the main roles and responsibilities.

  Comment: A full authorship and publication policy should be made available as part of the Investigator's Manual.

- Specify the main aspects of the data usage by third parties and with regards to sub-analyses and follow-up studies.

  Comment: A full data usage policy should be made available as part of the Investigator's Manual.

  Example:

  The first publication of report of the trial results shall be a comprehensive, joint publication or report by the sponsor, principal investigator, representatives of each trial centre, and associates coordinated by the sponsor. Thereafter, any subsequent publication or report related to the first publication or report should reference the original publication(s). After publication of the results of the trial, any participating centre may publish or otherwise use its own data provided that any publication of data from the trial gives recognition to the trial group and the sponsor and its associates and provided that the sponsor is entitled to refuse the association. The authors of the publication(s) are those who have contributed to the protocol development and/or to the analysis of the data. According to the main topic of the publication, the first author will be the investigator who contributes most.

  The sponsor should have the opportunity to review all proposed abstracts, manuscripts or presentations (collectively a Publication) regarding this trial at least 30 days or, for abstracts, at least five (5) working days prior to submission for publication/presentation. Review by the sponsor can be expedited to meet publication guidelines. Publications shall not include the

sponsor's confidential information or personal data on any trial participant, such as name or initials.

At the sponsor's request, the submission or other disclosure of a proposed Publication will be delayed a sufficient amount of time to allow the sponsor to seek patent or similar protection of any inventions, know-how or other intellectual or industrial property rights disclosed in the proposed Publication.

- Specify that publications of the trial's safety aspects will adhere to the extension of the CONSORT statement on Better Reporting of Harms in Randomized Trials: http://www.annals.org/content/141/10/781.full (websites accessed in September 2012).
- State that the IDMC should also review manuscript prior to publication to accept or reject the conclusions.

14. Financing and insurance

Comment: Separate documents on financing and insurance may be referred to for details requested in this section.

Funding overview

- Briefly describe how the trial will be funded.

14.1. Compensation to trial participants

- Describe how the trial participants will be compensated, if applicable.

  For example: Trial participants may be compensated directly or inkind for their time, effort and for costs to cover their travel expenses to the centre. Compensation will be made after the completion of each study visit. Trial participants will be compensated $ xx per visit during their participation in the trial, an amount to be agreed as locally appropriate with the local IEC/IRB. Site-specific compensation amounts will be documented in the site-specific Informed Consent Form approved by the Ethics Committee. Where multiple IEC/IRB are involved, the locally constituted IEC/IRB shall take precedence in issues related to compensation decisions.

14.2. Insurance for trial participants

- State insurance plan ensuring treatment of AEFI of the trial-related vaccination(s).

  For example: The sponsor and institution are responsible for having appropriate liability insurance. For research-related injuries and/or medical problems determined to result from receiving the Investigational Product, treatment including necessary emergency treatment and proper follow-up care which is not covered by the trial participant's medical or hospital insurance will be made available to the trial participant free of charge at

the expense of the sponsor, provided that the injury is not due to a negligent or wrongful act or omission by the trial doctor or his/her staff.

Comment: particular consideration should be given for trials with limitations on insurance or indemnification.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors are grateful for the support and helpful comments provided by the members of the INYVAX Steering Committee (Andreas Holtel, Jelle Thole, Martin Friede, Odile Leroy, Paul- Henri Lambert, Ulrich Heininger), and the Brighton Collaboration Science Board who are not a member of this working group (Jim Buttery, Paul T. Heath, Hector Izurieta, Najwa Khuri-Bulos, Miriam Sturkenboom, Heidi Larson). The authors also thank for review and comments made by the participants in the Reference Group (Christine Juergens, Brenda Mclaren, Claudia Schmidt, Maria Vazquez-Gragg, Ping Yuan, Arani Chatterjee, Sunil Shewale, Hanna Nohynek, Le Van Phung, Wan-Ting Huang, Hindra Irawan Satari, Bart Jacobs, Joan Puig-Barberà, James Southern, Anand Kawade, Reinaldo De Menezes Martins, Elisabeth Adderson, Tamar Lasky, Dana Orten, Birgit Thierry-Carstensen, Fernanda Tavares, Sanela Gajic, Elizabeth Williams, Thomas Verstraeten, Igor Smolenov, Amina Tebaa, Simbarashe Takuva, Joanie Johnson, Ahmed-Amr Abbassy, Chandrakant Lahariya, Thaddeus Zajdowicz, Hanne Nokleby, Eliane Santos, Frederick Varricchio, Elisabeth Loupi, benedicte Levron, Daniel Ankrah, Rosalind Rowland, Merita Kucuku, Shy Shorer, Eugena Tomini, Mark Makurath, Adwoa Bentsi-Enchill, Edwin David McIntosh, Yolanda Guerra Mendoza, Markku Partinen, Immanuel Barth, Christopher Wohlberg, Stephen Evans, Vasee Moorthy, Luc Hessel, Jelle Thole). We wish to also express our gratitude for the continuous administrative support and document coordination by Sabine Faisst, Brighton Collaboration Secretariat.

The INYVAX project is funded by the European Commission under the Framework programme 7, project number 223532. This document does not necessarily reflect the opinion of the European Commission.

Abbreviations

AEFI	Adverse Event Following Immunization
CIOMS	Council for International Organizations of Medical Sciences
CRF	Case Report Form
CSP	Central Safety Physician
DSMB	Data and Safety Monitoring Board
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDMC	The Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LMIC	Low and Middle Income Country
LSM	Local Safety Monitor

NIH	United States National Institutes of Health
SAE	Serious Adverse Event
SOP	Standard Operation Procedure
WHO	World Health Organization

References

1. Moorthy VS, Reed Z, Smith PG. MALVAC 2008: measures of efficacy of malaria vaccines in phase 2b and phase 3 trials – scientific, regulatory and public health perspectives. Vaccine. 2009 Jan; 27(5):624–8. [PubMed: 19061928]
2. Moorthy V, Reed Z, Smith PG. Measurement of malaria vaccine efficacy in phase III trials: report of a WHO consultation. Vaccine. 2007 Jul; 25(28):5115–23. [PubMed: 17577487]
3. Hanekom WA, Dockrell HM, Ottenhoff TH, Doherty TM, Fletcher H, McShane H, et al. Immunological outcomes of new tuberculosis vaccine trials: WHO panel recommendations. PLoS Med. 2008 Jul.5(7):e145. [PubMed: 18597551]
4. Kohl KS, Gidudu J, Bonhoeffer J, Braun MM, Buettcher M, Chen RT, et al. The development of standardized case definitions and guidelines for adverse events following immunization. Vaccine. 2007 Aug. 31(25):5671–4. [PubMed: 17400339]
5. Stober M. Multinational clinical trials: breaking language and cultural barriers. Applied Clinical Trials. 2003; (September):24–30.
6. FDA. Guidance for industry: clinical data needed to support the licensure of seasonal inactivated influenza vaccines. 2007 May.
7. Jorch G, Tapiainen T, Bonhoeffer J, Fischer TK, Heininger U, Hoet B, et al. Unexplained sudden death, including sudden infant death syndrome (SIDS), in the first and second years of life: case definition and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2007; 25(31):5707–16. [PubMed: 17408816]
8. Bonhoeffer J, Bentsi-Enchill A, Chen RT, Fisher MC, Gold MS, Hartman K, et al. Guidelines for collection, analysis and presentation of vaccine safety data in pre- and post-licensure clinical studies. Vaccine. 2009 Apr; 27(16):2282–8. [PubMed: 19056451]
9. Marshall W, Patricia S. Ethical challenges in trial design and informed consent for health research in resource-poor settings. Special Topics. 2011; (5)
10. Bines JE, Kohl KS, Forster J, Zanardi LR, Davis RL, Hansen J, et al. Acute intussusception in infants and children as an adverse event following immunization: case definition and guidelines of data collection, analysis, and presentation. Vaccine. 2004 Jan; 22(5–6):569–74. [PubMed: 14741146]
11. Ruggeberg JU, Gold MS, Bayas JM, Blum MD, Bonhoeffer J, Friedlander S, et al. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2007 Aug; 25(31):5675–84. [PubMed: 17448577]
12. Tapiainen T, Prevots R, Izurieta HS, Abramson J, Bilynsky R, Bonhoeffer J, et al. Aseptic meningitis: case definition and guidelines for collection, analysis and presentation of immunization safety data. Vaccine. 2007 Aug; 25(31):5793–802. [PubMed: 17574313]
13. Gidudu J, Sack DA, Pina M, Hudson MJ, Kohl KS, Bishop P, et al. Diarrhea: case definition and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2011 Jan; 29(5):1053–71. [PubMed: 21130754]
14. Sejvar JJ, Kohl KS, Bilynsky R, Blumberg D, Cvetkovich T, Galama J, et al. Encephalitis, myelitis, and acute disseminated encephalomyelitis (ADEM): case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2007 Aug; 25(31): 5771–92. [PubMed: 17570566]

15. Jones JF, Kohl KS, Ahmadipour N, Bleijenberg G, Buchwald D, Evengard B, et al. Fatigue: case definition and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2007 Aug; 25(31):5685–96. [PubMed: 17400340]
16. Michael Marcy S, Kohl KS, Dagan R, Nalin D, Blum M, Jones MC, et al. Fever as an adverse event following immunization: case definition and guidelines of data collection, analysis, and presentation. Vaccine. 2004 Jan; 22(5–6):551–6. [PubMed: 14741143]
17. Bonhoeffer J, Menkes J, Gold MS, de Souza-Brito G, Fisher MC, Halsey N, et al. Generalized convulsive seizure as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation. Vaccine. 2004 Jan; 22(5–6):557–62. [PubMed: 14741144]
18. Sejvar JJ, Kohl KS, Gidudu J, Amato A, Bakshi N, Baxter R, et al. Guillain-Barre syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2011 Jan; 29(3):599–612. [PubMed: 20600491]
19. Buettcher M, Heininger U, Braun M, Bonhoeffer J, Halperin S, Heijbel H, et al. Hypotonic-hyporesponsive episode (HHE) as an adverse event following immunization in early childhood: case definition and guidelines for data collection, analysis, and presentation. Vaccine. 2007 Aug; 25(31):5875–81. [PubMed: 17537554]
20. Bonhoeffer J, Vermeer P, Halperin S, Kempe A, Music S, Shindman J, et al. Persistent crying in infants and children as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation. Vaccine. 2004 Jan; 22(5–6):586–91. [PubMed: 14741148]
21. Beigel J, Kohl KS, Khuri-Bulos N, Bravo L, Nell P, Marcy SM, et al. Rash including mucosal involvement: case definition and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2007 Aug; 25(31):5697–706. [PubMed: 17403561]
22. Wise RP, Bonhoeffer J, Beeler J, Donato H, Downie P, Matthews D, et al. Thrombocytopenia: case definition and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2007 Aug; 25(31):5717–24. [PubMed: 17493712]
23. Kohl KS, Ball L, Gidudu J, Hammer SJ, Halperin S, Heath P, et al. Abscess at injection site: case definition and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2007 Aug; 25(31):5821–38. [PubMed: 17540485]
24. Halperin S, Kohl KS, Gidudu J, Ball L, Hammer SJ, Heath P, et al. Cellulitis at injection site: case definition and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2007 Aug; 25(31):5803–20. [PubMed: 17548135]
25. Kohl KS, Walop W, Gidudu J, Ball L, Halperin S, Hammer SJ, et al. Induration at or near injection site: case definition and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2007 Aug; 25(31):5839–57. [PubMed: 17553602]
26. Gidudu J, Kohl KS, Halperin S, Hammer SJ, Heath PT, Hennig R, et al. A local reaction at or near injection site: case definition and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2008 Dec; 26(52):6800–13. [PubMed: 18950670]
27. Rothstein E, Kohl KS, Ball L, Halperin SA, Halsey N, Hammer SJ, et al. Nodule at injection site as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation. Vaccine. 2004 Jan; 22(5–6):575–85. [PubMed: 14741147]
28. Kohl KS, Walop W, Gidudu J, Ball L, Halperin S, Hammer SJ, et al. Swelling at or near injection site: case definition and guidelines for collection, analysis and presentation of immunization safety data. Vaccine. 2007 Aug; 25(31):5858–74. [PubMed: 17548132]
29. Beigel J, Kohl KS, Brinley F, Graham PL, Khuri-Bulos N, LaRussa PS, et al. Generalized vaccinia as an adverse event following exposure to vaccinia virus: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2007 Aug; 25(31): 5745–53. [PubMed: 17537552]
30. Wenger P, Oleske JM, Kohl KS, Fisher MC, Brien JH, Graham PL, et al. Inadvertent inoculation as an adverse event following exposure to vaccinia virus: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2007 Aug; 25(31): 5754–62. [PubMed: 17537553]

31. Graham PL, LaRussa PS, Kohl KS. Robust take following exposure to vaccinia virus: case definition and guidelines of data collection, analysis, and presentation of immunization safety data. Vaccine. 2007 Aug; 25(31):5763–70. [PubMed: 17537551]

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2013.02.041.