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

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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 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.

☆ *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 Institute of Health (NIH) and Centers of Disease Control and Prevention (CDC).

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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 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.

Low and Middle Income Countries (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

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.

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