Guidelines on Clinical Evaluation of Vaccines: Regulatory Expectations

Proposed revision of WHO TRS 924, Annex 1

NOTE:

This document has been prepared for the purpose of inviting comments and suggestions on the proposals contained therein, which will then be considered by the Expert Committee on Biological Standardization (ECBS). Publication of this early draft is to provide information about the proposed *Guidelines on Clinical Evaluation of Vaccines: Regulatory Expectations*, to a broad audience and to improve transparency of the consultation process.

The text in its present form does not necessarily represent an agreed formulation of the Expert Committee. **Written comments proposing modifications to this text MUST be received by 15th March 2016 in the Comment Form available separately** and should be addressed to the World Health Organization, 1211 Geneva 27, Switzerland, attention: Department of Essential Medicines and Health Products (EMP). Comments may also be submitted electronically to the Responsible Officer: **Dr Ivana Knezevic** at email: **knezevici@who.int.**

The outcome of the deliberations of the Expert Committee on Biological Standardization will be published in the WHO Technical Report Series. The final agreed formulation of the document will be edited to be in conformity with the "WHO style guide" (WHO/IMD/PUB/04.1).

Recommendations and guidelines published by WHO are intended to be scientific and advisory in nature. Each of the following sections constitutes guidance for national regulatory authorities (NRAs) and for manufacturers of biological products. If an NRA so desires, these Guidelines may be adopted as definitive national requirements, or modifications may be justified and made by the NRA. It is recommended that modifications to these Guidelines be made only on condition that modifications ensure that the vaccine is at least as safe and efficacious as that prepared in accordance with the recommendations set out below. The parts of each section printed in small type are comments or examples for additional guidance intended for manufacturers and NRAs, which may benefit from those details.

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159   **1.   Introduction**

160

161   This guideline is intended to replace *WHO Technical Report, Series No. 924, Annex 1 Guidelines*

162   *on clinical evaluation of vaccines: Regulatory Expectations*, which was adopted by the Expert

163   Committee on Biological Standardization (ECBS) in 2001 (1). This document of 2001 has

164   served as a basis for setting or updating national requirements for the evaluation and licensing of

165   a broad range of vaccines as well as for WHO vaccine prequalification.

166

167   Following on the establishment of the document of 2001, more than 20 vaccine-specific

168   documents that include a section on clinical evaluation have been adopted by the ECBS, all of

169   which are intended to be read in conjunction with TRS 924, Annex 1 (2). These include

170   documents that address polio vaccines [OPV, IPV], whole cell pertussis and acellular pertussis

171   vaccines, meningococcal conjugate vaccines for serotypes A and C, pneumococcal conjugate

172   vaccines and vaccines intended to prevent diseases due to rotaviruses, dengue viruses, human

173   papillomaviruses and malaria parasites.

174

175   This guideline has been prepared to reflect the scientific and regulatory experience that has been

176   gained from vaccine clinical development programs since the adoption of the above mentioned

177   version in 2001. Many challenging issues surrounding appropriate and feasible vaccine clinical

178   development programs for specific types of vaccines have arisen in the intervening period. For

179   example, there has been increasing recognition of the potential need to base initial licensure of

180   certain vaccines on safety and immunogenicity data only (i.e. it is not feasible to generate pre-

181   licensure efficacy data) and in the absence of an established immunological correlate of

182   protection (ICP).

183

184   This guideline is intended for use by national regulatory authorities (NRAs), companies

185   developing and holding licences for vaccines, clinical researchers and investigators. It considers

186   the variable content of clinical development programs, clinical trial designs, the interpretation of

187   trial results and post-licensing activities. The content of the various sections is intended to assist

188   in the preparation and approval of clinical trial applications, applications for initial licensure and

189   applications to support post-licensure changes as well as to provide guidance on post-licensure

190   activities, such as pharmacovigilance and estimation of vaccine effectiveness.

191

192   The main changes (modification or expansion of previous text and additional issues covered) in

193   this revision compared to the above mentioned version of TRS No. 924, Annex 1, 2001 (1)

194   include, but are not limited to, the following:

195

196   *Immunogenicity*

197   • General principles for comparative immunogenicity studies, including selection of the

198   comparators, endpoints and acceptance criteria for concluding non-inferiority or

199   superiority of immune responses

200   • Situations in which age de-escalation studies may be inappropriate

201   • Assessing the need for and timing of post-primary doses

202   • Using different vaccines for priming and boosting

203   • Assessing the ability of vaccines to elicit immune memory or to cause hypo-

204   responsiveness

205   • Using immunogenicity data to predict vaccine efficacy, with or without bridging to

206   efficacy data

207   • The derivation and uses of immunological ICPs

208   • Vaccination of pregnant women to protect them and/or their infants

209

210   *Efficacy*

211   • Role and potential value of human challenge studies

212   • Need for and feasibility of conducting vaccine efficacy studies

213   • Selection of appropriate control groups in different circumstances

214   • Comparing extended with parent versions of vaccines

215   • Predicting vaccine efficacy when there is no ICP and vaccine efficacy studies are not

216   feasible

217   • Preliminary and confirmatory vaccine efficacy studies and their design

218   • Vaccines with modest efficacy and/or that provide a short duration of protection

219 • Extrapolating data between geographic/genetically diverse populations

220 • Role of sponsors and public health authorities in generating vaccine effectiveness data

221

222 *Safety*

223 • Detailed consideration of the collection and analysis of safety data from clinical trials

224 • Consideration of size of the pre-licensure database by type of vaccine and its novelty

225 • Consideration of the safety database by population sub-group

226 • Special safety considerations by vaccine construct

227 • Circumstances of limited safety data pre-licensure

228 • Use of vaccine registries and disease registries

229 • Particular issues for vaccine pharmacovigilance activities

230

231 Due to the fact that a separate document on nonclinical evaluation of vaccines was established

232 in 2003 (3), the section on that topic in the 2001 version has been removed. Furthermore, the

233 structure of the document has changed. In particular, a number of methodological

234 considerations have now been incorporated into relevant sections and subsections rather than

235 being described in a separate section. In line with the changes made in the document, the

236 Glossary and References have been updated.

237

238 The WHO has also made available several other guidelines of relevance to clinical development

239 programs for vaccines. These should be consulted as appropriate and include:

240 • Good clinical practice for trials on pharmaceutical products (4)

241 • Good manufacturing practice for pharmaceutical preparations (5)

242 • Good manufacturing practice for biological products (6)

243 • Guidelines on nonclinical evaluation of vaccines (3)

244 • Guidelines on nonclinical evaluation of vaccine adjuvants and adjuvanted vaccines (7)

245 • Guidelines on procedures and data requirements for changes to approved vaccines (8)

246 • Guidelines for independent lot release of vaccines by regulatory authorities (9)

247 • Recommendations for the evaluation of animal cell cultures as substrates for the

248 manufacture of biological medicinal products and for the characterization of cell banks (10)

249   • Clinical Considerations for Evaluation of Vaccines for Prequalification (11)

250   • The WHO manual *Immunization in practice* (12)

251   • WHO expert consultation on the use of placebos in vaccine trials (13)

252

253   Furthermore, guidance on various aspects of pre-licensure clinical development programs for

254   vaccines and post-licensure assessment is also available from several other bodies, such as the

255   International Conference on Harmonization (ICH), the European Medicines Agency (EMA), the

256   United States Food and Drug Administration (FDA) and the United Kingdom Medical Research

257   Council (MRC). These WHO guidelines are not intended to conflict with, but rather to

258   complement, these other documents.

259

260   **2.   Scope**

261

262   This guideline considers clinical development programmes for vaccines that are intended to

263   prevent infectious diseases in humans by eliciting protective immune responses that are

264   sufficient to prevent clinically apparent infections. It includes vaccines that may be given before

265   exposure or shortly after known or presumed exposure to an infectious agent to prevent onset of

266   clinical disease. Protective immune responses may be directed against one or more specific

267   antigenic components of micro-organisms or against substances produced and secreted by them

268   (e.g. toxins) that are responsible for clinical disease.

269

270   The guideline is applicable to vaccines which contain one of more of the following:

271   • Microorganisms that have been inactivated by chemical and/or physical means

272   • Live microorganisms that have been rendered avirulent in humans as a result of attenuation

273   processes or specific genetic modification

274   • Antigenic substances that have been derived from micro-organisms. These may be purified

275   from micro-organisms and used in their natural state or may be modified (e.g. detoxified by

276   chemical or physical means, aggregated or polymerized).

277   • Antigens that have been manufactured by synthetic processes or produced by live organisms

278   using recombinant DNA technology.

279   • Antigens (however manufactured) that have been chemically conjugated to a carrier
280   molecule to modify the interaction of the antigen with the host immune system.
281   • Antigens that are expressed by another micro-organism which itself does not cause clinical
282   disease but acts as a live vector (e.g. live viral vectored vaccines, live attenuated chimeric
283   vaccines).
284   In addition, although naked DNA vaccines are not specifically discussed in this guideline the
285   principles and development programs outlined are broadly applicable.
286
287   This guideline does not apply to:
288   • Therapeutic vaccines (i.e. used for treatment of disease)
289   • Vaccines intended for any purpose other than prevention of infectious diseases and the
290   consequences of infectious diseases.
291
292   **3.   Glossary**
293
294   The definitions given below apply to the terms used in this guideline. They may have different
295   meanings in other contexts.
296
297   *Adverse event (AE)*
298   Any untoward medical occurrence in a trial subject. An AE does not necessarily have a causal
299   relationship with the vaccine.
300
301   *Adverse event following immunization (AEFI)*
302   Any untoward medical occurrence that follows immunization using a licensed vaccine outside of
303   a clinical trial setting. An AEFI does not necessarily have a causal relationship with the use of
304   the vaccine. The AEFI may be any unfavourable or unintended sign, abnormal laboratory
305   finding, symptom or disease.
306
307   *Attack rate*
308   The proportion of the population exposed to an infectious agent who become (clinically) ill.
309

310 *Blinding*

311 A procedure in which one or more parties involved in a clinical trial are kept unaware of the

312 treatment assignment(s). Double blinding refers to the vaccinees/care-givers, investigator(s) and

313 sponsor staff being unaware of the treatment assignment during the conduct of the trial and at

314 least until after completion of the primary analysis.

315

316 *Booster dose*

317 A dose that is given at a certain time interval after completion of the primary series that is

318 intended to boost immunity to, and therefore prolong protection against, the disease that is to be

319 prevented.

320

321 *Case ascertainment*

322 The method adopted in a trial of vaccine efficacy for detecting cases of the infectious disease

323 intended to be prevented by vaccination.

324

325 *Case definition*

326 The pre-defined clinical and laboratory criteria that must be fulfilled to confirm a case of a

327 clinically manifest infectious disease in a study of vaccine efficacy or effectiveness.

328

329 *Clinical trial application*

330 An application submitted to a NRA by a sponsor for the purposes of gaining authorization to

331 conduct a clinical trial of an investigational or licensed vaccine at a trial site within the NRA's

332 jurisdiction. The contents and format of the application will vary as required by the relevant

333 NRA(s).

334

335 *Cluster randomization*

336 Randomization of subjects into a clinical trial by group (e.g. by households or communities) as

337 opposed to randomization of the individual subject.

338

339 *Geometric mean concentration*

340 The average antibody concentration for a group of subjects calculated by multiplying all values

341   and taking the *n*th root of this number, where *n* is the number of subjects.

342

343   *Geometric mean titre*

344   The average antibody titre for a group of subjects calculated by multiplying all values and taking

345   the *n*th root of this number, where *n* is the number of subjects.

346

347   *Good clinical practice (GCP)*

348   GCP is a process that incorporates established ethical and scientific quality standards for the

349   design, conduct, recording and reporting of clinical research involving the participation of

350   human subjects. Compliance with GCP provides public assurance that the rights, safety, and

351   well-being of research subjects are protected and respected, consistent with the principles

352   enunciated in the Declaration of Helsinki and other internationally recognized ethical guidelines,

353   and ensures the integrity of clinical research data.

354

355   *Good manufacturing practice (GMP)*

356   GMP is the aspect of quality assurance that ensures that medicinal products are consistently

357   produced and controlled to the quality standards appropriate to their intended use and as required

358   by the product specification.

359

360   *Immunological correlate of protection (ICP)*

361   An Immunological Correlate of Protection (ICP) is most commonly defined as a type and

362   amount of immunological response that correlates with vaccine-induced protection against a

363   clinically apparent infectious disease and is considered predictive of clinical efficacy. For

364   some types of vaccines the ICP may be the type and amount of immunological response that

365   correlates with vaccine-induced protection against infection (e.g. hepatitis A and B vaccines).

366   The ICP may be mechanistic (i.e. causative for protection, such as antibody that effects virus

367   neutralization or serum bactericidal antibody) or it may be non-mechanistic (i.e. non-causative,

368   an immune response that is present in those protected by vaccination, but not the cause of

369   protection (such as serum IgG against VZV in the context of prevention of herpes zoster).

370

371   *Immune memory*

372 An immunological phenomenon in which the primary contact between the host immune system

373 and an antigen results in a T-cell-dependent immune response, often referred to as priming of the

374 immune system. Effective priming results in development of memory B-cells and an anamnestic

375 immune response to post-primary doses, which are commonly referred to as booster doses.

376

377 *Immunogenicity*

378 The capacity of a vaccine to elicit a measurable immune response.

379

380 *Non-inferiority trial*

381 In the context of vaccine clinical development programs, non-inferiority trials may have the

382 primary objective of showing that the immune response(s) to one or more specific antigenic

383 components in a candidate vaccine are not inferior to immune responses to corresponding

384 antigenic components in a licensed vaccine. Alternatively, the primary objective may be to

385 demonstrate that a candidate vaccine has non-inferior efficacy to a licensed vaccine.

386

387 *Pharmacovigilance*

388 A practice of detecting, assessing, understanding, responding to and preventing adverse drug

389 reactions, including reactions to vaccines, in the post-licensure period.

390

391 *Posology*

392 The vaccine posology for a specific route of administration and target population includes:

393 • The dose content and volume delivered per dose

394 • The dose regimen (i.e. the number of doses to be given in the primary series and, if

395 applicable, after the primary series)

396 • Dose schedule (i.e. the dose intervals to be adhered to within the primary series and between

397 the primary series and any further doses)

398

399 *Post-licensure safety surveillance*

400 A system for monitoring AEFIs in the post-licensure period.

401

402 *Post-primary doses*

403   Additional doses of vaccine given after some time interval following the primary series of

404   vaccination, which may or may not boost the immune response.

405

406   *Primary vaccination*

407   First vaccination or series of vaccinations intended to establish clinical protection.

408

409   *Protocol*

410   A document that states the background, rationale and objectives of the clinical trial and describes

411   its designs, methodology and organization, including statistical considerations and the conditions

412   under which it is to be performed and managed. The protocol should be signed and dated by the

413   investigator, the institution involved and the sponsor.

414

415   *Randomization*

416   In its simplest form, randomization is a process by which n individuals are assigned to a test (n_T)

417   or control (n_C) treatment so that all possible groups of size $n = n_T + n_C$ have equal probability of

418   occurring. Thus, randomization avoids systematic bias in the assignment of treatment.

419

420   *Responder*

421   A vaccinee who develops an immune response (humoral or cellular) that meets or exceeds a pre-

422   defined threshold value using a specific assay. This term is most often used when there is no ICP

423   and when the clinical relevance of achieving or exceeding the pre-defined response is unknown.

424

425   *Responder rate*

426   The responder rate is the percentage of vaccinees achieving or exceeding the pre-defined level of

427   response.

428

429   *Serious adverse event (SAE) or serious AEFI (SAEFI)*

430   An adverse event is serious when it results in death, admission to hospital, prolongation of a

431   hospital stay, persistent or significant disability or incapacity, is otherwise life-threatening or

432   results in a congenital abnormality/birth defect. SAEs are such events that occur during clinical

433   trials. SAEFIs are such events that occur during post-licensure safety surveillance.

434

435 *Seroconversion*

436 A predefined increase in antibody concentration or titre. In subjects with no measurable antibody

437 prior to vaccination seroconversion is usually defined as achieving a measurable antibody level

438 post-vaccination. In subjects with measurable antibody prior to vaccination seroconversion is

439 commonly defined by a pre-defined fold-increase from pre- to post-vaccination. The definitions

440 may be adjusted depending on whether the lower limit of detection of the assay is or is not the

441 same as the lower limit of quantification.

442

443 *Sponsor*

444 The individual, company, institution or organization that takes responsibility for the initiation,

445 management and conduct of a clinical trial. The entity acting as a sponsor for a clinical trial is

446 usually the same as that which applies for clinical trial approval. The sponsor of a clinical trial

447 may not be the entity that applies for a license to place the same product on the market and/or the

448 entity that holds the license (i.e. is responsible for post-licensing safety reporting) in any one

449 jurisdiction.

450

451 *Superiority trial*

452 A trial with the primary objective of demonstrating that the immune response to one or more

453 antigenic components in a group that receives a candidate vaccine is superior to the

454 corresponding immune response in a control group.

455

456 *Vaccine efficacy*

457 An estimate of the reduction in the chance or odds of developing clinical disease after

458 vaccination relative to the chance or odds when not vaccinated against the disease to be

459 prevented. Vaccine efficacy measures direct protection (i.e. protection induced by vaccination in

460 the vaccinated population sample).

461

462 *Vaccine effectiveness*

463 An estimate of the protection conferred by vaccination in a specified population that measures

464 both direct and indirect protection (i.e. the estimate may reflect in part protection of non-

465   vaccinated persons secondary to the effect of the vaccine in the vaccinated population).

466

467   *Vaccine vector*

468   A vaccine vector is a genetically engineered micro-organism (which may be replication

469   competent or incompetent) that expresses one or more foreign antigen(s) (i.e. antigens derived

470   from a different micro-organism).

471

472

473   **4.   Vaccine Clinical Development Programs**

474

475   This Section considers:

476   ➤   Important considerations for clinical programs, including:

477   -   Consultations with regulatory authorities

478   -   Use of independent data review committees

479   -   Registering and reporting clinical trials

480   ➤   Typical clinical development programs for new candidate vaccines, including:

481   -   Main objectives of the clinical development program

482   -   Factors that determine the extent and content of the program

483   -   Stages of typical development programs

484   -   Programs that do and do not include vaccine efficacy trials

485   -   Alternatives for estimation of vaccine efficacy

486   ➤   Clinical evaluation trials after initial licensure

487

488   **4.1   General considerations**

489

490   For a new candidate vaccine the main objective of the clinical development program is to

491   accumulate adequate data to support initial licensure and appropriate use, as described in

492   Subsection 4.2. The essential elements of the program are:

493   •   To describe the interaction between the vaccine and the host immune response (Section 5)

494   •   To identify safe and effective dose regimens and schedules (Sections 5 and 6)

495   •   To provide estimates of vaccine efficacy by directly measuring efficacy or inferring efficacy

496   based on immune responses (Sections 5 and 6)

497   • To describe the safety profile (Section 7)

498   • To assess co-administration with other vaccines if this will be essential for use (Section 5)

499

500   After initial licensure, as described in Subsection 4.3:

501   • It is essential to monitor vaccine safety in routine use (Section 7).

502   • It is commonly appropriate to estimate vaccine effectiveness (Section 6)

503   • Depending on the content of the pre-licensure program, further trials of safety,
504   immunogenicity and/or efficacy may be conducted and the data may be used to extend or
505   otherwise modify the use of the vaccine via amendment of the prescribing information.

506

507   4.1.1   Consultation with National Regulatory Authorities (NRAs)

508

509   It is strongly recommended that dialogue with the appropriate NRAs occurs at regular intervals
510   during the pre-licensure clinical development program to agree on the content and extent of the
511   initial application dossier. This is especially important when:

512   a. The clinical program proposes a novel approach to any aspect of development for which
513   there is no precedent or guidance available

514   b. The proposed program conflicts with existing guidance to which the NRAs involved would
515   usually refer when considering the suitability of the program

516   c. There are particular difficulties foreseen in providing evidence to support an expectation of
517   vaccine efficacy (i.e. there is no immunological correlate of protection and a vaccine
518   efficacy study is not feasible)

519   d. There are other special considerations for the total content of the pre-licensure program. For
520   example, when it is necessary to use different vaccine constructs for priming and boosting to
521   achieve immune responses thought likely to be protective. In this case each constitutes a
522   separate vaccine but the clinical data required to support their licensure for use in tandem is
523   less than would be required for two vaccines intended to be used completely independently.

524

525   Further dialogue should ensue whenever additional clinical trials are planned with intent to
526   modify the prescribing information. In addition, it should be considered whether changes to the

527   manufacturing process of a vaccine before or after initial licensure need to be discussed with

528   NRAs to establish whether or not specific clinical trials are required to support the changes.

529   Consultation with NRAs is also essential when issues of vaccine safety or effectiveness arise in

530   the post-licensure period to determine any actions that are needed.

531

532   4.1.2   Use of independent data monitoring committees

533

534   It is common in vaccine trials that a data safety monitoring board (DSMB) is appointed to

535   provide independent ongoing assessments of safety data. In the pre-licensure program for a new

536   candidate vaccine it may be appropriate to have a DSMB in place even for the initial exploratory

537   trials and dose-finding trials, especially if the vaccine consists of a new construct and/or when it

538   may be anticipated that it could be very reactogenic. For other vaccines it may be considered

539   useful to have a DSMB in place if available data from the same or similar vaccines point to the

540   possibility of important safety issues or if the trial will enrol particular populations (e.g. infants

541   and toddlers, pregnant women or immunocompromised subjects). A DSMB may not be

542   considered necessary for trials with vaccines that include only established antigenic components

543   and adjuvants for which no particular safety problems are anticipated or when a licensed vaccine

544   is being investigated using an alternative posology or in a new population. If the DSMB charter

545   includes recommending that trials are terminated early for safety reasons there should be

546   appropriate stopping rules in place.

547

548   In vaccine efficacy trials it may also be appropriate to appoint an independent data adjudication

549   committee consisting of individuals with expertise relevant to the infectious disease to be

550   prevented. For example, such a group could be used to provide an independent review of the

551   eligibility of individual vaccinees for inclusion in the primary analysis population and/or to

552   identify cases of clinically apparent infections that meet the pre-defined case definition. If such a

553   committee is appointed to oversee one or more trials the protocol and statistical analysis plan

554   should clarify whether the conclusions of the adjudication committee will be used to conduct the

555   primary analysis and any secondary analyses that are pre-defined.

556

557   In some situations, it may be appropriate to appoint an independent data monitoring committee

558   to review the results of pre-planned interim analyses of safety and/or efficacy data when a certain

559   proportion of the intended sample size has reached a certain stage of participation. It may be

560   appropriate that the DSMB or some other independent data monitoring committee takes on this

561   responsibility. Protocols and statistical analysis plans may define futility criteria to be applied to

562   the results of one or more interim analyses that, if met, would result in a recommendation from

563   the independent committee to terminate the trial. Whenever an interim analysis is planned, expert

564   statistical input should be obtained to ensure that appropriate adjustments are made to protect the

565   power and integrity of the trial.

566

567   4.1.3   Registering and reporting clinical trials

568

569   Before any clinical trial is initiated (i.e. before the first subject receives the first medical

570   intervention in the trial) its details must be registered in a publicly available, free to access,

571   searchable clinical trial registry. The registry should comply with individual NRA requirements

572   and as a minimum should comply with the WHO international agreed standards.

573

574   The entry into the clinical trial registry site should be updated as necessary to include final

575   enrolment numbers achieved and the date of actual study completion (i.e. the last data collection

576   time point for the last subject for the primary outcome measure). If clinical trials are terminated

577   prematurely the entry should be updated to reflect this with a report of the numbers enrolled up

578   to the point of termination.

579

580   The key outcomes of a clinical trial must be posted in the results section of the entry in the

581   clinical trial registry within 12 months of study completion and/or posted on a publicly-available,

582   free-to-access, searchable website (e.g. that of the trial sponsor or Principal Investigator).

583

584   Each NRA may have specific requirements for reporting the results of completed trials and the

585   status of ongoing clinical trials conducted with a specific product within and without their

586   jurisdiction. Whatever these requirements, each regulatory submission (whether for clinical trial

587   approval, to support initial licensure or a post-licensure modification or to provide a product

588   safety update report) should include a listing of all completed and ongoing trials conducted with

589   the product by the sponsor. It is recommended that any trials that are known to the sponsor (e.g.

590   from searching registries or from publications) that were initiated by persons other than the

591   sponsor (e.g. by a public health body or academic institution or by another company that used

592   the product as a comparator) should also be listed.

593

594   **4.2**   **New candidate vaccines**

595

596   Examples of new candidate vaccines from the regulatory standpoint include:

597   i.   Vaccines that contain only new antigenic components (i.e. not previously used in

598   licensed vaccines)

599   ii.   Vaccines that contain both new (i.e. not in any licensed vaccine) and known (i.e. already

600   in licensed vaccines) antigenic components

601   iii.   Vaccines that contain a new adjuvant, with known and/or new antigenic components

602   iv.   Vaccines that contain only known antigenic components that have not previously been

603   combined all together into a single vaccine, with or without a known adjuvant

604   v.   Vaccines that contain only known antigenic components ± known adjuvants in a

605   combination   that is already licensed but the vaccine is produced by a different

606   manufacturer. This includes situations in which seed lots or bulk antigenic components

607   used to make a licensed vaccine are supplied to other manufacturers for their own vaccine

608   production.

609

610   For new candidate vaccines the content and extent of pre-licensure clinical development

611   programs will reflect how much is already known about the antigenic components and adjuvants

612   in the product. Some of the most important factors include:

613   a.   Number of the antigenic components (e.g. from the same or from several infectious

614   organisms)

615   b.   Nature of the antigenic components (e.g. manufactured with or without genetic

616   modification, live attenuated, live vectored)

617   c.   Inclusion of an adjuvant

618   d.   Disease(s) to be prevented

619   e.   The available options for predicting vaccine efficacy (e.g. inferring efficacy based on

620   established immunological correlates of protection or conducting vaccine efficacy trials)

621   f.   Age range and population for use (e.g. infants, elderly, pregnant women)

622   g.   Route of administration

623   h.   Likelihood of co-administration with other vaccines in routine use

624   i.   Vaccine-specific safety issues that may be anticipated

625

626   4.2.1   Safety and immunogenicity trials

627

628   The safety and immunogenicity of a new candidate vaccine should be evaluated in all pre-

629   licensure clinical trials. In the earliest stage of clinical development the primary objective of a

630   trial is usually to describe safety although immunogenicity data are also collected. In later trials

631   the primary objective is usually to address specific immunogenicity issues and the assessment of

632   safety may be a co-primary or secondary objective. In vaccine efficacy trials evaluations of

633   safety and immunogenicity are usually secondary objectives (see Subsection 4.2).

634

635   *4.2.1.1 Initial trials*

636

637   These are commonly referred to as Phase 1 trials.

638

639   The clinical program for new candidate vaccines commences with an exploration of safety and

640   of the interaction between the antigens proposed for inclusion in the candidate vaccine and the

641   human immune system. In most cases the first clinical trials are conducted in healthy young

642   adults before proceeding to conduct trials in other age groups and/or in subjects with underlying

643   conditions. Depending on the perceived benefit and risks of vaccination it may not be

644   appropriate or necessary to apply an age de-escalation approach (e.g. to move from adults to

645   adolescents, then to children aged 6-12 followed by younger children, toddlers and finally

646   infants) to sequential trials or groups within trials. For example, if a vaccine has negligible

647   potential benefit for older children it may be acceptable in some cases to proceed from trials in

648   adults to trials in infants and toddlers.

649

650   It is usual that these trials explore different doses of antigenic components and, if applicable, the

651   effect of adding an adjuvant in various amounts. For vaccines that contain more than one new

652   antigenic component the first trials may evaluate each one given alone before selecting possible

653   doses for use in combinations. When new antigenic components are to be added to a licensed

654   product the immune response to separate administrations and to the proposed combination

655   product are compared. For vaccines that contain only known antigenic components and

656   adjuvants the initial trials focus on the effects of combining them into a single formulation or the

657   effects of mixing immediately prior to injection (e.g. using a liquid formulation of some

658   component to reconstitute a lyophilized presentation of the others). Depending on the initial

659   results, sequential trials may explore formulations with adjusted amounts of one or more

660   antigenic components and/or the adjuvant.

661

662   *4.2.1.2 Further trials*

663

664   These are commonly referred to as Phase 2 trials.

665

666   Further safety and immunogenicity trials are conducted to build on the Phase 1 trial results. In

667   most cases these trials are conducted in subjects who are representative of the intended target

668   population for the vaccine at the time of initial licensure.

669

670   These trials are usually designed to provide sufficient immunogenicity data to support selection

671   of one or more candidate formulations for further trial i.e. to select the amounts of antigenic

672   components and, where applicable, adjuvants in each dose. They may provide adequate data to

673   determine the number of doses and dose intervals but the final vaccine posology is sometimes

674   established only after completion of confirmatory immunogenicity trials or vaccine efficacy

675   trials.

676

677   *4.2.1.3 Confirmatory (or pivotal) trials*

678

679   In many vaccine clinical development programs the confirmatory (or pivotal) trial(s) involve an

680   estimate of vaccine efficacy as described in Subsection 4.2.2.

681

682 In instances where vaccine efficacy trials do not need to be, or cannot be, conducted (see
683 Subsection 4.2.2), the confirmatory (or pivotal) trial(s) usually assess the immunogenicity of the
684 final selected vaccine formulation and posology in each target population. In this setting, they
685 are commonly referred to as Phase 3 safety and immunogenicity trials. It is usual that the
686 investigational formulations used in these confirmatory safety and immunogenicity trials (as well
687 as in confirmatory efficacy trials; see below) should be manufactured using validated processes
688 and should undergo lot release in the same way as intended for the commercial product.

689

690 4.2.2 Efficacy trials

691

692 Vaccine efficacy trials have the primary aim of evaluating the protective efficacy of a candidate
693 vaccine against an infectious disease. The immunogenicity data collected during vaccine efficacy
694 trials can be used to evaluate the relationship between immune parameters and efficacy and may
695 enable identification of immune correlates of protection (see Subsection 5.4). These trials also
696 provide an opportunity to collect extensive safety data using the final intended formulation and
697 dose regimen in the target population.

698

699 Preliminary vaccine efficacy trials may be conducted to explore the magnitude of protection that
700 may be possible and to inform the design of confirmatory vaccine efficacy trials (e.g. by
701 evaluating efficacy of different dose regimens and/or by estimating efficacy based on a range of
702 efficacy variables). If conducted, these are commonly referred to as Phase 2b trials. They are also
703 sometimes referred to as pilot efficacy trials or proof of concept efficacy trials.

704

705 Confirmatory vaccine efficacy trials that are designed and powered to provide statistically robust
706 estimates of vaccine efficacy are commonly referred to as Phase 3 (or pivotal) efficacy trials or
707 sometimes as field efficacy trials.

708

709 The need for and feasibility of evaluating the protective efficacy of a candidate vaccine should
710 be considered at an early stage of vaccine development because the conclusion will determine
711 the overall content of the pre-licensure clinical program and impact on its duration. In all
712 application dossiers that do not include an evaluation of vaccine efficacy the sponsor should

713   provide a sound justification for the lack of such data, taking into account the following:

714

715   a)   Efficacy data are not required

716

717   Vaccine efficacy trials are not necessary if it is established that clinical immunological data can

718   be used to predict protection against disease. For example, when there is an established

719   immunological correlate for protection against a specific disease (e.g. anti-toxin levels against

720   diphtheria and tetanus toxins, antibody against hepatitis B surface antigen) the candidate vaccine

721   should be shown to elicit satisfactory responses based on the relevant correlate(s).

722

723   b)   Efficacy data are usually required

724

725   Vaccine efficacy trials are usually required whenever a candidate vaccine is developed with

726   intent to protect against an infectious disease and one or more of the following apply:

727   • There is no established immunological correlate of protection that could be used to predict
728   the efficacy of the candidate vaccine.

729   • There is no existing licensed vaccine of documented efficacy against a specific infectious
730   disease to allow for immunobridging of a candidate vaccine to the efficacy of a licensed
731   vaccine.

732   • Immunobridging to the documented efficacy of a licensed vaccine against a specific
733   infectious disease is not considered to be possible because there is no known relationship
734   between specific immune response parameters and efficacy.

735   • There are sound scientific reasons to expect that vaccine efficacy cannot be extrapolated
736   from the population(s) included in the prior efficacy trial(s) with a candidate vaccine to one
737   or more other populations.

738   • There are sound scientific reasons to expect that vaccine efficacy that has been demonstrated
739   for the candidate vaccine against infectious disease due to specific strains (e.g. serotypes,
740   sub-types) cannot be extrapolated to other strains.

741

742   c)   Efficacy data cannot be provided

743

744   In some instances in which efficacy data are usually required it may not be feasible to conduct

745   efficacy trials. For example, if the candidate vaccine is intended to prevent an infectious disease

746   that:

747   o   Does not currently occur (e.g. smallpox)

748   o   Occurs in unpredictable and short-lived outbreaks that do not allow enough time for the

749   conduct of appropriately designed trials to provide a robust estimation of vaccine efficacy

750   (e.g. some viral haemorrhagic fevers)

751   o   Occurs at a rate that is too low for vaccine efficacy to be evaluated in a reasonably sized trial

752   population and period of time. This situation may apply:

753   a.   Due to natural rarity (e.g. plague, anthrax, meningitis due to *N. meningitidis* type B) of

754   the infectious disease

755   b.   Due to rarity of the infectious disease resulting from the widespread use of effective

756   vaccines. In this case the numbers required to conduct an adequately powered analysis

757   of the relative efficacy of a candidate vaccine vs. a licensed vaccine may be too large to

758   permit completion in any reasonable timeframe.

759   c.   When the aim is to evaluate vaccine efficacy against serotypes   or   subtypes   of   an

760   organism that occur rarely (e.g. pneumococcal conjugate vaccines and human

761   papillomavirus vaccines).

762

763   If it is not feasible to perform vaccine efficacy trials and there is no immunological correlate of

764   protection, it may be possible to support an assumption of the likely efficacy of a vaccine by

765   deriving a marker of protection from one or more of the following:

766   i)   Nonclinical efficacy trials

767   ii)   Passive protection trials (i.e. effects of normal or hyper-immune human gamma

768   globulin, use of convalescent sera) that may point to the sufficiency of humoral

769   immunity for prevention of clinical disease and suggest a minimum protective antibody

770   level that could be used as a benchmark in clinical trials with candidate vaccines

771   iii)   Trials of the acquisition of natural immunity that may support an approach as in ii)

772   iv)   Human challenge trials

773   v)   Comparison of immunological responses with those seen in past trials of similar

774   vaccines with proven protective efficacy (e.g. acellular pertussis vaccines) even though

775   the relationship between immune responses to one or more antigenic components and

776   efficacy remains unknown

777

778   4.2.3   Pivotal safety trials

779

780   Safety is an important secondary endpoint in all trials with the primary objective of assessing

781   immunogenicity or efficacy. In rare cases, the assessment of safety may be the primary or co-

782   primary objective in a pre-licensure Phase 3 (pivotal trial) that has immunogenicity and/or

783   efficacy as secondary objectives, as described in Subsection 7.2.3.

784

785   **4.3   Post-licensure clinical evaluations**

786

787   For all licensed vaccines safety data are collected as part of routine pharmacovigilance. On

788   occasion, additional pharmacovigilance in the form of trials designed to address specific safety

789   issues that were identified as potential concerns from pre-licensure trials may be conducted

790   post-licensure (see Section 7).

791

792   Whether or not vaccine efficacy trials were conducted prior to initial licensure it is usual to

793   evaluate vaccine effectiveness during routine use or by means of trials specifically designed to

794   provide estimates of effectiveness (see Subsection 6.3).

795

796   Further clinical trials are commonly conducted after first licensure and are sometimes performed

797   to address commitments made to NRAs. These trials may or may not be intended to support

798   modifications of the prescribing information and may include:

799   a.   Extension phases of trials that commenced before first licensure (e.g. to continue follow-up

800   of safety, efficacy and/or immune response, to evaluate the effects of further doses)

801   b.   Trials that evaluate the use of alternative dose regimens (e.g. reducing the number of doses)

802   and/or schedules (e.g. extending the interval between doses)

803   c.   Trials in additional populations (e.g. different age groups, populations with factors that

804   could   affect   their   immune   response,   such   as   pregnancy,   prematurity   and

805   immunosuppression)

806   d.   Trials to support changes in vaccine manufacture with potential to affect safety, efficacy or

807   immune response

808   e.   Trials to support co-administration with other vaccines

809

810   The nomenclature for these types of trial is variable. If these additional trials are conducted in

811   wholly new populations or with substantially different vaccination regimens, especially when

812   they are intended to provide support for changes to the prescribing information, they are

813   commonly referred to as Phase 2 or 3 trials. Trials that are intended to support more minor

814   changes, such as adding alternative dose regimens or extending the age range, are commonly

815   referred to as Phase 3b trials. Other types of post-licensure trials, such as those in which vaccines

816   are given in accordance with licensed uses and regimens, are more often referred to as Phase 4

817   trials. These include trials that are specifically designed to address specific safety issues or to

818   estimate vaccine effectiveness.

819

820   **5. Immunogenicity**

821

822   This Section considers:

823   ➤ The range of immunogenicity data that may be collected throughout the pre- and post-

824   licensure clinical development program

825   ➤ Collection of specimens for immunogenicity trials

826   ➤ Characterization of the immune response to a new candidate vaccine

827   ➤ Selection of the immune parameters to be measured

828   ➤ Assays for measuring humoral and cellular immune responses

829   ➤ Identification and uses of immunological correlates of protection

830   ➤ Objectives and designs of immunogenicity trials

831   ➤ Considerations for some specific types of immunogenicity trials, including:

832   -   Trials to identify formulations and posologies (primary and post-primary)

833   -   Comparative immunogenicity trials to bridge efficacy

834   -   Trials to extend or modify use

835   -   Co-administration trials

836   -   Trials in which pregnant women are vaccinated

837 - Trials to support major changes to the manufacturing process

838 - Lot to lot consistency trials

839

840 **5.1 General considerations**

841

842 Immunogenicity trials are conducted at all stages of pre-licensure vaccine development and

843 additional trials are commonly conducted in the post-licensure period. In all trials the evaluation

844 of immune responses rests on the collection of adequate specimens at appropriate time intervals

845 and measurement of immune parameters most relevant to the vaccine using validated assays.

846

847 In the clinical development program for new candidate vaccines that contain micro-organisms

848 or antigens not previously included in human vaccines immunogenicity trials should provide a

849 detailed understanding of the immune response to vaccination. Subsequent pre-licensure and

850 post-licensure clinical trials commonly evaluate and compare immune responses between trial

851 groups to address a range of objectives. Depending on the objectives, stage of development and

852 trial population the comparisons may be made with one or more of placebo, other formulations

853 or regimens of the same vaccine or licensed vaccines. In these trials the assessments and

854 analyses of the immune responses are primary objectives whereas the assessments of safety

855 may be co-primary or secondary objectives. In trials that are primarily intended to estimate

856 vaccine efficacy, assessment of the immune responses is usually a secondary objective but it is

857 important that data on immune responses are collected to support analyses of the relationship

858 between immunogenicity and efficacy, which may lead to identification of immunological

859 correlates of protection.

860

861 **5.2 Characterization of the immune response**

862

863 For micro-organisms and antigens that have not been used previously in human vaccines a

864 thorough investigation of their interaction with the human immune response should be conducted

865 as part of the overall clinical development program. For micro-organisms and antigens that are

866 already in licensed vaccines it is not usually necessary to repeat these types of investigations but

867 consideration should be given to conducting at least some trials in certain circumstances (e.g.

868   when a new adjuvant is to be added to known antigens, a different method of attenuation is used,

869   a different carrier protein is used for antigen conjugation or an antigen previously obtained by

870   purification from cultures is to be manufactured using recombinant technology).

871

872   The range of investigations conducted should take into account what is known about the immune

873   response that results from natural exposure and whether or not this provides partial or complete

874   protection that is temporary or lifelong. The range of investigations should also consider the

875   characteristics of the infecting micro-organism (e.g. whether there are multiple subtypes that

876   cause human disease) and the content of the vaccine (14). Investigations may include some or all

877   of the following:

878   •   Determination of the amount, class, sub-class and function of antibody elicited by the

879   vaccine

880   •   Description of the magnitude of the humoral and cell-mediated immune response to initial

881   and sequential doses and changes in the magnitude of responses with time elapsed since

882   vaccination

883   •   Assessment of the ability of the vaccine to elicit a T-cell dependent primary immune

884   response, with induction of immune memory (i.e. priming of the immune system) giving rise

885   to anamnestic responses i) on natural exposure ii) after further doses of the same vaccine

886   and/or iii) after further doses of a vaccine that contains closely related but non-identical

887   micro-organisms or antigens (i.e. cross-priming)

888   •   Assessment of the specificity and cross-reactivity of the immune response

889   •   Assessment of changes in antibody avidity with sequential doses, which may be useful when

890   investigating priming

891   •   Evaluation of factors that could influence the immune responses (e.g. presence of maternal

892   antibody, pre-existing immunity to the same or very similar organisms, natural or vaccine-

893   elicited antibody against a live viral vector)

894

895   **5.3   Measuring the immune response**

896

897   5.3.1   Collection of specimens

898

899　Immune responses to vaccination are routinely measured in serum (humoral immune responses)
900　and blood (cellular immune responses). For some vaccines it may be of interest to explore
901　immune responses in other body fluids that are relevant to the site at which the target micro-
902　organism infects and/or replicates (e.g. in nasal washes or cervical mucus), especially if it is
903　known or suspected that the systemic immune response does not show a strong correlation with
904　protective efficacy for the type of vaccine under trial (e.g. intranasal vaccination against
905　influenza). Nevertheless, to date specimens other than sera have not provided data that have been
906　pivotal in regulatory decision making processes and have not resulted in identification of ICPs.
907　Therefore the rest of this section focuses on the collection of sera.

908

909　Pre-vaccination samples should be collected from all subjects in the early immunogenicity trials
910　after which it may be justifiable to omit these samples or to obtain them from subsets (e.g. if the
911　initial trials indicate that antibody is rarely detectable or quantifiable prior to vaccination in the
912　target population). Pre-vaccination sampling remains essential if it is expected that the target
913　population will have some degree of pre-existing immunity either due to natural exposure and/or
914　their vaccination history since the assessment of the immune response will need to take into
915　account seroconversion rates and increments in geometric mean titres or concentrations from
916　pre- to post-vaccination. Pre-vaccination sampling is also necessary if it is known or suspected
917　that pre-existing immune status may have a positive (e.g. because pre-existing antibody reflects
918　past priming) or negative (e.g. due to maternal antibody interfering with primary vaccination
919　with certain antigens in infants) impact on the magnitude of the immune response to vaccination.

920

921　The timing of post-vaccination sampling should be based on what is already known about the
922　peak immune response and antibody decay curve after initial and, if applicable, sequential doses
923　(e.g. for vaccines that elicit priming the rise in antibody after a booster dose is usually much
924　more rapid compared to earlier doses). For antigens not previously used in human vaccines
925　sampling times may be based initially on nonclinical data and then adjusted when antibody
926　kinetic data specific to the antigen(s) under trial have been generated. As information is
927　accumulated the number and volume of samples taken from individual vaccinees may be reduced
928　to the minimum considered necessary to address the trial objectives.

929

930   5.3.2   Immunological parameters

931

932   Immunological parameters are measures that describe the humoral (e.g. antibody concentrations

933   or antibody titres depending on the assay output) or the cell-mediated (e.g. percentages of

934   sensitised T-cells) immune response. To date, immunological parameters other than those that

935   measure the humoral immune response have not played a pivotal or major role in vaccine

936   licensure so that the focus is usually on determination of antibody levels.

937   •   For known micro-organisms or antigens in a candidate vaccine the range of parameters to be

938   measured in clinical trials is usually selected from prior experience and whether or not there

939   is an established ICP.

940   •   For micro-organisms or antigens not previously included in human vaccines the selection of

941   parameters to be measured should take into account what is known about natural immunity.

942   For some infectious diseases the nature of the immune response to infection in animal

943   models may also be useful for parameter selection. In later clinical trials, after

944   characterization of the immune response, the parameters to be measured may be modified.

945

946   *5.3.2.1 Humoral immune response*

947

948   The humoral immune response is assessed from the post-vaccination appearance or increase

949   from pre-vaccination in antibody directed at specific micro-organisms or antigens in the vaccine.

950   •   Most weight is usually placed on functional antibody responses (e.g. serum bactericidal

951   antibody [SBA], toxin or virus neutralizing antibody, opsonophagocytic antibody [OPA])

952   but there may not be an appropriate assay available (e.g. for typhoid vaccines based on the

953   Vi polysaccharide) or the only available assays may have low feasibility for application to

954   large numbers of samples (e.g. because they are very labor intensive or require high-level

955   biocontainment facilities).

956   •   Alternatively, or in addition to the determination of functional antibody, the immune

957   response may be assessed by measuring total antibody (e.g. total IgG measured by ELISA)

958   that binds to selected antigens (or, on occasion, to specific epitopes). Only a proportion of

959   the total antibody detected may be functional.

960

961 The following should be taken into consideration when deciding how to measure the humoral
962 immune response:

a. If a strong correlation has already been established between total and functional antibody
   responses to a specific micro-organism or antigen it may be acceptable to measure only total
   IgG in further trials (e.g. antibody to tetanus toxin)

b. For antigens for which there is an established ICP it may suffice to measure only the
   relevant functional antibody (e.g. SBA for meningococcal vaccines) or total IgG (e.g. for
   antibody to tetanus toxin) response

c. If the ICP is based on total IgG there may be instances in which there is still merit in
   measuring functional antibody (e.g. for antibody to diphtheria toxin for which a micro-
   neutralization assay is available)

d. If there is no ICP the functional antibody response should be measured if this is feasible

e. Occasionally there may be more than one immunological parameter that measures functional
   antibody but one is considered to be a more definitive measure than the other (e.g.
   neutralizing antibody to influenza virus vs. antibody that inhibits haemagglutination), in
   which case the more definitive parameter may be determined at least in a subset

f. For some vaccines against certain viruses there is a potential that some of the total antibody
   detected has no protective effect (e.g. is non-neutralizing) but it could enhance cellular
   infection by wild-type virus and result in an increased risk of severe disease after
   vaccination (e.g. this may apply to dengue vaccines). To assess this possibility the routine
   measurement of total antibody to assess the humoral immune response to vaccination should
   be supported by other detailed investigations.

5.3.2.2 Cell-mediated immune response

For some types of infectious disease (such as tuberculosis) the assessment of the cell-mediated
immune response may have a major role in the assessment of the interaction between the
vaccine and the human immune system. In many other settings the evaluation of the cellular
immune response may serve to support the findings based on the humoral immune response
(e.g. when assessing the benefit of adding an adjuvant or when evaluating the degree of cross-
priming elicited by a vaccine).

992

993   The cell-mediated immune response is most commonly assessed by detecting and quantifying

994   sensitized T-cells in blood from vaccinees. These investigations may also serve to characterize

995   the predominant cytokines released and to detect differences in sensitization between T-cell sub-

996   populations. There are several methods that may be used. These are commonly based on

997   measuring the production of a range of cytokines following in-vitro stimulation of T-cells with

998   individual or pooled antigens.

999

1000   To date, the methodologies used for these and alternative types of assays have been variable and

1001   non-standardized. Nevertheless, the results may provide useful comparisons between treatment

1002   groups within any one study (e.g. could describe the effect, if any, of an adjuvant) based on

1003   comparing rates of "responders" defined by a magnitude of change in the assay readout from

1004   pre- to post-vaccination. If there are marked discrepancies in the patterns of responses observed

1005   between cell-mediated and humoral responses (e.g. if adding an adjuvant does have a major

1006   effect on antibody levels but does not increase the percentages of sensitized cells in one or more

1007   T-cell subsets) the findings should be carefully considered and discussed.

1008

1009   5.3.3   Assays

1010

1011   Assays of functional or total antibody that are used to report immune responses to vaccination

1012   (whether to the candidate vaccine or to co-administered vaccines) in trials intended to support

1013   licensure (i.e. in confirmatory trials) may be:

1014   • Commercially available assays specifically designed and intended for quantification of

1015   antibody that are considered acceptable to NRAs (i.e. have been marketed following a robust

1016   regulatory review by the same or by other NRAs).

1017   • In-house assays that have been validated according to similar principles recommended for

1018   quantitative lot release assays in the ICH Q2 (R1) document *Validation of Analytical*

1019   *Procedures: Text and Methodology* (15). In-house assays that are used in early trials that

1020   explore the immune response may be regarded as an exception and may report data using

1021   assays that have yet to be validated or which are not subsequently validated.

1022   • In-house assays that have been shown to be comparable to a reference assay (e.g. to an assay

1023   established in a WHO reference laboratory or to an assay that is established in a recognized

1024   public health laboratory and which has been used previously to support clinical trials that

1025   have been pivotal for licensure).

1026   In each case, it is expected that WHO International Standard reagents will be used in assay runs

1027   if these exist or omission of their use should be adequately justified.

1028

1029   Commercial assays suitable for quantification of the cell-mediated response to vaccination are

1030   not currently available but may be used in future. In-house assays that are used to detect and

1031   quantify cell-mediated immunity may be difficult to fully validate, in which case the results

1032   should not be used to make specific claims regarding clinical effect.

1033

1034   Clinical trial protocols should specify which assays will be used and in which laboratories.

1035   Clinical trial reports should include at least a summary of the assay methodology and its

1036   commercial or other validation status. For in-house assays the validation reports should be

1037   provided.

1038

1039   It is preferable that the same assays are used in the same laboratories throughout the clinical

1040   development program (including pre-and post-licensure trials) for an individual vaccine. It is

1041   also preferable that each assay (whether it measures the response to the candidate vaccine or to a

1042   concomitant vaccine) is run by one central laboratory. If this is not possible (e.g. because

1043   different laboratories have to be used, commercial or in-house assays change over time or a

1044   switch is made between in-house and commercial assays) the new and original assays should be

1045   shown to be comparable. As a minimum it is recommended that a selection of stored sera (e.g.

1046   covering a range of low to high results when using the previous assay) are re-run using the

1047   previous and new assays in parallel. The number of sera re-tested should be sufficient to support

1048   a statistical assessment of inter-assay variability.

1049

1050   The micro-organisms (e.g. in assays of SBA, OPA and virus neutralization) and the antigens

1051   (e.g. in ELISAs and for in-vitro stimulation of sensitized T-cells) used in the assay may affect

1052   both the result and the interpretation of the result. For example:

1053   • It is important to use purified antigen to avoid the possibility that the assay detects and

1054   measures antibody to any extraneous antigenic substances that may be in the vaccine.

1055   •   For vaccines that contain antigens from multiple strains of the same species (e.g. multiple

1056   bacterial capsular types) separate assays are needed to determine the immune response to

1057   each antigen.

1058   •   Although it is usually acceptable to conduct routine testing using the same micro-organisms

1059   or antigens present in the vaccine it may be very informative to perform additional testing, at

1060   least in subsets of samples, using circulating wild-type organisms or antigens derived from

1061   them in the assay. It is not expected that these additional assays will necessarily be validated

1062   since they are exploratory in nature. The results of additional testing can provide an

1063   indication as to whether the results of routine testing could represent an over-estimate of the

1064   immune response to circulating strains. This additional testing can also provide an

1065   assessment of the cross-reactivity of the immune responses elicited by the vaccine to other

1066   organisms of the same genus or species (e.g. to different flaviviruses, to different clades of

1067   influenza virus or to different HPV types) and guide the need to replace or add strains or

1068   antigens in a vaccine to improve or maintain its protective effect.

1069

1070   **5.4   Identification and use of immunological correlates of protection**

1071

1072   5.4.1   Immunological correlates of protection and their uses

1073

1074   To date, all established ICPs are based on humoral immune response parameters that measure

1075   functional or total IgG antibody. Examples of well-established ICPs include those for antibody

1076   to diphtheria and tetanus toxoids, polioviruses, hepatitis B virus and *H. influenzae* type b (Hib)

1077   polysaccharide (PRP) (16). In most cases, established ICPs have been shown to correlate with

1078   prevention of clinically apparent infectious disease but for some pathogens the ICP correlates

1079   with prevention of documented infection (e.g. hepatitis A and hepatitis B).

1080

1081   In some cases the ICP is a measure of the functional antibody response but if a strong correlation

1082   is shown between the results of assays of functional and total antibody, it may be possible to

1083   derive an alternative ICP based on total antibody (see Subsection 5.3.3).

1084

1085   Subsections 5.5.2 and 5.5.3 consider trial endpoints and the approach to analysis and

1086   interpretation of immunogenicity data in the presence or absence of an ICP and situations in

1087   which alternative approaches may be appropriate. For example, for some infectious diseases

1088   vaccine-elicited protection against clinical disease shows a broad correlation with a specific

1089   immunological parameter (e.g. with serum neutralising antibody elicited by HPV vaccines) but

1090   no cut-off value has been identified that shows a strong statistical correlation with protection in

1091   the short or longer-term in individuals or populations. In some other instances there is an

1092   indication of a threshold value that seems to broadly predict protection but the evidence is

1093   insufficient to regard this as an ICP applicable to a specific or to several different sub-

1094   populations or organism subtypes (e.g. IgG to specific pneumococcal serotypes). For some other

1095   infectious diseases there is no correlation that is well established between vaccine-elicited

1096   protection and measurable immune parameters (e.g. for acellular pertussis vaccines).

1097

1098   5.4.2   Establishing an ICP

1099

1100   Documentation of the immune response to natural infection, the duration of protection after

1101   clinically apparent infection (i.e. whether natural protection is life-long [solid immunity],

1102   temporary or absent) and the specificity of protection (i.e. whether the individual is protected

1103   only against specific subtypes of a micro-organism) should be taken into account when

1104   attempting to establish an ICP from clinical data. For example, to date, widely-accepted clinical

1105   ICPs have been established based on one or more of:

1106   • Serosurveillance and disease prevalence in specific populations

1107   • Passive protection using antibody derived from immune humans or manufactured using

1108   recombinant technology

1109   • Efficacy trials

1110   • Effectiveness trials

1111   • Investigation of vaccine failure in immunosuppressed populations

1112

1113   In the majority of cases clinical ICPs have been determined from vaccine efficacy trials that were

1114   initiated pre-licensure, often with long-term follow-up of subjects that extended into the post-

1115   licensure period. Efficacy trial protocols should plan to collect sufficient information to allow for

1116   analyses of the relationship between immune parameters and protection against clinically

1117   apparent disease. As a minimum this requires collection of post-vaccination samples from all or

1118   from a substantial subset of the vaccinated and control groups. Serial collection of samples over

1119   the longer-term along with follow-up surveillance for vaccine breakthrough cases has also served

1120   to support identification of ICPs.

1121

1122   To investigate the predictive capacity of a putative ICP protocols should pre-define the

1123   assessments to be applied to all cases of the disease to be prevented that occur in the vaccinated

1124   and control groups. These assessments should include investigation of the immune status of

1125   subjects and microbiological studies with the infecting micro-organisms whenever these have

1126   been recovered. For breakthrough cases from which there are both post-vaccination sera and

1127   organisms recovered it is recommended that functional antibody should be determined (or, if not

1128   possible, total antibody) for individuals against their own pathogen. An exploration of vaccine-

1129   elicited cell-mediated responses in individuals against their own pathogen may also be useful

1130   and, for some types of infectious diseases (such as tuberculosis), may be very important to

1131   further understanding of vaccine-associated protection. These data may be very important to

1132   investigate the broad applicability of the ICP depending on host and organism factors.

1133

1134   A single clinical ICP identified from a vaccine efficacy trial in a defined population may not

1135   necessarily be applicable to other vaccine constructs intended to prevent the same infectious

1136   disease. In addition, an ICP may not be applicable to other populations and disease setting. For

1137   example, putative ICPs have sometimes differed between populations of different ethnicities

1138   with variable natural exposure histories for subtypes of a single micro-organism. Thus the

1139   reliance that is placed on a clinical ICP, even if regarded as well-supported by the evidence,

1140   should take into account details of the efficacy trials from which it was derived.

1141

1142   Clinical ICPs have also been derived from or further supported by analyses of effectiveness data.

1143   The methods used to derive ICPs from effectiveness data have been very variable. In addition to

1144   the factors that may affect the relevance of ICPs derived from efficacy trials, estimates drawn

1145   from effectiveness data may in part reflect the type of immunization program in place and the

1146   extent to which protection of individuals relies on herd immunity rather than the initial and

1147 persisting immune response in the individual. The wider applicability of ICPs derived from such

1148 trials should be viewed in light of how and in what setting the estimates were obtained.

1149

1150 If it is not possible to derive a clinical ICP the interpretation of the human immune response data

1151 may take into account what is known about immunological parameters that correlate with

1152 protection in relevant animal models and any nonclinical ICPs that have been identified (e.g.

1153 from trials that assess passive protection and active immunization). This approach may be the

1154 only option available for interpreting immune responses to some new candidate vaccines.

1155 Nevertheless, ICPs derived wholly from nonclinical data should be viewed with caution and

1156 attempts should be made to obtain a clinical ICP whenever the opportunity arises (e.g. when the

1157 vaccine is used in an outbreak situation).

1158

1159 If conducted, human challenge trials may also provide preliminary evidence supporting an ICP.

1160 Nevertheless, these trials are usually conducted in non-immune healthy adults who are

1161 challenged with organisms that are not identical to, and do not behave like, virulent wild-types.

1162 Therefore these trials may point to a correlation between a specific immunological parameter and

1163 protection, which can be further investigated during the clinical development program.

1164

1165 **5.5   Immunogenicity trials**

1166

1167 5.5.1   Objectives

1168

1169 The objectives of pre-licensure and post-licensure clinical immunogenicity trials include (but are

1170 not limited to):

1171   i)   To select vaccine formulations and posologies (including primary and booster doses)

1172   ii)   To bridge the efficacy demonstrated in a specific population and using one vaccine

1173   formulation and posology to

1174   a) The same vaccine when used in other settings or with alternative posologies or

1175   b) A different vaccine intended to protect against the same infectious disease(s)

1176   as a licensed vaccine for which efficacy has been established

1177   iii)   To achieve the objectives as in ii) but in the absence of prior efficacy data to which a

1178   bridge can be made

1179   iv)   To support co-administration with other vaccines

1180   v)   To support maternal immunization with the primary intent to protect the infant

1181   vi)   To support major changes to the manufacturing process

1182   vii)   To assess lot to lot consistency (8)

1183

1184   Subsections 5.5.2 and 5.5.3 address some general considerations for the selection of endpoints,

1185   the design of comparative immunogenicity trials and the analysis and interpretation of the

1186   results. Subsection 5.6 provides additional details of issues to take into consideration when

1187   designing, analyzing and interpreting comparative immunogenicity trials that have one or more

1188   of objectives i) to vii).

1189

1190   5.5.2   General considerations for trial designs

1191

1192   Immunogenicity trials are almost without exception comparative trials. Comparative trials

1193   include those in which all subjects receive the same vaccine formulation but there are differences

1194   between groups in how or to whom the vaccine is administered (e.g. using a different dose or

1195   dose interval, administering the vaccine to different age groups) and trials in which at least one

1196   of the trial groups receives an alternative treatment, which may be placebo and/or another

1197   licensed vaccine.

1198

1199   The design of comparative immunogenicity trials is driven by the characteristics of the vaccine,

1200   the trial objectives, the stage of clinical development, the trial population, the availability and

1201   acceptability of suitable comparators and what is known about immune parameters that correlate

1202   with protection (including whether or not there is an established ICP).

1203

1204   In comparative immunogenicity trials subjects should be randomized to one of the trial groups at

1205   enrolment. This also applies to trials that enroll sequential cohorts of subjects (e.g. in ascending

1206   dose trials in which at least some subjects are assigned to receive placebo or another vaccine). In

1207   some cases it may be appropriate that subjects who meet certain criteria (e.g. completed all

1208   assigned doses in the initial part of the trial) are re-randomized at a later stage of the trial to

1209   receive a further dose of a test or control treatment.

1210

1211   Whenever possible, comparative immunogenicity trials should be double blind. If the vaccines to

1212   be compared are visually distinguishable, it is preferable that designated persons at each trial site

1213   administer the products. Vaccinees (or their parents/guardians) and all other trial staff should

1214   remain unaware of the treatment assignment. If this is not feasible, or if the vaccines to be

1215   compared are given by different routes or at different schedules, the assays should be conducted

1216   by laboratory staff unaware of the treatment assignment.

1217

1218   In trials intended to provide only descriptive analyses of the immunogenicity data the trial

1219   sample size is usually based on considerations of feasibility and collection of sufficient safety

1220   data to support the design of sequential trials. Trials that aim to assess superiority or non-

1221   inferiority between vaccine groups should be sized according to the intended power and the pre-

1222   defined margins.

1223

1224   *5.5.2.1 Endpoints*

1225

1226   The choice of the primary trial endpoint and the range of other endpoints for immunogenicity

1227   trials should take into account Subsections 5.2, 5.3 and 5.4. Protocols should pre-define the

1228   primary, secondary and any other (which may be designated tertiary or exploratory) endpoints.

1229   Trial protocols may pre-define multiple co-primary endpoints:

1230   • For vaccines intended to protect against multiple subtypes of the same micro-organism (e.g.

1231   human papillomavirus vaccines, pneumococcal conjugate vaccines)

1232   • For combination vaccines, including vaccines that contain multiple micro-organisms (such

1233   as measles, mumps, rubella vaccine) or multiple antigens (such as combination vaccines

1234   used for the primary immunization series in infants)

1235

1236   The following should be taken into consideration when selecting the primary endpoint(s)

1237   following primary vaccination:

1238

1239   i.   When an ICP has been established the primary endpoint is usually the percentage of

1240   vaccinees that achieves an antibody level at or above the ICP, which is sometimes referred
1241   to as the seroprotection rate.

1242

1243 ii.   When there is no established ICP the primary endpoint is usually based on the parameter
1244   that is known or could be anticipated to best correlate with efficacy (e.g. a measure of
1245   functional antibody or, if no functional assay is available, a measure of total IgG).

1246   ➢ In some instances there may not be an ICP but there may be evidence to support
1247   application of a threshold value (i.e. the primary endpoint may be the percentage of
1248   vaccinees that achieves antibody levels at or above the threshold value, which is
1249   sometimes referred to as the responder rate).

1250   ➢ If there is no ICP or threshold that could be applied it may be appropriate that the primary
1251   endpoint is based on the seroconversion rate or on some other definition of the magnitude
1252   of the immune response that differentiates responders from non-responders. Comparisons
1253   of post-vaccination seropositivity rates may also be informative if pre-vaccination rates
1254   are very low.

1255

1256 For assessment of the immune response following administration of a vaccine to subjects who
1257 are already primed against one or more micro-organisms or antigens in the vaccine an
1258 anamnestic immune response is anticipated so that seroprotection, seroconversion (when defined
1259 by fold-rise from pre- to post-boost) and seropositivity rates after the booster dose will likely be
1260 very high. In these cases the most sensitive immunological parameter for detecting differences
1261 between groups may be the geometric mean concentration or titre.

1262

1263 After primary vaccination and after any additional doses the results of all immunological
1264 parameters measured should be reported, including seroprotection (if defined), seropositivity and
1265 seroconversion rates, geometric mean concentrations or titres and the reverse cumulative
1266 distributions, regardless of the pre-defined primary endpoint.

1267

1268 *5.5.2.2 Exploratory trials*

1269

1270 In the initial stages of vaccine clinical development, and when commencing further vaccine

1271   development to substantially modify the initial prescribing information, exploratory trials are

1272   commonly conducted to provide preliminary data on safety and immunogenicity. The assessment

1273   of the immune response may be designated as co-primary with safety or secondary. Exploratory

1274   trials are not usually powered or designed to address specific hypotheses. To obtain a clear

1275   picture of safety, these trials may include a placebo group if this is considered to be acceptable

1276   (e.g. a placebo group is commonly used in initial trials with a new candidate vaccine in healthy

1277   adults).

1278

1279   *5.5.2.3 Superiority trials*

1280

1281   Trials intended to detect superiority of immune responses are most often conducted during the

1282   selection of candidate vaccine formulations and posologies for further clinical investigation. It is

1283   common that these trials plan to assess whether a specific candidate vaccine formulation elicits

1284   superior immune responses compared to no vaccination against the disease to be prevented

1285   and/or compared to alternative formulations of the candidate vaccine. Initial dose selection trials

1286   are not usually formally powered to demonstrate superiority but this may be considered for

1287   larger trials that are intended to select a final formulation and posology for further investigation.

1288

1289   Superiority trials are also conducted when an adjuvant is proposed for inclusion in the vaccine,

1290   in which case it is usually expected that the immune response to at least one of the antigenic

1291   components of an adjuvanted formulation should be superior to that for a non-adjuvanted

1292   formulation that is otherwise identical. However, if addition of an adjuvant is intended to reduce

1293   the amount(s) of antigen(s) required (which may increase vaccine production capacity) it may

1294   suffice that the adjuvanted formulation with the reduced antigen dose is shown to be at least as

1295   immunogenic (i.e. non-inferior) as a non-adjuvanted formulation containing a higher dose.

1296

1297   Some trials may be designed to assess superiority between certain groups and non-inferiority

1298   between others or to assess superiority of immune responses to single or multiple antigenic

1299   components. For example, whilst adding an adjuvant may improve the immune responses to one

1300   or more antigenic components it should also not have a negative effect that is of potential clinical

1301   significance on the immune responses to all other antigenic components. In addition, a trial may

1302   be designed to establish that specific immune responses are at least non-inferior between trial

1303   groups and, if the pre-defined non-inferiority criteria are met, to then assess whether the

1304   responses are superior.

1305

1306   *5.5.2.4 Non-inferiority trials*

1307

1308   Most comparative immunogenicity trials are intended to show that the test vaccinated groups

1309   achieve comparable immune responses to the selected reference groups. Not all such trials need

1310   to be formally designed and powered to demonstrate non-inferiority but trials that are intended to

1311   be pivotal (i.e. the application for licensure or to modify the license is to be based mainly or

1312   wholly on the trial) should be adequately designed and powered to demonstrate non-inferiority

1313   using a pre-defined and justifiable non-inferiority margin. It is recommended that protocols and

1314   statistical analysis plans for each trial are developed in conjunction with an appropriately

1315   experienced statistician.

1316

1317   Factors to consider regarding the stringency of the non-inferiority margin include the clinical

1318   relevance of the endpoint, seriousness of the disease to be prevented and the vulnerability of the

1319   target population. More stringent margins may be appropriate when the vaccine is intended to

1320   prevent severe or life-threatening diseases and will be used in particularly vulnerable populations

1321   (e.g. infants and pregnant women). If a new candidate vaccine is known to offer substantial

1322   benefits in terms of safety or improved coverage, less stringent margins may be considered. In

1323   contrast, a more stringent margin could be considered when there is a potential for a downward

1324   drift in immunogenicity such as that which could occur when a new candidate vaccine can be

1325   compared only with vaccines that were themselves approved based on non-inferiority trials (see

1326   Subsection 5.6.2.1). As a result of these considerations it is possible that different non-inferiority

1327   margins may be considered appropriate to interpret immune responses to any one specific

1328   antigenic component in different settings.

1329

1330   As a general rule, for the purposes of establishing non-inferiority between vaccine groups

1331   based on GMT or GMC ratios for antibody titres or concentrations, it is suggested that the

1332   lower bound of the 95% confidence interval around the ratio (test vs. reference vaccine) should

1333   not fall below 0.67. Under certain circumstances, NRAs may consider allowing a lower bound

1334   of 0.5. The criterion should be selected taking into account whether or not an ICP has been

1335   identified. In addition, any marked separations between the reverse cumulative distributions of

1336   antibody titres or concentrations should be discussed in terms of the potential clinical

1337   implications, even if these occur only at the lower or upper ends of the curves.

1338

1339   When comparing seroprotection rates, seroconversion rates or percentages of vaccines with

1340   immune responses that are above a pre-defined threshold, sponsors frequently select a non-

1341   inferiority margin of 10%, which gives modest sample sizes. There is very rarely any

1342   justification provided for this margin nor is there any discussion of the possible consequences

1343   of a candidate vaccine eliciting seroprotection or seroconversion rates or percentages with

1344   responses above a pre-defined threshold that are lower those in the licensed vaccine group to

1345   such an extent that the lower 95% confidence interval around the difference (test − reference)

1346   approaches -10%. If a sponsor does pre-define such a margin without adequate justification,

1347   the implications of the actual 95% confidence intervals that are observed should be reviewed

1348   in light of the considerations described above.

1349

1350   5.5.3   Analysis and interpretation

1351

1352   A statistical analysis plan should be finalized before closing the trial database and unblinding

1353   treatment assignments (if these were blinded). This should include any planned interim analyses,

1354   which should be adequately addressed in terms of purpose, timing and any statistical adjustments

1355   required.

1356

1357   The immunogenicity data from all subjects with at least one result for any immunological

1358   parameter measured in the trial should be included in the clinical trial report. The analysis of the

1359   immune response based on any one parameter is commonly restricted to all subjects with a pre-

1360   vaccination measurement (if this is to be obtained from all subjects) and at least one post-

1361   vaccination measurement. Protocols may also restrict the primary analysis population to subjects

1362   with pre- and post-vaccination results who received all the assigned doses within pre-defined

1363   windows around the intended schedule and had no other major protocol violations (e.g. met the

1364 inclusion and exclusion criteria). Other analysis populations of interest may be pre-defined in

1365 accordance with the primary or secondary objectives (e.g. age sub-groups, pre-vaccination

1366 serostatus). Whatever the pre-defined primary analysis population, all available immunogenicity

1367 data should be presented in the clinical trial report.

1368

1369 If a trial fails to meet the pre-defined criteria for superiority and/or non-inferiority with respect to

1370 any of the antigenic components the possible reasons for the result and the clinical implications

1371 should be carefully considered before proceeding with clinical development or licensure. The

1372 considerations may take into account the basis for setting the pre-defined criteria (e.g. does

1373 failure to meet the criteria strongly imply that lower efficacy may result), the comparisons made

1374 for all other immune parameters measured (e.g. were criteria not met for only one or a few of

1375 many antigenic components of the vaccine), any differences in composition between the test and

1376 the comparator vaccines that could explain the result, the severity of the disease(s) to be

1377 prevented and the overall anticipated benefits of vaccine, including its safety profile. Subsection

1378 5.6 provides some further examples and issues to consider.

1379

1380 Additional analyses of the data that were not pre-specified in the protocol and/or the statistical

1381 analysis plan (i.e. *post hoc* analyses) should generally be avoided. If conducted, they should

1382 usually be viewed with caution although the results may stimulate further clinical trials to

1383 investigate specific issues.

1384

1385 **5.6   Specific considerations for trial design and interpretation**

1386

1387 This Subsection should be read in conjunction with Subsection 5.5

1388

1389 5.6.1   Selection of formulation and posology

1390

1391 The vaccine formulation is determined by the numbers of micro-organisms or amounts of

1392 antigens and, if applicable, adjuvant that is to be delivered in each dose as well as the route of

1393 administration.

1394

1395   The vaccine posology for a specific route of administration includes:

1396   • Dose content (as for formulation) and volume delivered per dose

1397   • Dose regimen (number of doses to be given in the primary series and, if applicable, after the

1398   primary series)

1399   • Dose schedule (dose intervals within the primary series and between the primary series and

1400   any further doses)

1401

1402   The vaccine posology for any one vaccine may vary between target populations (e.g. age groups

1403   and according to prior vaccination history) in one or more aspects (content, regimen or

1404   schedule).

1405

1406   The following sections outline the immunogenicity data that are usually generated to support the

1407   vaccine formulation and posology and to assess the need for, and immune response to, additional

1408   doses of the vaccine after completion of the primary series. Section 7 addresses the importance

1409   of the safety profile when selecting vaccine formulations and posologies.

1410

1411   *5.6.1.1 Selecting the formulation and posology for initial licensure*

1412

1413   The vaccine formulation and posology that is initially approved should be supported by safety

1414   and immunogenicity data, with or without efficacy data, collected throughout the pre-licensure

1415   clinical development programme. At the time of initial licensure the data should at least support

1416   the formulation and posology for the primary series, which may consist of one or more doses.

1417

1418   Depending on the intended formulation of the new candidate vaccine the following

1419   considerations may apply:

1420

1421   i) Whenever a new candidate vaccine contains any micro-organisms or antigens not previously

1422   used in human vaccines, with or without others already used in human vaccines, the initial trials

1423   usually explore the immune responses to different amounts of each of the new micro-organisms

1424   or antigens when given alone in non-immune healthy adult subjects. These trials should describe

1425   the dose-response curve and may indicate a plateau for the immune responses above a certain

1426   dose level. The next trials usually evaluate immune responses to further doses at various dose

1427   intervals to evaluate the kinetics of the immune response as well as any increment in immune

1428   response that is achieved by further doses. The transition from trials in healthy adults to trials in

1429   subjects in the target age range at the time of initial licensure (if this is not confined to young

1430   adults) should occur as soon as this can be supported taking into account the safety profile.

1431

1432   However, evaluating the immune response to each of the new micro-organisms or antigens alone

1433   may not be a feasible undertaking. For example, if the vaccine construct is manufactured in such

1434   a way that production of individual antigens is not feasible then the evaluation of the appropriate

1435   vaccine dose may be based solely on studies with the entire construct. Another example concerns

1436   vaccines intended to protect against multiple subtypes of an organism. In this case, the use of

1437   micro-organisms or antigens that could be regarded as broadly representative in the first trials

1438   may provide some idea of the likely response to other subtypes. Further trials may then explore

1439   formulations that contain increasing numbers of the subtypes with the objective of assessing the

1440   effect of combining them into a single product on the immune response.

1441

1442   ii) For new candidate vaccines that contain known antigenic components not previously

1443   combined together into a single vaccine the initial trials are usually conducted in subjects within

1444   the age ranges approved for licensed vaccines that contain some or all of the same antigenic

1445   components. The aim is to demonstrate non-inferiority of immune responses to each of the

1446   intended antigenic components when combined into a candidate formulation with co-

1447   administration of licensed vaccines that together provide all of the same antigenic components.

1448   The same approach applies whenever the antigenic components are not combined into a single

1449   formulation but the contents of more than one pre-formulated product have to be mixed

1450   immediately before administration to avoid a detrimental physico-chemical interaction.

1451

1452   iii) For new candidate vaccines that contain known and one or more new antigenic components

1453   the initial trials may aim to demonstrate non-inferiority of immune responses to each of the

1454   known antigenic components when combined into a candidate formulation with separate

1455   administrations of known and new antigenic components. It may also be informative to include a

1456   control group that receives co-administration of known and new antigenic components. The

1457   exact design depends on the availability of a single licensed vaccine containing the known

1458   antigenic components or whether more than one licensed vaccine has to be given.

1459

1460   iv) For any vaccine formulation to which an adjuvant is to be added there should be adequate

1461   data already available (which may apply to known adjuvants) or data should be generated (new

1462   adjuvants or when using any adjuvant with a new antigenic component) to demonstrate that

1463   addition of the adjuvant elicits a superior immune response to one or more antigenic components

1464   without a potentially detrimental effect on any other antigenic components. Alternatively, data

1465   should demonstrate that including the adjuvant allows for the use of a much lower dose of an

1466   antigenic component to achieve the desired level of immune response. Trials should evaluate a

1467   sufficient range of combinations of antigenic components and adjuvant to support the final

1468   selected formulation.

1469

1470   v) The total data generated should be explored to identify the criteria to be applied for the

1471   determination of an appropriate shelf-life of the vaccine. This is usually of particular importance

1472   to vaccines that contain live micro-organisms. Depending on data already generated, it may be

1473   necessary to conduct additional trials with formulations known to contain a range of micro-

1474   organism numbers or antigen doses to identify appropriate limits at end of shelf-life.

1475

1476   vi) Comparative immunogenicity trials may be needed to determine schedules appropriate for

1477   specific target populations, taking into account the urgency to achieve protective immunity (i.e.

1478   based on diseases to be prevented and their epidemiology). The data generated across all the

1479   trials should determine the minimum period that should elapse between doses and the effects of

1480   delaying doses to support acceptable windows around scheduled doses. Additionally, for some

1481   vaccines it may be useful to explore the shortest time frame within which doses may be

1482   completed without a detrimental effect on the final immune response (e.g. for vaccines for

1483   travelers who may need to depart at short notice and for vaccines intended to provide post-

1484   exposure prophylaxis).

1485

1486   The assessment of the effects of dose interval and the total time taken to complete the primary

1487   series is a particular issue for vaccines intended for use in infants due to the very wide range of

1488   schedules in use in different countries (e.g. 3-dose schedules include 6-10-14 weeks and 2-4-6

1489   months). In general, experience indicates that the magnitude of the post-primary series immune

1490   responses broadly correlates with the age of infants at the time of the final dose. If a trial using a

1491   6-10-14 weeks or 2-3-4 months schedule demonstrates highly satisfactory immune responses it is

1492   reasonable to expect that schedules that either commence later in infancy, use longer dose

1493   intervals and/or in which the final dose is given at 5-6 months or later will also be highly

1494   satisfactory. In contrast, the results of the latter types of schedules cannot be used to support use

1495   of earlier and more condensed schedules.

1496

1497   vii) All of the data generated in accordance with points i) to vi) should be taken into account

1498   when selecting the final formulation and posology or posologies. The selection process is more

1499   straightforward if there are established ICPs that can be applied to interpretation of the results for

1500   at least some of the antigenic components. In the absence of an ICP, which frequently applies to

1501   new micro-organisms or antigens, the posology may be selected from considerations of any

1502   plateau effects that are observed and the safety profile of various doses and regimens.

1503

1504   It is not unusual that the final selected formulation and posology to some extent represents a

1505   compromise between immunogenicity and safety or, for combination vaccines, between the

1506   potential benefits of a vaccine that can protect against multiple types of infectious disease with

1507   some negative effects on immune response that may occur. These negative effects may result

1508   from a physicochemical interaction between vaccine components and/or a negative immune

1509   interference effect for some antigenic components with or without a positive immune

1510   interference effect for some others. The rationale for the final selection requires careful

1511   discussion in the application dossier.

1512

1513   *5.6.1.2 Amending or adding posologies after initial licensure*

1514

1515   Clinical trials conducted after first licensure may be designed to address one or more of the

1516   following:

1517   a.   Change the number of doses or dose intervals. In this case the control group should be

1518   vaccinated using the licensed posology and the trial should be conducted in a population

1519   for which the vaccine is already licensed.

1520   b.   Use of the licensed posology in a new population (e.g. in subjects who are younger or

1521   older than the currently licensed age group; in subjects with specific underlying

1522   conditions, such as immunosuppression). In this case the trial should compare use of

1523   the licensed posology in the new target population and the population for which the

1524   vaccine is already licensed.

1525   c.   Use of an alternative to the licensed posology in a new population. In this case the

1526   alternative posology administered to the new population should be directly compared

1527   with the licensed posology in the licensed population.

1528   d.   Support alternative routes of administration for the licensed formulation (e.g. adding sub-

1529   cutaneous or intra-dermal injection to intra-muscular use).

1530

1531   Post-licensure clinical trials may also be conducted to support changes in formulation.

1532   Formulation changes other than adding or removing a preservative or removing thiomersal from

1533   the manufacturing process usually result in a modified product that is considered to be a new

1534   candidate vaccine from a regulatory standpoint (i.e. it would require a new application dossier

1535   and adequate trials to support separate licensure).

1536

1537   *5.6.1.3 Post-primary doses*

1538

1539   a.   Need for post-primary doses

1540

1541   The need to administer additional doses, and the timing of these doses, may be determined

1542   before and/or after first licensure.

1543

1544   To date, very few licensed vaccines are recommended only for use in a primary series. Examples

1545   include inactivated hepatitis A vaccines and hepatitis B vaccines containing recombinant surface

1546   antigen [HBsAg] for which very long term follow-up continues to suggest that additional doses

1547   are not necessary to maintain protection in those who had a robust immune response to the

1548   primary series. For all other vaccines one or more additional doses of the same or another

1549   vaccine that protects against the same disease(s) is recommended or the prescribing information

1550   states that it is not yet known whether further doses will be necessary.

1551

1552   If experience with other similar vaccines clearly indicate that additional doses of a new candidate

1553   vaccine will be needed the clinical development program should incorporate this in the overall

1554   assessment of immune responses.

1555

1556   If it is not known whether post-primary doses of a new candidate vaccine will be needed to

1557   maintain protection it is preferable that this should be determined from long-term follow-up of

1558   subjects who were enrolled in efficacy trials and/or from post-licensure effectiveness trials.

1559   Although the long-term monitoring of antibody persistence is important, these data alone cannot

1560   determine if another dose is needed unless there is evidence or a strong reason to expect that

1561   failure to maintain circulating antibody above a certain level (e.g. above the ICP if there is one)

1562   is associated with risk of breakthrough disease (even when the primary series of the vaccine

1563   elicited an immune memory response).

1564

1565   Until it is clear whether or not additional doses are needed, it is prudent to plan to obtain data on

1566   the immune response to additional doses at different intervals after the last dose of the primary

1567   series so that data are available should it become clear that an additional dose is required.

1568

1569   b. Assessment of priming during the primary series

1570

1571   Not all vaccines elicit a T-cell-dependent immune response that results in priming of the immune

1572   system and an anamnestic response to further doses. The administration of post-primary doses of

1573   a new candidate vaccine that contains one or more micro-organisms or antigens not previously

1574   used in human vaccines provides an opportunity to assess whether there was successful priming

1575   of the immune system during the primary series, in which case subsequent doses will serve to

1576   boost the immune response (see Subsection 5.2).

1577

1578   When assessing the immune response to additional doses and determining whether or not the

1579   primary series elicited immune memory the following should be taken into account:

1580   a.   Trials in which additional doses are administered may be extension phases of primary series

1581   trials or new trials in subjects with documented vaccine histories.

1582   b. When assessing whether the primary series elicited immune memory the optimal design is to
1583   compare subjects who previously completed a full primary series of the candidate vaccine
1584   with a control group consisting of subjects not previously vaccinated. Control subjects
1585   should be matched for age and for any host or demographic factors that might impact on
1586   their immune response (e.g. they should be resident in similar areas so that any natural
1587   exposure is likely similar).

1588   c. If the new candidate vaccine elicited immune memory in the primary series the immune
1589   response to the additional (i.e. booster) dose should usually be superior to that observed in
1590   individuals who have not been vaccinated against the disease to be prevented based on
1591   comparisons of the geometric mean concentrations or titres of antibody. The percentages
1592   that achieve seropositivity or seroprotection (as defined) may not be different between the
1593   two groups if a single dose of the vaccine is highly immunogenic even in unprimed
1594   individuals.

1595   d. The immune response to the additional dose in primed and unprimed subjects may also be
1596   differentiated based on the rapidity of the rise in antibody levels (faster in primed) and in
1597   terms of antibody avidity (greater in primed).

1598   e. If the immune response as measured by geometric mean antibody concentrations or titres in
1599   the primed group is not superior to that in controls this does not always mean that the
1600   primary series did not elicit immune memory. For example, this may occur when natural
1601   priming has occurred in a substantial proportion in the control group that was not previously
1602   vaccinated against the disease to be prevented, in which case the rapidity of response and
1603   measurements of avidity may also not be distinguishable between groups. If natural priming
1604   has occurred it may or may not be detectable from pre-vaccination antibody levels in the
1605   control group.

1606   f. If an immune memory response is elicited in the primary series it may be possible to achieve
1607   a robust anamnestic response using a much lower dose of an antigenic component compared
1608   to the primary series. A lower boosting dose may also provide a better safety profile (e.g. as
1609   occurs with diphtheria toxoid).

1610   g. For polysaccharide-protein conjugate vaccines that elicit immune memory it may be
1611   informative to compare boosting with the same type of conjugate used for priming with an

1612   alternative conjugate (e.g. to prime with a tetanus toxoid conjugate and boost with a
1613   CRM197 conjugate and *vice versa*).

1614   h. It may also be informative to assess the ability of a candidate vaccine to achieve cross-
1615   priming by using heterologous antigenic components for priming and boosting. This may be
1616   assessed by comparing boosting with the same vaccine used to prime with administration of
1617   a formulation (which may be a licensed vaccine or an unlicensed product manufactured
1618   specifically for the trial) containing a different micro-organism or antigen that is known to
1619   be closely related but not identical to that in the vaccine (e.g. material derived from an
1620   influenza virus of a different clade).

1621   i.   Elicitation of an immune memory response to a vector for an antigen after the first dose(s)
1622   may interfere with or wholly prevent the immune response to the antigen after subsequent
1623   doses (e.g. this may be observed when using adenoviruses capable of infecting humans as
1624   live viral vectors). It is essential to understand whether or not this occurs since it may
1625   necessitate the use of a different vector for the antigen or an entirely different vaccine
1626   construct to deliver subsequent doses.

1627   j.   There are some antigens that not only do not elicit an immune memory response but also
1628   demonstrate hypo-responsiveness to further doses. The best known examples are some of
1629   the unconjugated meningococcal and pneumococcal polysaccharides (17, 18). In the past
1630   these were sometimes administered to assess whether corresponding conjugated
1631   polysaccharides had elicited immune memory in the primary series based on the premise
1632   that this would better mimic the immune response to natural exposure compared to
1633   administration of a further dose of the conjugate. This practice is not recommended since it
1634   is possible that a dose of unconjugated polysaccharide could result in blunted immune
1635   responses to further doses of the conjugate.

1636

1637   5.6.2   Using immunogenicity data to predict efficacy

1638

1639   Immunogenicity data may be used to predict efficacy with varying levels of confidence when:

1640   a.   There is a well-established ICP that can be used to interpret the immune responses to a
1641   specific antigenic component (see Subsections 5.4 and 5.5). Comparative
1642   immunogenicity trials are recommended since they provide a control for interpretation of

1643   any unexpected findings and for safety. Depending on the objectives the comparator may

1644   be the same vaccine used as currently licensed or a licensed vaccine that has been widely

1645   used with no known problems regarding its effectiveness and which contains all or as

1646   many as possible of the same antigenic components as the candidate vaccine.

1647   b.   It is possible to use immune responses to bridge to estimates of vaccine efficacy obtained

1648   from well-designed clinical trials (i.e. to conduct bridging trials); see Subsection 5.6.2.1.

1649   c.   There is no ICP nor is it possible to bridge to a prior demonstration of efficacy; see

1650   Subsection 5.6.2.2.

1651

1652   *5.6.2.1 Bridging to efficacy data*

1653

1654   There are two main situations to consider. In both cases comparative immunogenicity trials

1655   designed to demonstrate non-inferiority are recommended. The choice of comparator is a critical

1656   factor for interpretation of the results.

1657

1658   i) Modifying the use of the same vaccine for which efficacy has been estimated

1659

1660   As described in Section 6, vaccine efficacy trials are usually conducted in specific target

1661   populations, characterised by factors such as age, region (which may define endemicity for some

1662   infectious diseases) and health status, using the intended final vaccine posology. Before or after

1663   initial licensure trials may be conducted with the aim of extending the use of the vaccine to other

1664   populations and/or to support alternative posologies.

1665

1666   When a different age group or posology is proposed or when extending use from

1667   immunocompetent to immunocompromised subjects it is usually very clear that a bridging trial is

1668   necessary. Whether or not a bridging trial is necessary to support use in regions other than where

1669   the estimate of efficacy was obtained requires careful consideration. Such trials should be

1670   required for licensure only if there are compelling scientific reasons to expect that the immune

1671   response to the vaccine, and therefore its efficacy, could be significantly different due to host

1672   factors (such as common underlying conditions that may affect immune responses) and/or

1673   geographical factors (such as distributions of subtypes of organisms, levels of natural exposure

1674   and for trials in infants the possibility that high levels of maternal antibody could interfere with

1675   responses to the primary series).

1676

1677   The usual trial design involves a direct comparison between the new population and/or posology

1678   and a control group in which subjects representative of the efficacy trial population receive the

1679   previously studied posology. It may also be acceptable that an indirect comparison is made with

1680   the immunogenicity data that were obtained during the efficacy trial, in which case the vaccine

1681   formulation and assay used should be the same as used in the efficacy trial whenever possible.

1682

1683   a.   If the vaccine used in the efficacy trial is no longer available the comparator should be as

1684   similar as possible to the original. Over time, it may be that the only bridge back to the

1685   efficacy data is via a comparison with a licensed vaccine that was itself licensed based on a

1686   bridging efficacy trial. As the number of bridging steps that has occurred between the

1687   original efficacy data and the licensed comparator vaccine increases, so the reliance that may

1688   be placed on a demonstration of non-inferiority to predict efficacy is weakened. This

1689   consideration also applies when the vaccine for which efficacy was estimated has been

1690   extended based on bridging efficacy for the shared subtypes (e.g. when additional subtypes

1691   have been added) and the extended vaccine has replaced the original vaccine in the market.

1692   b.   If the assay has changed and has not been or cannot be directly compared to the original

1693   assay used during the efficacy trial it may be possible to re-assay stored sera collected

1694   during the prior efficacy trial in parallel with the sera from the new trial population.

1695

1696   If it remains unknown which immunological parameter best correlates with efficacy it is

1697   preferable that the primary comparison between vaccines is based on functional antibody

1698   whenever this is feasible.

1699

1700   ii) Inferring the efficacy of a new candidate vaccine

1701

1702   In this case the main evidence of efficacy for licensure comes from one or more bridging

1703   efficacy trials. The same considerations regarding primary comparison, choice of comparative

1704   vaccine and assay apply as described above.

1705

1706   If the new candidate vaccine is an extended version of a licensed vaccine and/or it contains

1707   additional subtypes of an organism not included in a licensed vaccine the interpretation of the

1708   immune responses to the unshared types in a comparative immunogenicity trial is not

1709   straightforward. Approaches that could be considered include comparing immune responses to

1710   each additional subtype with a mean response across all subtypes or the lowest response to an

1711   individual subtype included in the vaccine for which efficacy was demonstrated. Both of these

1712   approaches may provide a route to licensure but the limitations of these comparisons to predict

1713   efficacy should be taken into account when considering the overall benefit-risk relationship for

1714   the new vaccine and the collection of effectiveness data in the post-licensure period is

1715   recommended.

1716

1717   *5.6.2.2 Other approaches*

1718

1719   When there is no ICP nor is it possible to bridge to a prior demonstration of efficacy licensing a

1720   new candidate vaccine is problematical. This situation is most likely to apply to new vaccines

1721   against rare infectious diseases such as some viral haemorrhagic fevers, for which outbreaks do

1722   not occur in substantial numbers of persons or are of short durations, and some micro-organisms

1723   that could be used for bioterrorism purposes. Another important situation is the development of

1724   influenza vaccines against potential pandemic strains.

1725

1726   Approaches may include establishing a nonclinical model of efficacy that is thought to be

1727   relevant to the human infection and identifying which immunological parameter best correlates

1728   with protection (and if possible a putative ICP), trials of natural infection and protection against

1729   further disease and any passive protection data that may be available from nonclinical or clinical

1730   trials. If a vaccine has already been licensed based on evidence derived from one of these

1731   approaches any changes to the vaccine usage is subject to the same issues.

1732

1733   Although licensure of vaccines based on these approaches means that it is not likely to be

1734   possible to achieve a high level of confidence in the level of efficacy in humans, having available

1735   vaccines that have already been subjected to a full review of quality and nonclinical data as well

1736   as at least some safety and immunogenicity data in humans does mean that they could be ready

1737   for rapid use in an emergency situation. Nevertheless, for these products it is particularly

1738   essential that protocols are developed in advance of any such emergency so that adequate data

1739   can be collected to assess efficacy/effectiveness whenever the opportunity arises.

1740

1741   5.6.3   Co-administration trials

1742

1743   Comparative immunogenicity trials intended to support co-administration of a vaccine with one

1744   or more other vaccines (i.e. administration at the same time but using different limbs for

1745   injection or multiple routes of administration) should demonstrate non-inferiority for immune

1746   responses to each of the co-administered antigenic components (see Subsection 5.5.3). The

1747   immunological parameters applied to each comparison may differ depending on vaccine content.

1748   It should be noted that co-administration may also enhance the immune response to certain

1749   antigens but so far there have not been instances in which this has been regarded as a cause for

1750   concern since the safety of co-administration has been acceptable.

1751

1752   When there are multiple licensed products containing the same antigenic components that could

1753   be co-administered with the vaccine under trial (e.g. combination vaccines intended for the

1754   routine infant primary immunization series) it is not feasible nor should it be necessary to

1755   conduct trials with each licensed product. The vaccine(s) chosen for trial should be as

1756   representative as possible of the range of licensed products.

1757

1758   An exception arises when there are several different types of polysaccharide-protein conjugate

1759   vaccines available that may be co-administered with the vaccine under trial. This is usually only

1760   an issue when the vaccine under trial contains protein that is the same as, or similar to, that in

1761   available conjugates. In this case it is important to appreciate that the results obtained with any

1762   one conjugate may not be applicable to other types of conjugate (e.g. lack of immune

1763   interference with a tetanus toxoid conjugate does not rule out that this could occur with a

1764   CRM197 conjugate).

1765

1766   If multiple doses of the co-administered vaccines are needed it is usual that the comparison

1767   between groups is made only after completion of all doses. The schedule at which the vaccines

1768   are co-administered may also be an issue if there are several possible alternatives (e.g. as applies

1769   to vaccines for the primary immunization series in infants and for vaccines against hepatitis A

1770   and B). Consideration may be given to using a schedule that is most likely to detect an effect if

1771   there is one.

1772

1773   These trials usually have the following designs:

1774   • Randomized parallel group trials in which different groups of subjects receive the vaccine

1775   under trial alone, the vaccine intended for co-administration and both together. If there is

1776   more than one additional vaccine that may be co-administered at the same time additional

1777   groups should receive each of these vaccines alone. In this case it is useful for interpretation

1778   of any observed effects to also add groups that each receives the vaccine under trial with one

1779   of the additional vaccines as well as a group that receives them all together.

1780   • Randomized trials that use a staggered administration design. This approach is necessary

1781   when it is not possible to withhold any antigenic components to be co-administered (e.g.

1782   during the infant primary schedule). In these trials one group receives the co-administered

1783   vaccines at a chosen schedule while the control group receives either the vaccine under trial

1784   or the vaccine to be co-administered at the same schedule as the test group and the other

1785   vaccine is given one month later (or other appropriate interval). For completeness, an

1786   additional control group may be used in which the order of staggered vaccine

1787   administrations is reversed. The final dose and sampling occurs at least one month later

1788   compared to the co-administration group which, in infants, could have some impact on the

1789   magnitude of the immune response.

1790

1791   5.6.4   Immunization of pregnant women

1792

1793   *5.6.4.1 Aims of immunization during pregnancy*

1794

1795   Immunization during pregnancy may be undertaken with the primary aim to:

1796

1797   a.   Protect the mother. For any candidate vaccine under development for prevention of an

1798   infectious disease in which the target population includes adolescents and adults there

1799   is a need to consider the importance of generating data in pregnant women to support

1800   its use. The considerations should take into account the nature of the vaccine construct

1801   (e.g. does the vaccine contain a live organism that is replication-competent), whether

1802   pregnant women can reasonably avoid exposure to an infectious agent (e.g. by not

1803   travelling) and whether they may have the same risk of exposure but a greater risk of

1804   experiencing severe disease compared to non-pregnant women of the same age.

1805

1806   b.   Protect the infant from an infectious disease for a limited period after birth by means of

1807   trans-placental transfer of maternal antibody. In this case there may be a potential benefit

1808   to the mother (e.g. influenza, acellular pertussis) or no or negligible potential benefit to

1809   the mother (e.g. respiratory syncytial virus and Streptococcus Group B).

1810

1811   *5.6.4.2 Dose-finding in pregnancy*

1812

1813   For new candidate vaccines intended for use in pregnant women and for licensed vaccines not

1814   authorized for use in pregnancy the first clinical trials to support this use should be conducted in

1815   non-pregnant adults, including or consisting only of women of child-bearing age (19). Once

1816   there are adequate relevant nonclinical data with satisfactory findings and some data on immune

1817   responses in non-pregnant women data should be obtained from pregnant women, covering a

1818   representative age range, so that the effects of pregnancy on the immune response can be

1819   evaluated. The doses tested initially in pregnant women should be based on the non-pregnant

1820   adult data but may need to be adjusted (in terms of antigen dose or dose regimen) after review of

1821   results from initial trials due to the effects of pregnancy on the immune system. Additional

1822   considerations for dose-finding when the aim is primarily to protect the infant are provided in

1823   Subsection 5.6.4.3.

1824

1825   In all trials conducted in pregnant women adequate mechanisms should be in place to document

1826   the outcome of the pregnancy, including the duration of gestation at time of delivery, the

1827   condition of the infant at birth and the presence of any congenital conditions. Depending on the

1828   type of vaccine, it may also be considered appropriate to collect information on developmental

1829   milestones at least during the first few years of life.

1830

1831   *5.6.4.3 Passive protection of infants*

1832

1833   Transfer of IgG across the placenta does not occur to any extent until the third trimester. If the

1834   vaccine is not expected to benefit the mother, then administration in the third trimester should be

1835   studied. If the aim is also to provide some benefit to the mother, administration earlier in

1836   pregnancy should be studied. In this case, since the immune response to vaccination changes as

1837   pregnancy progresses and women do not always access healthcare early on, the effect of dosing

1838   at different times during pregnancy should be evaluated.

1839

1840   If it is expected that a substantial proportion of adults are likely to already have evidence of

1841   humoral immunity against the infectious disease to be prevented so that the aim of vaccination

1842   during pregnancy is to increase the amount of antibody transferred to the fetus, the trials in

1843   pregnant women may need to include exploration of doses and, if more than one dose is needed,

1844   dose intervals in seropositive as well as seronegative adults.

1845

1846   When the aim is primarily to protect the infant, dose-finding trials in pregnant women should

1847   include measurement of antibody levels in cord blood samples taken at delivery. The number of

1848   samples obtained should be sufficient to provide an estimate of inter-individual variability. In

1849   addition, efforts should be made to collect cord blood data that cover a range of times between

1850   maternal vaccination and delivery, that allow for evaluation of the effects of unexpected early

1851   delivery and which measure the impact of placental dysfunction (e.g. based on infants of low

1852   birth weight for their gestational age). The cord blood levels in infants born to vaccinated

1853   mothers who receive the final selected vaccine posology should be clearly superior to that in

1854   infants born to mothers who were not vaccinated, regardless of the pre-vaccination serostatus of

1855   the mothers. Secondary analyses could examine whether this finding also applies within subsets

1856   of mothers who were seronegative or seropositive prior to vaccination.

1857

1858   The duration of detectable maternal antibody in infants should be documented. To avoid multiple

1859   bleeds in individual infants this may be documented by randomization of mothers such that their

1860   infants are sampled only once or a few times at staggered defined intervals so that the total data

1861   are used to describe the antibody decay curve. These data are particularly important when it is

1862   planned that passive protection via maternal antibody will be followed by active vaccination of

1863   infants against the same antigen(s).

1864

1865   If there is an immune correlate of protection established for the infectious disease to be

1866   prevented the aim of the immunogenicity trials should be to identify a maternal vaccination

1867   regimen that results in cord blood levels that exceed the ICP in a high proportion of new born

1868   infants. If there is no ICP, an efficacy trial in infants is usually needed (see Section 6).

1869

1870   5.6.5   Changes to the manufacturing process

1871

1872   Changes made to the product composition (e.g. addition of, removal of, or change in adjuvants or

1873   preservatives) or manufacture (changes to process, site or scale) during the pre-licensure clinical

1874   development program or after licensure do not always need to be supported by comparative

1875   clinical immunogenicity trials between the prior and the newer products.

1876

1877   For example, it is common that the scale of manufacture changes during the pre-licensure

1878   development program but this step alone would not be expected to have a clinically significant

1879   effect in the absence of other changes. In addition, the later confirmatory trials usually use

1880   product from final scale process. Also, any clinical effects of changes to the manufacturing

1881   process during the pre-licensure program may be evident from the results of sequential trials in

1882   similar populations or may not matter if the pivotal immunogenicity and/or efficacy trials use

1883   vaccine made using the final process. If this is not the case, and for all changes that are made

1884   post-licensure, consideration must be given to whether a clinical trial to compare vaccine

1885   manufactured using the prior and new processes is required. This decision must be taken on a

1886   case by case basis after a full evaluation of the in-vitro and any nonclinical in-vivo data

1887   describing and supporting the change. It is usually acceptable that a single lot of vaccine made

1888   using each process is sufficient for the comparison.

1889

1890   In the post-licensure period there may be many changes to the manufacturing process over time.

1891   Over time it is possible that each one of these was considered too minor to merit conduct of a

1892   clinical trial but the product that results from multiple minor changes could be substantially

1893   different to that which was initially licensed. When considering the potential impact of what

1894   seems to be a relatively minor change to the production process that, not alone, would merit a

1895   clinical trial it may be important to consider the full history of changes that have been allowed

1896   without clinical data and to consider whether the sum total of changes could have a clinical

1897   impact. In this situation, when many years have passed, a clinical trial of the current compared to

1898   the original licensed vaccine will not be possible. If disease surveillance suggests that there could

1899   be a problem with vaccine effectiveness, a clinical trial that compares the current vaccine with

1900   another licensed vaccine for which there is a lot of clinical experience may be considered useful.

1901

1902   5.6.6   Lot-to-lot consistency trials

1903

1904   Some NRAs request lot-to-lot consistency trials during the pre-licensure clinical development

1905   program for all new candidate vaccines. Where these trials are not requested as a routine they

1906   may be considered for certain types of vaccines where there is inherent variability in

1907   manufacture of the product. If requested, the rationale for conducting the trial and the objectives

1908   should be very clear.

1909

1910   In these trials the usual expectation is that 95% confidence interval around each pairwise

1911   comparison of the post-vaccination geometric mean concentrations/titres falls within pre-defined

1912   limits. The clinical implications of results that show that one or more comparisons do or do not

1913   meet the pre-defined criteria set around the ratios are unknown and interpretation of the results

1914   should take into account all of the available immune response data.

1915

1916 **6.   Efficacy and effectiveness**

1917

1918 | This Section considers: |
| :--- |
| ➢   Approaches to determination of efficacy |
| ➢   Human challenge trials |
| ➢   Preliminary and confirmatory (pivotal) efficacy trials |
| ➢   Design and conduct of efficacy trials, including control groups |
| ➢   Approaches to determination of vaccine effectiveness |

1919

1920

1921

1922

1923

1924

1925 **6.1   Approaches to determination of efficacy**

1926

1927 6.1.1   Human challenge trials

1928

1929 In some settings it may be useful and appropriate to obtain an initial assessment of vaccine

1930 efficacy from human challenge trials in which vaccinees are deliberately exposed to an infectious

1931 agent in a controlled setting. Human challenge trials are not always feasible or appropriate, as

1932 discussed in Appendix 1. When they can be performed, human challenge trials have potential to

1933 streamline and so accelerate vaccine development. They may be of particular use:

1934 o   When there is no appropriate nonclinical model (e.g. when a candidate vaccine is

1935   intended to protect against an infectious disease that is confined to humans).

1936 o   When there is no known immunological correlate of protection.

1937 o   When vaccine efficacy trials (as described above and in detail in the sections that follow)

1938   are not feasible.

1939

1940 Like all model systems human challenge trials have limitations in terms of their relevance to

1941 natural infection and their ability to predict protection under very variable circumstances (e.g. in

1942 terms of time elapsed between vaccination and exposure to a pathogen and the impact of

1943 pathogen dose on development of clinically apparent infection). Nevertheless, they may suffice

1944 to rule out vaccines or doses that seem unlikely to have useful protective efficacy and to select

1945 the most promising formulations and regimens for further trial. See Appendix 1 for further

1946 information.

1947

1948   Later on in the clinical development program, usually after safety and immunogenicity trials

1949   have identified one or more potentially effective vaccination regimens for further evaluation,

1950   vaccine efficacy may be assessed against naturally acquired infectious disease.

1951

1952   6.1.2   Preliminary efficacy trials

1953

1954   Based on the available safety and immunogenicity data it may be considered appropriate to

1955   evaluate vaccine efficacy initially in dose-finding trials (which may include different doses

1956   and/or different numbers of doses or dose intervals) or in small-scale trials that evaluate a single

1957   vaccination regimen before proceeding to confirmatory (pivotal) trials.

1958

1959   Whenever possible the general features of these trials (such as case definitions and method of

1960   case ascertainment) should resemble those expected to be applied in confirmatory trials of

1961   efficacy. However, it is sometimes the case that preliminary efficacy trials are used to inform the

1962   final design of confirmatory efficacy trials. For example:

1963   o   By applying various case definitions the results may be used to identify or refine the most

1964   appropriate case definition for confirmatory trials.

1965   o   By exploring efficacy in specific subgroups in preliminary trials the confirmatory trials

1966   may be designed to ensure adequate numbers of cases per subgroup of interest.

1967   o   The method of case ascertainment used may be assessed for feasibility in larger trials

1968   with a greater number of, and more geographically widespread, trial sites.

1969   o   The immunogenicity and efficacy data may be used to support a provisional assessment

1970   of potential correlates of protection.

1971

1972   If the candidate vaccine is intended to prevent a severe and/or life-threatening infectious disease

1973   for which there is no, or at least no very satisfactory, vaccine already available, individual NRAs

1974   may agree to accept an initial application for licensure based on one or more preliminary efficacy

1975   trial or trials. In these cases it is essential that sponsors and NRAs should discuss and agree the

1976   main features of the design of the trials before initiation, including the sample size, so that,

1977   subject to promising results, the data may be considered robust and sufficient.

1978
1979   The availability of a vaccine licensed on the basis of preliminary efficacy data has potentially
1980   important implications for the acceptability and feasibility of initiating or completing
1981   confirmatory efficacy trials that include a control group that does not receive active vaccination.
1982   These issues should be discussed between NRAs and sponsors so that expectations for provision
1983   of confirmatory efficacy data are agreed prior to the start of any trials that could potentially
1984   support initial licensure.
1985
1986   6.1.3   Confirmatory (pivotal) efficacy trials
1987
1988   A single confirmatory vaccine efficacy trial or more than one trial may be conducted, depending
1989   on considerations described in Subsection 6.2 below.
1990
1991   In pivotal efficacy trials, the primary objective is usually to estimate vaccine efficacy over a pre-
1992   defined time frame after completion of the primary vaccination schedule, which may comprise
1993   one or more doses. Confirmatory trials may evaluate a single or more than one vaccination
1994   regimen and may or may not include evaluations of efficacy before and after booster doses. As
1995   applicable to the individual candidate vaccine, a range of secondary efficacy objectives may be
1996   defined although the trial will not be formally powered for these analyses.
1997
1998   **6.2   Design and conduct of efficacy trials**
1999
2000   The protective efficacy of a vaccine against a specific infectious disease is usually defined as the
2001   reduction in the chance of developing the disease after vaccination relative to the chance when
2002   not vaccinated as determined in a prospective randomized controlled trial. Vaccine efficacy (VE)
2003   is therefore derived from the proportionate reduction in disease attack rate (AR) between the
2004   control group that did not receive vaccination against the infectious disease potentially
2005   preventable by the candidate vaccine (ARU) and the vaccinated (ARV) group(s). VE can be
2006   calculated from the relative risk (RR) of disease among the vaccinated group as (ARU-
2007   ARV/ARU) x 100 and (1-RR) x 100.
2008

2009   Much less often, vaccine efficacy may be determined in a prospective randomized trial in which

2010   the efficacy of the candidate vaccine is compared to that of a licensed vaccine intended to

2011   prevent the same infectious disease.

2012

2013   The following sections consider issues that apply to both types of trial, including some specific

2014   trial designs that may be considered along with some issues for analysis of the data. Details of

2015   statistical methodologies are beyond the scope of this guidance and only broad principles are

2016   described.

2017

2018   6.2.1   Selection of trial sites

2019

2020   Vaccine efficacy trials require the presence of a sufficient burden of clinical disease to enable

2021   estimates to be obtained from feasible numbers of subjects and within a reasonable timeframe.

2022   The infectious disease to be prevented may occur at sufficiently high rates to enable efficacy

2023   trials to be conducted only in confined areas. Even when the disease to be prevented is more

2024   widespread, it may be necessary to confine efficacy trials to specific affected areas for reasons

2025   that may include feasibility of dealing with multiple NRAs and ethics committees, need to ensure

2026   adequacy of monitoring and desire to accumulate representative numbers of cases due to specific

2027   serotypes or subtypes.

2028

2029   Sponsors may have to conduct feasibility assessments to accurately ascertain clinical disease

2030   rates in various age subgroups of populations before selecting trial sites. Any nationally-

2031   recommended non-vaccine-related preventive measures that are in place (e.g. prophylactic drug

2032   therapy in high risk individuals or settings, use of insect repellents and bed nets) should be

2033   identified and the trial should be conducted against a background of these additional

2034   interventions.

2035

2036   Trial sites need to be sufficiently accessible to allow regular monitoring visits. Sponsors may

2037   have to engage in site capacity building exercises prior to trial initiation, including training of

2038   study personnel, and may need to provide essential infrastructure to support the trial (e.g. to

2039   ensure that there are adequate blood collection and processing facilities, refrigeration facilities

2040   suitable for the vaccine and/or sera, competent laboratories, data handling capacity and

2041   communication methods to allow electronic randomization schemes, rapid reporting of safety

2042   data or other trial issues to the sponsor).

2043

2044   6.2.2   Candidate (test) vaccine group(s)

2045

2046   If previous data do not support selection of a single dose or regimen of the candidate vaccine for

2047   assessment of efficacy, trials may include one or more groups in which subjects receive the

2048   candidate vaccine (e.g. more than one dose or schedule may be evaluated). In some instances one

2049   or more placebo doses may need to be interspersed with candidate vaccine doses to enable

2050   matching of all regimens under trial in a double-blind design (e.g. if 2 or 3 doses of the candidate

2051   vaccine are to be compared with the control group).

2052

2053   6.2.3   Control (reference) group(s)

2054

2055   Control groups comprise all subjects who do not receive the candidate vaccine. Usually only one

2056   control group is enrolled in any one trial. On occasion, it may be considered important to include

2057   more than one of the possible types of control groups that are discussed below.

2058

2059   *6.2.3.1 Control groups not vaccinated against the infectious disease to be prevented*

2060

2061   In most cases vaccine efficacy trials employ a control group that does not receive vaccination

2062   against the disease to be prevented by the candidate vaccine. In double-blind trials the control

2063   group may receive:

2064

2065   o   A true placebo (i.e. material without any pharmacological activity). This has the advantage

2066   of providing safety data against a control that has no pharmacologically active components.

2067   However, the use of an injectable placebo may not be acceptable to one or more of NRAs,

2068   ethics committees, investigators, trial subjects or their parents/guardians at least in some age

2069   groups (e.g. there may be particular objections raised against true placebo injections in

2070 infants). In contrast, there is usually no objection to use of a true placebo when the
2071 candidate vaccine is administered orally or by nasal installation.

2072

2073 o If a true placebo is not acceptable to one or more of the above interested parties the control
2074 group may receive a licensed vaccine that has no effect on the infectious disease to be
2075 prevented by the candidate vaccine but may have some benefit for recipients. In some cases
2076 both licensed vaccine and placebo doses may have to be used to match the candidate vaccine
2077 regimen. Due to distinctive visual characteristics or markings on presentations of licensed
2078 vaccines it may not be possible to wholly maintain double-blind conditions. In this case
2079 those site staff who prepare and/or administer trial vaccines should not otherwise be
2080 involved in trial conduct. Difficulties may also arise if the candidate vaccine is injected in a
2081 different fashion (i.e. subcutaneous, intradermal, intramuscular) to the only suitable licensed
2082 vaccine(s) that could be given to controls. In this case it may be possible to screen the
2083 administration site to prevent vaccine recipients and care-givers observing the specific
2084 method of injection.

2085

2086 o A licensed vaccine that has an effect on the infectious disease to be prevented only when due
2087 to some of the total serotypes or subtypes in the candidate vaccine. In this case the licensed
2088 vaccine provides a control group that is not vaccinated against the additional types in the
2089 candidate vaccine (i.e. unshared types).

2090

2091 If there are major objections to use of placebo injections but there is no potentially beneficial
2092 licensed vaccine that would be suitable for the target age group, the control group may be
2093 randomized to receive no vaccine. This is an undesirable situation and should be regarded as a
2094 last resort since it precludes the use of any form of blinding of trial personnel or participants
2095 (including care-givers).

2096

2097 *6.2.3.2 Control groups vaccinated against the infectious disease to be prevented*

2098

2099 In this case the control group receives a vaccine that is already licensed to prevent the same
2100 infectious disease as the candidate vaccine. This approach is used when it is not acceptable to

2101   employ a control group that is not vaccinated against the infectious disease to be prevented

2102   because there is at least one available licensed efficacious vaccine that is recommended for use

2103   in areas where the disease occurs.

2104

2105   On occasion, the control group receives a vaccine that may prevent the same infectious disease

2106   as the candidate vaccine but only when due to some of the total serotypes or subtypes in the

2107   candidate vaccine. Therefore the control group is vaccinated against the shared types but is not

2108   vaccinated against the unshared types.

2109

2110   If there is more than one licensed vaccine that could be used it is important that selection of the

2111   control vaccine takes into account the available evidence supporting its efficacy and, if relevant,

2112   whether it appears to have similar efficacy against all serotypes or subtypes of the pathogen

2113   involved. It is also necessary to discuss the choice of comparator with NRAs in countries where

2114   the sponsor will seek a licence for the candidate vaccine to ascertain the acceptability of an

2115   estimate of relative efficacy against a product that may be unlicensed or, at least, not the product

2116   in widespread use. This is especially important if one multi-country pivotal trial will be

2117   conducted, in which case the same vaccine should be given to the control group at all trial sites.

2118   If it is not possible to use the same control vaccine in all regions where efficacy is to be

2119   evaluated consideration should be given to conducting different efficacy trials with different

2120   vaccines used in the control groups.

2121

2122   On occasion, there may be at least one licensed vaccine available in one or more countries to

2123   prevent the same infectious disease as the candidate vaccine but there may be other countries in

2124   which the disease of interest occurs in which:

2125   o   No such vaccine is yet licensed and/or

2126   o   No such vaccine is included in the routine immunization schedule and/or

2127   o   There are sound reasons to consider that no licensed vaccine is likely to provide useful

2128   efficacy (e.g. because the licensed vaccine does not cover or is known/expected to have

2129   poor efficacy against the serotypes or subtypes that are most prevalent in a specific

2130   region).

2131   In these situations, after careful consideration by all interested parties (i.e. sponsor, NRAs, ethics

2132   committees, local public health authorities and investigators) it may be deemed appropriate to

2133   use a control group that is not vaccinated against the disease to be prevented.

2134

2135   6.2.4   Trial designs

2136

2137   *6.2.4.1 Randomization*

2138

2139   The unit of randomization is most often the individual. Alternatives include the household or the

2140   cluster under trial (e.g. a school population or a local community). Randomization of groups or

2141   clusters rather than individuals may be preferred:

2142   o   When a vaccination program is to be conducted in a geographical area or community

2143   o   When it is logistically easier to administer the vaccine to groups than to individuals

2144   o   When vaccination is anticipated to reduce transmission of the infectious agent

2145

2146   *6.2.4.2 Types of trial design*

2147

2148   The absolute protective efficacy of a vaccine is most commonly assessed in prospective

2149   randomized trials that compare rates of clinically apparent disease (e.g. an acute clinical illness)

2150   or established infection (e.g. chronic infection that is known to predispose to serious clinical

2151   disease) between a candidate vaccine group and a control group.

2152

2153   The simplest design involves randomization of equal numbers of subjects to each of the

2154   candidate vaccine group and the control group (i.e. 1:1). In trials that employ a control group that

2155   is not vaccinated against the disease to be prevented but there are clinical data already available

2156   to strongly support the likely efficacy of a candidate vaccine, it may be appropriate (subject to

2157   statistical considerations and an assessment of the impact on the total trial sample size) to use

2158   unbalanced randomization to reduce the chance that subjects will be randomized to the control

2159   group (e.g. 2:1 or 3:1 so that the majority of trial subjects receive the candidate vaccine).

2160

2161   Trials may plan to follow up trial subjects for the primary efficacy endpoint for a fixed period of

2162   time after the last dose of the primary series. The time at which the primary analysis is conducted

2163   is based both on the anticipated rate of occurrence of the primary efficacy endpoint in the control

2164   group and the feasibility of retaining subjects on trial for prolonged periods. Alternatively, based

2165   on anticipated rates of the primary efficacy endpoint in the control group and an expected or

2166   minimum desirable level of efficacy of the candidate vaccine, a case-driven approach may be

2167   taken. In this design the primary analysis is conducted once a pre-specified number of total cases

2168   (i.e. in a double-blind setting based on the anticipated numbers in test and control group required

2169   to demonstrate the projected vaccine effect) has been detected.

2170

2171   Alternative designs that allow for a comparison with a control group that is not vaccinated

2172   against the disease to be prevented, at least in the short-term, may include (but are not limited to)

2173   the following:

2174

2175   i) In a step-wedge trial the candidate vaccine is administered to pre-defined groups in a

2176   sequential fashion. Each pre-defined group is a unit of randomization. These may be

2177   geographical groups or groups defined by host factors (e.g. age) or other factors (e.g. attendance

2178   at a specific school or resident within a specific healthcare catchment area). Such a design may

2179   be chosen when there is good reason to anticipate that the vaccine will do more good than harm

2180   (affecting the equipoise associated with randomization to a control group that is not vaccinated

2181   against the disease to be prevented) and/or when it is impossible to deliver the intervention

2182   simultaneously to all trial participants. This design may also be used to evaluate vaccine

2183   effectiveness (see Subsection 6.3).

2184

2185   ii) In a ring vaccination trial the direct contacts of a case, and sometimes secondary contacts,

2186   may be randomized to vaccine or control or may be randomized to receive immediate

2187   vaccination or vaccination after a delay period (20). This type of pre-exposure cohort trial

2188   usually requires smaller sample sizes than prospective randomized controlled trials. The trial

2189   design assumes that there is an equal chance of vaccinees and non-vaccinees being infected and

2190   developing the infectious disease as a result of contact with an index case.

2191

2192   These types of trials may be particularly applicable when the infectious disease to be prevented

2193   is associated with a relatively high incidence of secondary cases in susceptible populations.

2194 Therefore the use of this trial design requires prior knowledge of the infectivity of the infectious

2195 agent and proportion of infections that are clinically apparent as well as the general susceptibility

2196 of the trial population.

2197

2198 The follow-up period for subjects after contact with the index case should cover the upper limit

2199 of the incubation period, taking into account the period during which the index cases were

2200 infectious and the contact period. The inclusion period for new cases and controls and their

2201 contacts should be set at a maximum of six months following the detection of the first case.

2202 Inclusion over a longer period may introduce bias in favour of vaccine efficacy, because the

2203 exposure to the infecting pathogen and thus the risk of infection will be reduced in the

2204 vaccinated groups or clusters compared with that in groups or clusters that are not vaccinated

2205 against the disease to be prevented.

2206

2207 iii) There are some situations in which the vaccine is not intended, or at least not primarily

2208 intended, to protect the vaccinees themselves against a clinically apparent infectious disease. The

2209 most common example is the vaccination of mothers during the last trimester of pregnancy,

2210 when IgG most efficiently crosses the placenta, to protect the infant during the early months of

2211 life (see Subsection 5.6.4). This strategy may or may not be followed by active immunization of

2212 infants, provided that suitable vaccines exist. If vaccine efficacy is measured in infants the unit

2213 of randomization is the mother.

2214

2215 6.2.5 Clinical endpoints

2216

2217 Preliminary efficacy trials may have an objective to identify the primary and/or secondary

2218 endpoints for confirmatory trials. Therefore the primary endpoint in preliminary efficacy trials

2219 may be different to that selected for confirmatory efficacy trials.

2220

2221 *6.2.5.1 Primary endpoints*

2222

2223 In most instances, the focus of vaccine efficacy trials is on the prevention of clinically apparent

2224 infections that fit the primary case definition based on clinical and laboratory criteria. The

2225   primary endpoint is also usually defined by the timeframe in which the case occurred in relation

2226   to dosing.

2227

2228   If an organism is able to cause a range of infections (e.g. from life-threatening invasive

2229   infections to common infections that are not serious if adequately treated), the primary endpoint

2230   in any one trial should be carefully selected in accordance with the proposed indication(s).

2231

2232   A candidate vaccine may contain antigens derived from one or several types (serotypes, subtypes

2233   or genotypes) of the same species. It is also possible that there may be some potential for cross-

2234   protection against types not included in the vaccine (e.g. as observed with rotavirus vaccines and

2235   human papilloma virus vaccines). For these types of vaccines it is usual that the primary

2236   endpoint comprises cases due to any of the types included in the vaccine and the trial is powered

2237   for this composite endpoint. It is not usually possible to power the trial to formally assess

2238   efficacy against individual types in the vaccine or to assess cross-protection against types not in

2239   the vaccine.

2240

2241   Alternative primary endpoints may include:

2242   o Clinical manifestations of latent infection (e.g. herpes zoster)

2243   o Established chronic infections that may be asymptomatic but predispose to infection-related

2244   disease later in life (e.g. chronic hepatitis B infection; persistent infection with HPV)

2245   o Other markers that predict progression to clinically apparent disease (e.g. histological changes

2246   that are established pre-cursors of malignant neoplasia)

2247

2248   *6.2.5.2 Secondary endpoints*

2249

2250   As applicable to the individual candidate vaccine and the definition of the primary endpoint,

2251   important secondary endpoints may include:

2252   •   Cases that occur after each dose, when the vaccine schedule includes multiple doses

2253   and/or a booster

2254   •   Cases due to each of the individual types of the species included in the vaccine

2255 • Cases due to the species (i.e. regardless of whether caused by types that are and are not

2256 included in the candidate vaccine)

2257 • Cases due to non-vaccine types

2258 • Cases according to host factors (e.g. age, region)

2259 • Cases meeting various criteria reflecting disease severity

2260 • Duration and/or severity of the illness, which may include clinical (e.g. duration of

2261 fever or rash) and laboratory measurements (e.g. duration of shedding)

2262

2263 In accordance with Subsection 5.4, one important secondary objective should be to attempt to

2264 identify a correlate of protection or, at least, a threshold value.

2265

2266 There are no vaccines indicated for the prevention or interruption of carriage, implying an effect

2267 on transmission. In addition, there are no vaccines indicated for prevention of transmission.

2268 Eradication of carriage and/or reduction in disease transmission that is not directly linked to

2269 and/or accompanied by a clinical benefit of vaccination to the individual is not usually

2270 considered to be sufficient to support licensure. Sponsors contemplating trials in which these are

2271 primary endpoints are advised to consult widely with NRAs.

2272

2273 6.2.6   Case definition

2274

2275 As part of the pre-defined primary efficacy endpoint the protocol should describe the clinical and

2276 laboratory criteria that must be met to define a case.

2277 o If a case is a clinically apparent infection it is essential that the definition includes core

2278 clinical features. It should also list acceptable sampling and laboratory processing

2279 methods to confirm the presence of the target pathogen and/or to detect infection by

2280 serological findings.

2281 o If the endpoint is the result of infection (e.g. evidence of persistence of infection or a

2282 histological change) then details of sampling (frequency and method) and grading (if

2283 applicable) should be included.

2284

2285 Adequate case definitions should also be provided for secondary endpoints. For example, if the

2286   primary endpoint is all clinically apparent infections due to the types in the vaccine the

2287   secondary analyses may focus on cases that meet specific criteria for severity, cases that require

2288   medical contact or hospitalization and cases that are due to organism types not actually included

2289   in the vaccine.

2290

2291   Whenever possible, centralized laboratories should be used and standard shipping procedures

2292   should be established for samples. If this is not feasible then information on assay performance

2293   between laboratories should be obtained and presented. The sensitivity, specificity and

2294   reproducibility of all the methods used should be included in the trial reports. If no well-

2295   validated methods for establishing infection and/or progression of infection exist during the

2296   period of pre-licensure clinical development then experimental laboratory methods could be

2297   used. It would usually be expected that these experimental methods are validated before using

2298   them to analyse specimens obtained during the pivotal trials.

2299

2300   See Subsection 4.1.2 regarding the use of an adjudication committee.

2301

2302   6.2.7   Case ascertainment

2303

2304   It is critical that the same methodology for case detection is applied in all treatment groups and

2305   throughout the duration of the trial. Active case ascertainment usually requires frequent

2306   monitoring and contact with vaccinees or their care-givers. Passive case ascertainment is usually

2307   based on vaccinees or care-givers presenting to or otherwise contacting a local healthcare facility

2308   due to the onset of specific symptoms. In this case it is common that contact is triggered by one

2309   or more of a list of signs or symptoms given to trial subjects or their care-givers at the time of

2310   randomization and they may be instructed to contact a specific healthcare facility. Alternatively

2311   or in parallel, cases may be detected based on monitoring all local clinics and hospitals for cases.

2312

2313   For efficacy endpoints based on clinically apparent disease, the possible range of clinical

2314   presentations will determine the mode of case ascertainment. For example, this may be hospital-

2315   based for cases of life-threatening infections or community based for less severe infections. If

2316   community based, case detection may depend on family practitioners and on first suspicion of

2317   infection by vaccinated subjects themselves or their parents/guardians. In each case, it is

2318   critically important that the individuals who are most likely to initiate detection of a possible

2319   case should have clear instructions. These may need to cover issues such as criteria for

2320   stimulating contact with designated healthcare professionals, telephone contacts, initial

2321   investigations and further investigations once a case is confirmed.

2322

2323   For efficacy endpoints other than clinically apparent disease, it becomes critical that subjects are

2324   monitored at regular intervals to detect clinically non-apparent infections or changes in other

2325   selected markers (e.g. the appearance of histological changes). The frequency of visits, and

2326   acceptable windows around the visits, should be laid down in the trial protocol and must be

2327   carefully justified.

2328

2329   The appropriate period of case ascertainment during a trial requires special attention and will be

2330   determined mainly by the characteristics of the disease to be prevented and the claim for

2331   protection that is sought at the time of initial authorization. For infectious diseases that have

2332   marked seasonality, at least in some geographic locations, it is usual to plan for a primary

2333   analysis at least when all vaccinees have been followed through one complete season. In these

2334   settings it is usual to conduct an enrolment campaign over a very short period just before the

2335   expected season onset. However, it may be necessary to repeat the exercise before the next

2336   season to meet the pre-defined sample size, in which case the opportunity should be taken to

2337   collect all cases that occur in the second season for the initial vaccination campaign cohort.

2338

2339   6.2.8   Duration of follow-up

2340

2341   At the time of conducting the primary analysis for the purposes of obtaining initial licensure, the

2342   duration of follow-up in vaccine efficacy trials may be relatively short (e.g. 6-12 months) and

2343   insufficient to detect waning protection, if this exists. Therefore, case ascertainment should

2344   continue in the vaccine efficacy trial populations and/or waning protection should be assessed

2345   during post-licensure effectiveness trials. These data may serve to indicate the need for and

2346   optimal timing of booster doses and to estimate efficacy after booster doses.

2347

2348   6.2.9   Analysis of efficacy

2349

2350   *6.2.9.1 Sample size calculation*

2351

2352   The trial sample size should be calculated based on:

2353   i.   The selected primary efficacy endpoint, including the possibility that the primary

2354   endpoint may be a composite of cases due to any of the organism types included in

2355   the candidate   vaccine;

2356   ii.   The primary analysis population (see below) and

2357   iii.   According to the primary hypothesis (i.e. superiority or non-inferiority and the pre-

2358   defined criteria).

2359

2360   If the primary analysis population represents a subset of the total randomized population the

2361   sample size calculation should include an adequate estimation of numbers likely to be excluded

2362   from the primary analysis for various reasons. In addition, if considered necessary, a blinded

2363   review of total numbers enrolled who are eligible for the primary analysis population may be

2364   conducted after a pre-defined number has been randomized so that the trial sample size can be

2365   adjusted accordingly.

2366

2367   *6.2.9.2 Analysis populations*

2368

2369   Clinical efficacy is usually assessed in the total randomized trial population (i.e. those who are

2370   assigned to receive vaccine and/or control) and in pre-defined subsets of the randomized

2371   population.

2372

2373   In maternal immunization trials of clinical efficacy it may be appropriate that trials are powered

2374   to assess vaccine efficacy only in the offspring. If a secondary or exploratory analysis is

2375   conducted in mothers the case definition will likely need to be different.

2376

2377   The pre-defined trial populations should include as a minimum:

2378   o   All randomized subjects (i.e. the full analysis set)

2379   o   All vaccinated subjects regardless of the numbers of assigned doses actually received and

2380   whether or not they were administered within the pre-defined windows

2381   o   Subsets of all vaccinated subjects separated according to any evidence of prior exposure

2382   to the   infectious disease under trial (e.g. baseline seropositivity vs. seronegativity)

2383   o   The *per protocol* population should be confined to subjects who have generally complied

2384   with the protocol and have received all assigned doses within pre-defined windows. In

2385   addition, this population should be confined to those with no evidence of prior

2386   exposure to the infectious agent (or specific serotypes or subtypes) at baseline.

2387   Depending on the target pathogen this subset may also be defined based on prior

2388   vaccination history.

2389

2390   Other populations may be appropriate for some pre-defined secondary or exploratory analyses.

2391   For example:

2392   o   Those who completed specific numbers of assigned doses or received all doses within

2393   pre-defined windows around the scheduled trial visits, i.e. analyses of efficacy according

2394   to adherence to the vaccination regimen

2395   o   Subgroups defined by demographic factors known or postulated to impact on vaccine

2396   efficacy

2397

2398   *6.2.9.3 Primary analysis*

2399

2400   It is common in vaccine efficacy trials that the pre-defined primary analysis is based on

2401   estimating efficacy in the *per protocol* population and on rates of true vaccine failures, i.e. the

2402   calculation of efficacy takes into account only those cases with onset after a minimum time had

2403   elapsed after completion of the assigned doses. For example, depending on knowledge of the

2404   kinetics of the immune response, true vaccine failures may be limited to cases with onset more

2405   than a specified number of days or weeks after the final dose of the primary series. In addition,

2406   for a vaccine that contains antigens from only certain serotypes or subtypes, the primary analysis

2407   may be based on cases due to vaccine types only.

2408

2409   In trials that compare a candidate vaccine with a group that is not vaccinated against the disease

2410 to be prevented the aim is to demonstrate that the lower bound of the 95% confidence interval

2411 around the estimate of vaccine efficacy is above a pre-defined percentage (which will always be

2412 above zero). The pre-defined percentage should be selected based on the sponsor's expectation

2413 of the point estimate of vaccine efficacy and taking into account what might be viewed as the

2414 minimum level of efficacy that could be considered clinically important. The sample size

2415 calculation is based on this objective.

2416

2417 In trials that compare a candidate vaccine with an active control the aim is to demonstrate non-

2418 inferiority of the candidate vs. the control vaccine, with calculation of the 95% confidence

2419 intervals around the difference in rates of breakthrough infections. This requires a pre-defined

2420 non-inferiority margin, which should be justified in accordance with prior estimates of vaccine

2421 efficacy for the disease to be prevented, and level of alpha on which the sample size calculation

2422 depends. If the sponsor also intends to assess superiority of the candidate vaccine over the active

2423 control the statistical analysis plan should pre-define a hierarchical assessment so that superiority

2424 is assessed only after establishing that the non-inferiority has been demonstrated.

2425

2426 *6.2.9.4 Other analyses*

2427

2428 The full range of secondary and exploratory analyses will depend on the pre-defined endpoints.

2429 Some of these analyses may be conducted in specific predefined trial populations. For example,

2430 important sensitivity analyses to support the primary analysis include those based on all proven

2431 cases whenever they occurred after randomization and in each analysis population. If the

2432 schedule includes more than one dose then analyses should be conducted that count cases from

2433 the time of each dose for all subjects who were dosed up to that point.

2434

2435 If the primary analysis was confined to cases due to organism types included in the vaccine then

2436 additional analyses should evaluate efficacy based on all cases regardless of the serotype or

2437 subtype responsible. If there are sufficient numbers of cases, these analyses may provide some

2438 indication of any cross-protection provided by the antigens in the vaccine.

2439

2440 Depending on the case definition, other analyses may be based on cases that met some but not all

2441   of the case definition criteria, cases that were severe and cases that required a medical

2442   consultation or hospitalization.

2443

2444   *6.2.9.5 Other issues*

2445

2446   <u>Vaccines that contain antigens derived from several serotypes, subtypes or genotypes</u>

2447

2448   As discussed in Section 4.3.5, it is not usually possible to power the trial to formally assess

2449   efficacy against individual types in the vaccine. Secondary or, at least, exploratory analyses

2450   should be planned to describe efficacy against the various types represented in the vaccine and, if

2451   there is an expectation of cross-protection, against types not included. If the data suggest

2452   unusually low efficacy against any type in the vaccine it may be necessary to explore this matter

2453   in further trials.

2454

2455   <u>Magnitude of vaccine efficacy</u>

2456

2457   The point estimate of vaccine efficacy and 95% confidence intervals that are obtained may

2458   indicate that a relatively modest proportion of cases can be prevented. This fact alone does not

2459   preclude licensure provided that the sponsor can substantiate that the vaccine efficacy observed

2460   represents an important clinical benefit. For example, if the vaccine prevents life-threatening

2461   infections for which there is no very effective specific therapy and for which no vaccine or no

2462   more effective vaccine is available.

2463

2464   <u>Extrapolation of vaccine efficacy</u>

2465

2466   Vaccine efficacy can only be estimated in geographical areas where there is sufficient disease to

2467   support trial feasibility. In most instances it is not necessary for any one NRA to request

2468   provision of efficacy data from within its own jurisdiction nor is it feasible to conduct a study

2469   that provides robust results within a single country. Any such requests should only be made

2470   when there are scientifically sound reasons to think that vaccine efficacy could be substantially

2471   lower compared to that observed in the areas where Phase 3 trials were conducted. In addition,

2472   such requests should not be made if there is a good scientific justification to use immunobridging

2473   to support extrapolations of efficacy between populations (see Section 5 on bridging efficacy).

2474

2475   **6.3   Approaches to determination of effectiveness**

2476

2477   Vaccine effectiveness reflects direct (vaccine induced) and indirect (population related)

2478   protection during routine use. Thus, the assessment of vaccine effectiveness can provide useful

2479   information in addition to any pre-authorization estimates of protective efficacy. Even if it was

2480   not feasible to estimate the protective efficacy of a vaccine pre-authorization it may be possible

2481   and highly desirable to assess vaccine effectiveness during the post-authorization period. The

2482   information gained from assessments of vaccine effectiveness may be particularly important to

2483   further knowledge on the most appropriate mode of use of a vaccine (e.g. need for booster doses

2484   in at least some segments of the population to maintain adequate protection over time).

2485

2486   Vaccine effectiveness may be estimated:

2487   i) In observational cohort trials that describe the occurrence of the disease to be prevented in

2488   the target population over time. However, there is no randomization step and there is the

2489   potential for considerable biases to be introduced. One such approach is the screening

2490   method.

2491   ii) During phased (e.g. in sequential age or risk groups) introduction of the vaccine into the

2492   target population in which the groups might form the units of randomization (i.e. using a

2493   stepped wedge design).

2494

2495   iii) Using other designs, of which a wide range has been used in different circumstances. For

2496   example, using a case test-negative trial design. In this modification of a case control trial

2497   subjects with symptoms suggesting the infectious disease under trial and seeking medical

2498   care are tested for the infectious agent of interest. The cases are those who are positive and

2499   controls are those who are negative for the pathogen of interest. If vaccinated cases are less

2500   severely ill and seek care less frequently than cases that occur in individuals not vaccinated

2501   against the disease to be prevented, then an appropriate adjustment for illness severity is

2502   required to avoid bias in effectiveness estimates (21).

2503

2504 Vaccine effectiveness is affected by a number of factors, including:

2505 o   Vaccination coverage of the population

2506 o   Pre-existing immune status of the population

2507 o   Differences in types included in a vaccine compared to predominant circulating types

2508 o   Changes in circulating predominant types over time

2509 o   Transmissibility of the pathogen and any effect that introduction of routine vaccination

2510   may have had on transmission rates

2511

2512 It may not be possible or appropriate for sponsors to conduct trials to estimate vaccine

2513 effectiveness themselves since regional or national networks may be necessary to ensure that

2514 cases are reliably detected. For some types of disease the use of data collected by means of

2515 national or international registries may be appropriate. In addition, in some jurisdictions the

2516 estimation of vaccine effectiveness is not considered to fall within the remit of the license holder.

2517

2518 Whatever the local requirements and arrangements, sponsors should discuss the arrangements for

2519 ongoing disease surveillance and the potential for estimating effectiveness with public health

2520 authorities in countries where the vaccine is to be used and where appropriate surveillance

2521 systems are in place. The plans for estimation of effectiveness should also be agreed with NRAs

2522 at the time of licensure and the requirements for reporting of effectiveness data to the NRA

2523 either via the sponsor or directly from a public health authority should be clarified.

2524

2525 It may be that reliable estimates of effectiveness can only be obtained in certain countries in

2526 which vaccination campaigns are initiated and where there is already a suitable infrastructure in

2527 place to identify cases. Therefore, it would likely be inappropriate to extrapolate any estimates of

2528 effectiveness that are obtained to other modes of use (such as introducing the same vaccine to

2529 different or only to highly selected sectors of the population).

2530

2531 **7. Safety**

2532

2533 This Section considers:

2534   ➢   Evaluating safety in clinical trials 2535   -   Safety as a primary or secondary endpoint 2536   -   Recording and categorisation of adverse events within trials 2537   -   Size of the pre-licensure safety database 2538   ➢   Post-licensure safety surveillance 2539   -   Spontaneous reporting 2540   -   Roles of the license holders and NRAs

2541

2542   7.1   General considerations

2543

2544   Safety should be assessed in all clinical trials that are conducted pre- or post-licensure. The

2545   assessment of safety may be the only primary objective, a co-primary objective or a secondary

2546   objective in a clinical trial. Since the methods for collection, analysis and interpretation of safety

2547   data during clinical trials contrast with those applicable to post-licensure routine safety

2548   surveillance they are considered separately.

2549

2550   In principle, many of the approaches to documenting and reporting safety data during clinical

2551   trials and the conduct of pharmacovigilance activities for vaccines are similar to those for all

2552   medicinal products. The sections that follow should be read in conjunction with the extensive

2553   guidance that is available from many publications and on the websites of WHO, CIOMS, the

2554   ICH and individual regulatory bodies. The focus of the sections is on some methods and

2555   practises that are different for vaccines compared to other medicinal products and on some issues

2556   that may need to be addressed due to the vaccine composition.

2557

2558   7.2   Assessment of safety in clinical trials

2559

2560   As described in Subsection 4.1.2 the use of a DSMB should be considered before commencing

2561   clinical trials. If the DSMB's role includes recommending early termination of a trial there

2562   should be appropriate stopping rules in place.

2563

2564   7.2.1   Safety as a primary or secondary endpoint

2565

2566   *7.2.1.1   Safety as a primary endpoint*

2567

2568   In the early clinical trials with a new candidate vaccine the assessment of safety may be the only

2569   primary objective or a co-primary objective. It is very unusual that the assessment of safety is a

2570   primary objective in pre-licensure trials conducted later in the development program. Where this

2571   has occurred the focus has been on a specific safety issue (e.g. intussusception in pre-licensure

2572   trials with rotavirus vaccines that were developed after the first vaccine had indicated a potential

2573   association with vaccination). The assessment of one or more safety aspects is the primary

2574   objective in post-licensure safety trials, which involve detailed monitoring during routine

2575   immunization programs.

2576

2577   When the assessment of safety is the primary objective of a clinical trial it is usual that the

2578   primary analysis is based on a specific safety endpoint (e.g. rates of a certain adverse event [AE],

2579   rates of AEs within a specific system organ class [SOC] or rates of AEs that may be part of a

2580   clinical syndrome of interest). These trials should be powered to address the pre-specified

2581   hypothesis. The exception is in trials that are exploratory in nature, such as initial trials with new

2582   candidate vaccines intended to provide a preliminary assessment of the safety of ascending doses

2583   or sequential doses.

2584

2585   *7.2.1.2 Safety as a secondary endpoint*

2586

2587   In vaccine efficacy trials and in immunogenicity trials the assessment of safety is usually a

2588   secondary objective. These trials are not powered *a priori* to support formal statistical

2589   conclusions from analyses of rates of all or specific AEs between trial groups but simple

2590   statistical comparisons are commonly used as an initial screening for any differences in rates

2591   between groups of subjects**.** If such analyses are conducted they should be pre-specified in the

2592   protocol and in the statistical analysis plan. If there are any findings indicating statistically

2593   significant differences in rates of AEs (overall, by SOC or by PT) they need to be interpreted

2594   with caution due to the fact that the trial was not primarily designed to address pre-specified

2595   hypotheses regarding safety endpoints. Nevertheless, the findings may indicate that it is

2596   appropriate to design and power further pre- or post-licensure clinical trials to further investigate

2597   and quantify the potential risks.

2598

2599   7.2.2   Recording and reporting adverse events

2600

2601   *7.2.2.1 Methods*

2602

2603   Adverse events and serious adverse events (SAEs) should be reported and recorded by

2604   investigators and sponsors according to detailed procedures described in the trial protocol and in

2605   accordance with requirements for expediting reporting to NRAs.

2606

2607   In safety and immunogenicity trials it is usually expected that all AEs, whether solicited or

2608   unsolicited, are collected for defined periods after each dose from all randomized subjects or all

2609   randomized subjects who received at least one dose of assigned treatment (see Subsections

2610   7.2.2.2 and 7.2.2.3). In vaccine efficacy trials involving large numbers of subjects, taking into

2611   account the safety profile observed in the previous trials and the numbers from which detailed

2612   safety data have already been obtained, it may be acceptable that all AEs are collected from a

2613   randomized subset. In this case all SAEs and any pre-specified adverse events of special interest

2614   (AESIs) should be collected from all randomized subjects. It may also be acceptable that only

2615   SAEs and AESIs are collected during long-term safety follow-up.

2616

2617   *7.2.2.2 Solicited signs and symptoms*

2618

2619   After each dose of a vaccine or placebo, local and systemic solicited signs and symptoms should

2620   be documented for a pre-defined post-dose period by vaccinees or their care-givers by

2621   completing a daily diary record. These diaries should be filled in each day and users should

2622   receive instructions in their completion before vaccination commences. The duration of

2623   collection of data in diaries should be at least 5-7 days after each dose but longer periods (e.g.

2624   10-14 days) may be appropriate for vaccines that contain live micro-organisms, depending on

2625   whether or not they are replication-competent.

2626

2627 For injectable vaccines the local signs and symptoms to be documented are usually pain, redness

2628 and swelling in all age groups. When two or more vaccines are given by injection at the same

2629 time, the diary card should ensure that separate data are recorded for each injection site (for

2630 example, these are usually into different limbs and therefore the diary card should contain

2631 separate records by right and left arm and/or leg). For vaccines given by other routes, alternative

2632 local signs and symptoms may be identified as representing local AEs (e.g. sneezing after

2633 intranasal dosing). The systemic signs and symptoms are determined by the age range in the trial

2634 (e.g. those appropriate for infants will not be wholly applicable to toddlers and older subjects)

2635 and the route of administration (e.g. nausea and vomiting could be solicited symptoms for

2636 vaccines given orally).

2637

2638 For subjective symptoms (e.g. pain, fatigue, myalgia) a simple scoring system should be

2639 included in the diaries to allow for a grading of severity. For objective signs, the quality of the

2640 information collected can be improved by methods such as issuing digital thermometers to each

2641 vaccinee or care-giver for application at a specific site (e.g. oral or axillary in infants, with

2642 recordings made at specific time of the each day) and using transparent plastic measuring

2643 devices to record the extent of redness and swelling.

2644

2645 Any self-administered treatments used to address signs or symptoms (such as antipyretic and

2646 analgesic medicines) and whether there was any contact with, or treatment administered by, a

2647 healthcare professional should be captured. If a supply of a specific anti-pyretic or analgesic was

2648 given out at the time of each dose for use as needed, or as instructed in accordance with the

2649 protocol, the post-dose usage recorded in the diary should be checked against returned supplies.

2650 If prior safety data suggest that pre-vaccination antipyretic use is appropriate, this can be

2651 administered and recorded by trial staff at the vaccination visit and the diary cards should collect

2652 any post-vaccination doses administered.

2653

2654 At each trial visit, whether it involves face-to-face or telephone contact between the vaccinee

2655 and/or care-giver and trial staff, the diary cards should be checked for level of completion and

2656 further instructions given as needed to improve data recording after the next dose is given. At

2657 face-to-face visits the prior vaccination site(s) should be inspected for any remaining signs such

2658   as induration. Also, vaccinees or care-givers should be asked about the maximum extent of signs

2659   (e.g. to determine whether whole limb swelling occurred). Any unresolved local or systemic

2660   signs and symptoms should be recorded and action taken as appropriate.

2661

2662   *7.2.2.3 Unsolicited AEs*

2663

2664   In addition to signs and symptoms that are pre-specified for collection of data, vaccinees and/or

2665   their care-givers should be questioned at each trial visit for the occurrence of any AEs since the

2666   last visit. For each AE the timing of onset in relation to vaccination, whether a healthcare

2667   professional was consulted, whether hospitalisation occurred and any treatment that was given

2668   (prescribed or non-prescribed) should be captured. Sponsors may also wish to record any days

2669   off school or off work for vaccinees and days off work for their care-givers.

2670

2671   A checklist of symptoms that could possibly reflect the onset of a pre-specified AESI may be

2672   useful to identify potential cases of various syndromes (such as auto-immune diseases) at an

2673   early stage and to ensure that there is careful follow-up. In addition, questions should be posed to

2674   elicit whether certain AEs have occurred that could be anticipated in the age group studied. For

2675   example, to determine whether persistent inconsolable crying or hypotonic hypo-responsive

2676   episodes occurred in infants. Where well-established and widely-applied definitions of these and

2677   other AEs are available, the reports received should be classified using these criteria.

2678

2679   Although solicited signs and symptoms are AEs, it is usual that clinical trial reports tabulate

2680   safety data separately for these and for unsolicited AEs. The classification of AEs should use a

2681   standardised scheme, such as MedDRA, to categorise AEs by SOC and PT. If the classification

2682   scheme is updated during conduct of the trial the clinical trial report should indicate how the

2683   changes impact on the tabulations.

2684

2685   *7.2.2.4 Other investigations*

2686

2687   The collection of data on routine laboratory tests (haematology, chemistry and urinalysis) is not

2688   commonly perceived to be necessary in clinical trials with vaccines. If the sponsor or NRA

2689   considers that there is a good rationale for obtaining these data at certain time points the results

2690   should be generated in appropriately certified laboratories and reported using well-established

2691   grading scales for abnormalities.

2692

2693   For vaccines that contain live organisms (including attenuated wild-types, organisms that have

2694   been genetically engineered to render them non-virulent and/or non-replicative and live viral

2695   vector vaccines) additional investigations related to safety should usually include the detection of

2696   viraemia and assessments of shedding (quantity and duration). Organisms recovered from

2697   vaccinees may also be subjected to genetic analyses to determine any instances of recombination

2698   with wild types and reversion to virulence and/or replication competency.

2699

2700   In the case of vaccines administered to pregnant women measures of growth and development in

2701   their infants may be important safety parameters.

2702

2703   7.2.3   Categorization of adverse events

2704

2705   *7.2.3.1 Causality*

2706   Section 8.5 of the WHO Global Manual on Surveillance of Adverse Events Following

2707   Immunization (22) recommends that in clinical trials the investigator should make a judgement

2708   of relatedness to vacination for all solicited signs and symptoms and unsolicited AEs. The

2709   investigator's assessment may also be commented on by the sponsor. The assessment of

2710   relatedness to vaccination should take into account factors such as:

2711   a) Plausibility of relatedness, taking into account the vaccine construct. For example, live

2712   attenuated vaccines may be associated with modified manifestations of natural infection

2713   (e.g. rashes).

2714   b) Timing in relation to dosing. Whilst most vaccine-related AEs occur within 1-2 weeks after

2715   a dose there may reasons to suspect that illnesses with onset many months after the last dose

2716   could be related to prior vaccination. For example, for some powerful adjuvants there is a

2717   hypothetical concern that rates of auto-immune diseases may increases in genetically-

2718   prediposed sub-populations.

2719   c) Concurrent illnesses common in the trial age group or documented in the case report form

2720   and the anticipated background rates, if known. This is a particular issue for vaccines

2721   administered to infants and young children in whom intercurrent illnesses are relatively

2722   common.

2723   d) The frequency with which any one AE occurred in groups that received the candidate

2724   vaccine compared to groups that received another vaccine or placebo.

2725   e) Any correlation between rates of any one AE and dose of antigenic components.

2726   f) Changes in rates of any one AE with sequential doses.

2727   g) The results of medical investigations (e.g. diagnostic tests for concurrent illnesses) and of

2728   autopsies (e.g. in cases of sudden infant death).

2729

2730   *7.2.3.2 Severity*

2731

2732   Sufficient data should be collected for each solicited sign and symptom and unsolicited AE to

2733   make an assessment of severity. Wherever possible widely used grading scales should be used

2734   and/or the same scales should be applied throughout the clinical development program.

2735

2736   *7.2.3.3 Other categorization*

2737

2738   The classification of AEs as serious and the categorisation of frequencies should follow

2739   internationally-accepted conventions, as described in Section 3.1.2 of the WHO Global Manual

2740   on Surveillance of Adverse Events Following Immunization (22). Frequencies of solicited signs

2741   and symptoms by subject and of AEs in each treatment group should be calculated based on the

2742   denominator of all vaccinated subjects in that group. Frequencies of solicited signs and

2743   symptoms after each dose should use the number that received each dose.

2744

2745   7.2.4   AE reporting rates within and between trials

2746

2747   During any one clinical development program the reporting rates for all and/or for specific types

2748   of AEs, whether solicited or unsolicited, in clinical trials may demonstrate:

2749

2750   i) Differences between candidate vaccines and control groups within a clinical trial. For
2751   example, differences in AE rates may be anticipated between a candidate vaccine and a
2752   placebo group or a group that receives a licensed vaccine that does not have a similar
2753   composition to the candidate vaccine. Any marked differences between a candidate vaccine
2754   and a licensed vaccine that has the same or very similar composition are generally not
2755   anticipated and may require further investigation.

2756

2757   ii) Differences between clinical trials that may be observed in one or both of the candidate
2758   vaccine and control groups for total or specific AE reporting rates. Whenever this occurs it
2759   is important to consider the possible explanations, taking into account whether or not the
2760   same effect on the pattern of reporting rates is observed in groups that receive candidate
2761   vaccines and licensed vaccines and whether the study was double-blind or open-label. These
2762   differences between trials may reflect real and anticipated differences in vaccine
2763   reactogenicity between trial populations (e.g. age-related differences for specific AEs, such
2764   as higher fever rates in trials conducted in infants and toddlers compared to those in older
2765   children and adults). In contrast, marked differences in reporting rates between trials
2766   conducted in similar age ranges but in different geographical locations would not usually be
2767   anticipated. When there is no clear explanation for the differences observed, consideration
2768   should be given to the possibility that there has been incomplete reporting of AEs and
2769   further investigation is merited.

2770

2771   **7.3   Size of the pre-licensure safety database**

2772

2773   A total database of 3000 subjects across all trials and populations provides a 95% chance of

2774   observing one instance of an AE that occurs on average in 1 in 1000 subjects. This number may

2775   be regarded as a generally applicable target for the minimum total pre-licensure safety database

2776   for a new candidate vaccine that contains one or more antigenic components not previously used

2777   in human vaccines. Nevertheless, this figure should not be applied to application dossiers for any

2778   type of new candidate vaccine without further considerations, which include the following:

2779   a. Fewer than 3000 subjects may be acceptable if the new candidate vaccine consists only of

2780   antigenic components already licensed in other vaccines for which there is considerable

2781   experience in routine use.

2782   b. The total number exposed in clinical trials may cover many age sub-groups or a single age

2783   group may predominate. It may be acceptable that the majority of subjects included in the

2784   safety database come from a specific age range unless the available data point to some

2785   specific safety concerns that require further investigation in other age groups before

2786   licensure.

2787   c. For specific types of vaccines (e.g. innovative constructs) or specific modes of use (e.g. in a

2788   population considered to be vulnerable or otherwise at high risk that could predispose them

2789   to certain adverse events) individual NRAs may require that considerably more than 3000

2790   subjects are exposed prior to initial licensure.

2791   d. Additional considerations may apply to vaccines that contain antigenic components not

2792   previously used in human vaccines but for which efficacy trials are not possible. A large

2793   pre-licensure safety database is highly desirable for a vaccine with potential to be

2794   administered to very large numbers in an emergency situation (e.g. influenza pandemic

2795   vaccines, vaccines against certain viral haemorrhagic fevers or smallpox vaccines).

2796   Nevertheless, the safety profile documented in the initial safety and immunogenicity trials

2797   may lead to some reluctance to unnecessarily expose large numbers of subjects in the

2798   absence of an immediate threat and/or to expose large numbers in particular population

2799   subsets. Therefore NRAs may consider licensing these types of vaccines based on a

2800   relatively small safety database provided that very detailed plans are in place at the time of

2801   licensure for monitoring of safety should it be necessary to give the vaccine to large

2802   numbers of individuals at some future time.

2803

2804   **7.4   Post-licensure safety surveillance**

2805

2806   The requirements of individual NRAs for reporting of safety data collected from post-licensure

2807   safety surveillance activities should be consulted. NRAs should provide publicly-available

2808   guidance regarding their requirements for the content and timing of periodic reports of safety

2809   data and for any expedited reporting considered necessary. License holders should demonstrate

2810   that they have adequate capability and appropriate staff to collect, interpret and act upon the

2811   safety data received.

2812

2813   It has become routine that at the time of initial licensure there are detailed proposals in place for

2814   post-licensure safety surveillance activities, often in the form of risk management plans. These

2815   documents and proposals are then routinely updated at intervals in line with additional data that

2816   become available. They usually outline the safety specification for the vaccine based on all

2817   available safety data at the time of submitting each version of the plan along with details of

2818   routine and proposed additional pharmacovigilance and risk minimisation activities.

2819

2820   When planning pharmacovigilance activities for a vaccine, it is important to take into account

2821   that in addition to routine pharmacovigilance (i.e. passive surveillance), important information

2822   may come from:

2823   i)   Data from enhanced safety surveillance (active surveillance) put in place by public health

2824   bodies when a vaccine is introduced into a national routine immunization program or when

2825   the use of a vaccine within a program changes significantly (e.g. an entirely different age

2826   group is vaccinated for the first time).

2827   ii) Large databases that link information in patient records on vaccination history with

2828   occurrence of specific types of illness. These can be interrogated to explore links between

2829   specific vaccines and safety issues in the short and longer-term.

2830   iii) Various types of registries intended to capture details of use in specific populations. For

2831   example, there are registries that collect information on exposure of pregnant women to

2832   various types of vaccines and the outcome of the pregnancy (including rates of spontaneous

2833   abortion, premature delivery and congenital malformations in the infants). There are also

2834   registries that capture specific types of disease that could be of relevance to specific types of

2835   vaccines.

2836

2837   The limitations of each of these approaches are well known, which underlines the need to

2838   consider all sources along with additional data that may come from post-licensure trials.

2839

2840   As with other medicinal products the same vaccine may be marketed by different license holders

2841   in various countries and regions so that systems need to be in place at the time of licensure to

2842   facilitate rapid sharing of safety information between companies, between companies and NRAs

2843   and between NRAs. An additional consideration for vaccines is that when a safety signal is

2844   identified for any one vaccine it may or may not be possible to ascribe the AEFIs observed to

2845   any one antigenic component of the vaccine or to an adjuvant. Furthermore, if there was

2846   concomitant administration of vaccines in some or all cases generating the signal it may not be

2847   possible to ascribe the AEFI to only one of the products co-administered. The same or very

2848   similar antigenic component(s) or adjuvant in the vaccine(s) from which the signal arose may be

2849   in several other licensed products marketed worldwide. Ultimately several different companies

2850   and NRAs without established data sharing agreements may need to be involved. As a result, the

2851   actions taken, if any, and the speed at which action has been taken, are sometimes very variable

2852   between countries. These issues underscore the need for efficient use of electronic databases to

2853   facilitate rapid data sharing.

2854

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3011

3012 **Appendix 1. Human Challenge Trials**

3013

3014 There are many reasons a developer might wish to conduct with humans a "challenge-
3015 protection" study that might normally be conducted in animals. Animal models are often quite
3016 imprecise in reflecting human disease and many infectious organisms against which a
3017 developer might wish to develop a vaccine are species-specific for humans. Human Challenge
3018 Trials may be safely and ethically performed in some cases, if properly designed and
3019 conducted. Tremendous insight into the mode-of-action and the potential for benefit in the
3020 relevant species, humans, may be gained from challenge trials. However, there are also
3021 limitations to what challenge trials may be able to ascertain, because like animal model
3022 challenge-protection studies, a human challenge trial represents a model system. Because there
3023 are often such significant limitations to animal models however, the model system of the
3024 human challenge trial may significantly advance, streamline, and/or accelerate vaccine
3025 development (1).

3026

3027 It will be important to consider the regulatory framework where the human challenge trial may
3028 be conducted, because in some countries, challenge stocks are expected to be handled in the
3029 same manner as vaccines and to be studied under a Clinical Trial Authorization (Approval,
3030 CTA), whether or not an investigational vaccine is to be used in the same clinical investigation
3031 protocol. For example, a challenge trial might be conducted to titrate the challenge organism in
3032 humans before using the challenge in a vaccine study, in order to know the proper dose of the
3033 challenge organism to give and to characterize the symptoms, kinetics, shedding,
3034 transmissibility, and so forth to expect from the challenge. In such cases (when challenge
3035 should be studied under CTA), there is greater clarity about regulatory expectations, including
3036 quality of the challenge stock to be used, as the CTA regulations or requirements would apply.
3037 However, in many countries, because the challenge stock is not itself a medicinal product, such
3038 studies would not be under the purview of the NRA's review and approval and much less
3039 clarity exists on regulatory expectations and quality matters in such cases. Ideally, a challenge
3040 stock should match in quality terms what is expected of an investigational vaccine at the same
3041 clinical Phase of development (understanding that a pathogenic challenge strain will not have
3042 the "safety" of a hopefully innocuous vaccine). Likewise, ideally a human challenge study

3043 should match the same expectations for conduct of a vaccine study, e.g., compliance with

3044 GCP, approval of a CTA. However, there may not exist a regulatory framework to promulgate

3045 such expectations in the country where the challenge study is to be conducted. Thus, it may be

3046 necessary for regulators to consider and develop an appropriate regulatory pathway or

3047 framework for the quality of the challenge stock and the conduct of the challenge study, when

3048 clarity is not apparent in their existing system. This may require new legislation to give

3049 regulators the necessary authority, and it is encouraged that regulators should have this

3050 authority. Trial sponsors, vaccine developers, researchers, and so on should determine from the

3051 relevant NRA what regulatory expectations they may have when clarity does not exist, if the

3052 human challenge study is intended to support the development of a vaccine candidate they

3053 would like to ultimately license (i.e. gain marketing authorization).

3054

3055 It is also important to note that not all diseases for which vaccines might be developed are

3056 suitable to consider conducting human challenge trials. In many cases, human challenge with a

3057 virulent or even a potentially attenuated organism would not be considered ethical or safe. For

3058 example, if an organism causes a high case fatality rate (or there is a long and uncertain latency

3059 period) and there are no existing therapies to prevent or ameliorate disease and preclude death,

3060 then it would not be appropriate to consider human challenge trials with such an organism.

3061 However, when the disease an organism causes has an acute onset and can be readily and

3062 objectively detected and existing efficacious treatments (whether curative or palliative) can be

3063 administered at an appropriate juncture in disease development to prevent significant

3064 morbidity (and eliminate mortality), a human challenge trial might be considered.

3065

3066 **1. Purposes of human challenge trials**

3067 A developer may conduct human challenge trials to accomplish one or more of a number of

3068 aims. The aims of the study determine what clinical Phase the study may be considered to be.

3069 Human challenge trials are often a type of efficacy study, but not all would be considered a

3070 "Phase 3" study. Purposes of human challenge trials could include one or more of the

3071 following:

3072 • Characterization of the challenge stock and model system: titration, symptoms, kinetics,

3073 shedding, transmissibility, etc.

3074 • Clearer understanding of pathogenesis of and immunity to the organism in order to guide
3075 decisions on what (type and/or quantity) immune responses a vaccine might need to
3076 accomplish in order to protect against that disease, i.e. insight for vaccine design (studies for
3077 this purpose may be referred to as experimental medicine studies)

3078 • Identification of potential immune correlates of protection (ICP, which would then require
3079 validation in a traditional efficacy study)

3080 • Identification of optimal trial design for Phase 3 traditional efficacy trial(s), e.g. case
3081 definitions, endpoints, study design aspects

3082 • Generation of appropriate hypotheses to be formally tested in traditional efficacy trials

3083 • Proof-of-concept that a particular vaccine candidate might be capable of protection or not

3084 • Down- or Up-selection among various potential lead vaccine candidates to advance only the
3085 best to large Phase 2b or Phase 3 efficacy trials and to eliminate those that are unworthy of
3086 advancement

3087 • De-risk or "left-shift"[1] risk of failure in a vaccine development program

3088 • Comparison of vaccine performance in endemic settings vs. in efficacy trial population[2],
3089 including evaluating impact of prior immunity

3090 • Support emergency use of an investigational vaccine, e.g. in a pandemic

3091 • Basis for licensure (this purpose would generally be an exception rather than the rule)

3092 • Exploration post-licensure whether immunity to vaccination wanes and if or when booster
3093 doses might be required for durable protection[3]

3094 • Others

3095 Not all situations would support accomplishing each of the aims above. For example, if the
3096 human challenge model system does not adequately mimic the wild-type disease and situation
3097 in which a vaccine would need to protect, then a human challenge trial would not be usable as
3098 a basis for licensure. But, it might still serve well one or more of the other purposes above. It

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[1] When looking at a timeline of vaccine development graphed from early to the left and late to the right, shifting the risk of failure earlier in the timeline, or left, could result in significant cost (and resource)-savings and minimize lost opportunity costs by abandoning an unpromising candidate before taking greater expenditures from higher phase clinical trials, not to mention minimizing risk to human subjects by not conducting large efficacy studies of vaccines that would not prove efficacious

[2] Target population in a particular country may have a higher rate of individuals with e.g., sickle cell trait or different nutritional status or greater parasitic load in "normal" flora, any of which might affect immune responsiveness and thus, efficacy, compared to the efficacy trial population

[3] This might entail challenge study in adults to extrapolate when children might need booster doses

3099   might even be considered by regulators as supportive of licensure, but not a sole or primary

3100   basis.

3101

3102   **2. Purpose influences study design, which influences regulatory use and decision-making**

3103   Obviously, the aim of the human challenge trial guides its study design. Consequently, even

3104   for the same disease, the challenge model may vary depending on the purposes and design of

3105   the study to be conducted. In some cases (e.g. to serve as a basis for licensure or to identify

3106   appropriate efficacy trial design and case definitions), the challenge model might need to

3107   mimic as closely as feasible wild-type disease. In other cases, consideration might be given to

3108   use of an attenuated challenge organism (e.g., an earlier but under-attenuated vaccine

3109   candidate) or a model system in which objective early signs (e.g. parasitaemia, viraemia)

3110   signaling onset of disease symptoms, which could trigger initiation of treatment to prevent

3111   actual disease onset or morbidity.

3112

3113   Another important consideration for a human challenge model system would be its positive

3114   and negative predictive utility. If used for down-selection or de-risking, the negative predictive

3115   utility of the model to identify vaccine candidates that would not warrant advancement into

3116   large human efficacy studies should be high. If intended to be used for licensure, the positive

3117   predictive utility of the model system would need to be nearly as compelling and credible as a

3118   traditional efficacy trial might be. Thus, the purpose of the study would influence the design,

3119   which would in turn influence the conclusions about and the decisions that might be made

3120   from the study results.

3121

3122   **3. Some key ethical considerations**

3123   Ethics in clinical trials, as in medicine, follow the precept of "do no harm." By their nature

3124   (intentionally infecting humans with disease-causing organisms), human challenge trials would

3125   seem to fly in the face of this basic precept. Further, clinical trials should be designed and

3126   conducted in a manner that minimizes risks to human subjects while maximizing the potential

3127   to benefit. Consideration must be given both to potential individual risks and benefits, as well

3128   as to potential societal benefits (and risks, such as release into the environment of a pathogen

3129   that might not otherwise be present). Provisions in clinical trial ethics are made for situations

3130   in which there may be greater than minimal risk but no (or little) potential for individual

3131   benefit, but when knowledge may be gained to the benefit of the larger societal population

3132   with whom the potential trial participant shares significant characteristics. Justification for

3133   asking trial participants to accept the risk from a challenge may take some considerations from

3134   the justifications that support inclusion of placebos in controlled clinical trials.

3135

3136   Acknowledgement is due to the reality that some individuals are greater risk-takers than others,

3137   while some individuals are quite risk-averse and would not be accepting of the risk of

3138   receiving a challenge. Key to asking individuals to accept the risk from a challenge study in

3139   which they may not except to receive individual benefit is the element of informed consent.

3140   Adults may consent when they are well-informed and understand what risks they are accepting

3141   to take, even if those risks may be considerably greater than minimal (e.g. accepting that they

3142   will develop an acute, but manageable, disease that will resolve but in the meantime may cause

3143   considerable morbidity, e.g. severe diarrhea managed with fluid and electrolyte replacement).

3144   Thus, in appropriate situations, it can be considered ethical to ask informed adults to consent to

3145   volunteer and participate in a human challenge trial whether they will receive an

3146   investigational vaccine that may or may not protect them from the challenge organism, a

3147   placebo that will not protect them, or only the challenge organism itself. However, accepting

3148   such risks requires absolutely the elements of voluntary consent based on truly being informed.

3149   It is for this reason (need for truly informed consent), consideration of conducting human

3150   challenge studies in children or any other vulnerable population, who would have diminished

3151   capacity to give informed consent, would not be deemed acceptable at this time.

3152

3153   The need to minimize risks to subjects in clinical trials calls for due consideration to whether

3154   or not the challenge organism need be pathogenic or not, or to what degree. As stated above,

3155   the aim or purpose of the study may drive this decision, but the ethics of minimizing to the

3156   extent feasible within the frame of sound science any risks to human subjects should also bear

3157   due consideration in this regard. It should also be obvious that the credibility of the data to

3158   support regulatory decision-making need be taken into account.

3159

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