Specific aspects regarding clinical assessment of early phase trials for vaccines

FAMHP

BRUSSELS

15.09.2023

Inne CRÈVECOEUR

famhp

federal agency for medicines and health products

.be

Scope of the presentation

The presentation covers specific aspects regarding clinical assessment of early phase trials for **prophylactic vaccines**, with a **main focus on First-in-Human (FIH) trials**.

Requirements for subsequent early phase trials may be different/less stringent, depending on the data and overall evidence available for the vaccine and/or platform.

For live-attenuated vaccines, additional/more stringent criteria may be needed, which are not discussed in detail in this presentation.

Requirements for a specific study are always assessed on a **case-by-case** basis.

What is considered acceptable or required can change over time (e.g. when new data emerges, when updated guidelines are published, when national recommendations change, when new alternatives are available …).

Specific situations are recommended to be discussed in a Scientific-Technical Advice.

General aspects

The protocol should include a clear and complete description of the study, including also a description of the clinical relevance and scientific justification of the study.

Particularly important in early phase trials is a proper justification for:

- **study population;**
- **safety evaluation, follow-up and study duration;**
- **overall study design, including:**
  - **sentinel approach;**
  - **staggering process;**
  - **stopping criteria;**
  - comparator/placebo arm;
- dose levels tested and schedule;
- endpoints;
- sample size;
- study procedures.

Study population

Main inclusion criteria

- **Age**:
  - 18-50 years is acceptable; 18-40 years is considered ideal;
  - older adults might be included in certain circumstances, provided sound justification and a staggered age-escalation design.
- **Healthy** individuals, as established by medical history, clinical examination and laboratory assessment.
- Women of childbearing potential should have a **negative pregnancy test** at screening and agree to continue using **contraception** during the treatment period and for at least 2 months post-last dose.

Described criteria are standard in most early phase vaccine trials, however, a case-by-case assessment is always needed.

Study population

Main exclusion criteria (1/2)

- Individuals who have received any **other vaccine** within 28 days prior to enrolment in the study or who are planning to receive any vaccine up to 14 days after the last vaccination.
- Individuals who receive treatment with **immunosuppressive** therapy or other immune-modifying drugs, including cytotoxic agents or systemic corticosteroids, e.g. for cancer or an autoimmune disease, or planned receipt during the study period.
    - Criteria in general applies to recent/ongoing chronic administration (which could e.g. be defined as more than 14 days in total within 6 months prior to the first vaccine dose).
    - In case of non-chronic administration (e.g. short duration systemic corticosteroids), individuals should not be enrolled until discontinuation of therapy for a sufficiently long period.

Described criteria are standard in most early phase vaccine trials, however, wording could differ. A case-by-case assessment is always needed.

Study population

Main exclusion criteria (2/2)

- Individuals who received any **blood/plasma products or immunoglobulins** within 60 days prior to Day 1 or plan to receive it during the study period.
- Confirmed or suspected **immunosuppressive or immunodeficient condition**.
- **Autoimmune or other immune-mediated disease** (or history of).
- Individuals with a known or suspected history of **allergic reaction or hypersensitivity** to any component of the study vaccine.
- **Acute disease and/or fever** at the time of planned vaccination.

Described criteria are standard in most early phase vaccine trials, however, wording could differ. A case-by-case assessment is always needed.

Safety evaluation

Solicited local and systemic Aes

Standardly to be collected for **7 days** post-vaccination.

- **Main local solicited AEs**: Injection site Pain/Tenderness; Erythema/Redness; Swelling/Induration
- **Main systemic solicited AEs**: Fatigue; Malaise; Myalgia; Headache; Nausea; Body Temperature

Complete list of solicited AEs to be monitored depends on the vaccine and available (non-)clinical data. Case-by-case assessment is always needed.

Unsolicited AEs

Standardly to be collected for **28 days** post-vaccination.

Safety evaluation

Serious Adverse Events (SAEs)

Standardly to be collected **up to the end of the study.**

Adverse Event of Special Interest (AESI)

Standardly to be collected **up to the end of the study (or shorter period if justified).**

Events to be considered as AESI are:

- for vaccines using the same platform or antigen as an authorised vaccine: identified risks defined in the RMP of a vaccine using the same platform or antigen, such as GBS, ADEM, myocarditis, anaphylaxis;
- for vaccines with a (novel) adjuvant: Potential Immune Mediated disorders (pIMDs);
- for live attenuated vaccines: safety events associated with the natural disease.

Study design

Sentinel approach

- Each cohort should start with a small number of sentinel subjects who receive the study vaccine prior to vaccination of the entire cohort.
- The maximum number of sentinel participants to be vaccinated on a single day should be limited.
- Each sentinel participant should be observed for at least 60 minutes prior to vaccination of the next one.
- Remaining participants in the cohort can be vaccinated after review of at least 48 hours safety data of all the sentinel participants, and in the absence of safety concerns.
- Each sentinel cohort should be vaccinated at one single site.
- It is recommended to apply the same process to subsequent doses, in case of a multi-dose schedule.

The described approach is standard and frequently used. However, alternative approaches could be acceptable and will be assessed on a case-by-case basis.

The described approach is appropriate for non-live vaccines.
For live-attenuated vaccines, longer intervals may be needed.

Study design

Staggered approach

- Dose escalation may be done after review of at least 7-days safety data (including lab data) of the complete previous cohort.
- In case of multiple vaccinations, the safety review required to start administration of the next doses of a given dose level should be clearly described in the protocol. All available data, and at least 7-days safety data after the first dose should be reviewed.

In FIH trials, there should be at least 60 minutes post-vaccination observation with appropriate medical treatment of all subjects.

The described approach is appropriate for non-live vaccines.
For live-attenuated vaccines, longer intervals may be needed.

Stopping criteria

Individual stopping rules

Always needed **when at least two doses** are administered to an individual in the study.

Contra-indications for subsequent vaccination in general include at least:

- participants who experienced any hypersensitivity/allergic reaction after the previous study vaccination;
- participants who experience any SAE judged to be related to study vaccination, including hypersensitivity/allergic/anaphylactic reactions;
- participants who develop any clinically significant medical condition which, in the opinion of the Investigator, may pose additional risk to the participant if he/she continues to participate in the study;
- participants who become pregnant;
- participants who decided to interrupt contraceptive measures.

Stopping criteria need to be aligned with relevant exclusion criteria. When inclusion/exclusion criteria are re-checked prior to each vaccination, not all criteria may be needed.

Different wordings could also be acceptable.

Stopping criteria

Study stopping rules

Always needed in Phase 1 studies.

Rules should include, but not be limited to:

- 'A **serious adverse event considered at least possibly related** to the study vaccine by the investigator in one subject, irrespective of the time since vaccine administration'.

→ Meeting one of these rules results in stopping of vaccination in the entire study.

- Rules referring to **'severe' (grade 3) non-serious adverse reactions, at least possibly related** to the study vaccine.
    - These should include Solicited local and systemic AEs, Unsolicited AEs (including laboratory safety AEs).
    - The number of subjects experiencing an event that leads to stopping of the cohort needs to be specified.

→ Meeting one of these rules results in stopping of vaccination in the entire study; or in the affected cohort and cohort(s) with a higher dose level. This needs to be clarified in the protocol.

Different wordings could also be acceptable.

Conclusion

- Early phase trials for vaccines need to be in line with the **EMA guideline** on first-in-human and early clinical trials.

- **Specific considerations** were discussed for **early phase vaccine trials** (in particular FIH) concerning the study population, safety evaluation, study design (including sentinel approach and staggered approach) and stopping criteria.

  However, requirements for a specific study are always determined on a **case-by-case** basis.

- It is strongly recommended to seek **Scientific-Technical Advice** in advance to discuss the design of FIH trial or specific situations in Phase 1, 2 and 3 trials.

Thank you for your attention!

Questions?

Contact

Federal Agency for Medicines and Health Products – FAMHP

Avenue Galilée - Galileelaan 5/03
1210 BRUSSELS

tel. + 32 2 528 40 00
fax + 32 2 528 40 01
e-mail welcome@fagg-afmps.be

www.famhp.be

Follow the FAMHP on Facebook, Twitter and LinkedIn

Your medicines and health products, our concern

famhp

.be