How to design a clinical trial from phase I to III: general principles

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Clinical Development Phases

- **Phase I**: safety & immunogenicity
- **Phase II**: safety & immunogenicity
- **Phase III**: efficacy, safety
- **Phase IV**: post licensure, immunogenicity, effectiveness, safety

Clinical Study = Clinical Trial
Clinical Study (trial) design components

- Statistical Power
- Stopping Rules
- Compliance
- Ascertainment of outcome
- Analysis and Interpretation
- Choice of the reference study population
- Study End-points
- Allocation study regimens
Study design components

Choice of the reference study population
Choice of the study population in clinical trials

- **Phase I**: Healthy Adults
- **Phase II/III**: reference/target population in whom the vaccine will be used/ or on a step design for infants indication/vulnerable population
- **Age-groups**
- **Feasibility in terms**
  - Willingness to participate
  - Study Procedures Compliance
  - Logistics
  - Ethics (assent, consent, national requirements, vulnerable population)
Clinical study population

- **Phase I**: Healthy men and women aged between 18 and 45 years with no comorbidities were eligible for inclusion. (Ramsauer K et al. Immunogenicity, safety, and tolerability of a recombinant measles-virus-based chikungunya vaccine: a randomised, double-blind, placebo-controlled, active-comparator, first-in-man trial. Lancet Infect Dis. 2015 May;15(5):519-27.)

- **Phase II**: Study A was conducted among healthy children between 12 and 23 months of age at Centre pour le Développement des Vaccins in Bamako, Mali, and the Medical Research Council Laboratories in Basse, Gambia. (Samba O.Sow et al. Immunogenicity and Safety of a Meningococcal A Conjugate Vaccine in Africans. N Engl J Med 2011;364:2293-304.)
Clinical study population

**Phase III**: The trial included 10,000 men and women from age 16 to 65 years, with or without antibodies against hepatitis E, from a region where both genotypes 1 and 4 co-circulate with the zoonotic genotype 4 predominating.

Study design components

Choice of the reference study population

Study End-points
Establishment of objectives and endpoints

- Endpoints measure the objective

- In phase I: objectives and endpoints are usually exploratory and no formal statistical hypothesis is formulated

- In phase II-III the primary endpoint: will determine the sample size and main outcome of the study
Establishment of objectives and endpoints

Phase II&III non inferiority study

- The **primary objective** of each study was to demonstrate that the PsA-TT vaccine was not inferior to the PsACYW vaccine.

- The **primary endpoint** for immunogenicity was seroconversion, defined as an SBA titer that was at least four times as high as that at baseline 28 days after immunization.

Establishment of objectives and end-points

Secondary end-points

- **Safety**: i.e. solicited adverse reactions (or local and systemic post-immunization reactions, Adverse events, Serious adverse events,
- **Immunogenicity** using secondary immunological endpoints, immunogenicity using other assay (i.e. ELISA or functional assay)
Establishement of objectives and endpoints

Phase III study: efficacy study

- **The primary endpoint** was prevention of hepatitis E in participants who received three doses of vaccine (ie, the per-protocol population) during the 12 months from the 31st day after receipt of the third dose.

- **Case definition:** a case of acute hepatitis E in a participant needed to fulfill three conditions: acute illness lasting for at least 3 days; abnormal serum ALT concentration 2.5-times the upper limit of normal range or greater; and positive hepatitis E virus IgM and RNA, ≥4-times increase in hepatitis E virus IgG, or both.

Sensitivity and specificity of case definition

- **Case definition** should be validated before starting phase II/III or embarking in a VE study.
- **Sensitivity and specificity** of a case definition (or serological assay) can vary in different populations, age-groups, previous disease exposure, health status, etc.
- **Sensitivity:**
  - Probability of a subject being positive according to the case definition if the disease is truly present.
- **Specificity:**
  - Probability of a subject being negative according to the case definition if the disease is truly absent.
Diagnostic spectrum of pneumonia
Expert Rev Vaccines 8(8) 1051-1061 (2009)

Clinical diagnosis

Any Rx abnormality

Lobar consolidation

Culture-proven bacterial pneumonia

Sensitivity

Specificity
Study design components

Choice of the reference study population

Study End -points

Allocation study regimens
Randomization of allocation to vaccine or control or placebo groups

- **Randomization** ensures that each patient has an equal chance of receiving any of the treatments under study.
- **Each individual** has the same chance of receiving each of the possible regimen.
- **Randomization** minimize bias in regimen allocation:
  - Known and unknown confounding variables will be equally distributed.
  - On average study groups will tend to be comparable with respect to baseline variables (given a sufficient sample size).
- **Regimen allocation** by randomization can be stratified (i.e. by age-group, country, site).
Study design components

Choice of the reference study population

Study End-points

Allocation study regimens

Ascertainment of outcome
Ascertainment of outcome: how to avoid bias

- A critical aspect is to ensure that the ascertainment of the outcome of interest (i.e. subjects with adverse events after immunization, subjects with clinical acute hepatitis, etc etc) is not biased by the collection of more or less accurate information from one or another of the study groups.

- This is achieved by blinding to study group all personnel (double-blind) involved in the study to eliminate the potential for observational bias.
Blinding

- **Double blind design**: study site personnel and sponsor personnel are blind to vaccine groups
- **Single blind design**: only the site personnel is blind to vaccine groups
- **Observer blind**: Only the site staff involved in the ascertainment of outcome is blind to vaccine groups
  - Blind studies require strict rules (site procedures/SOPs, labelling, packaging, rules for breaking the blind, DSMB etc)
- **Open label**: unblind study
The double-blind design strength is to eliminate the potential for observational bias.

The double-blind design is an ESSENTIAL component of any trial in particular Vaccine Clinical Efficacy studies and Vaccine Safety studies.

E9ICH- General Considerations for Clinical Trials
Study design components

Choice of the reference study population

Study End-points

Allocation study regimens

Compliance

Ascertainment of outcome
Assess and maintain compliance

- Critical to keep the subjects lost-to-follow up at the minimum and ensure that they are compliant with study procedures: **compliance may become a true operational challenge for even simple studies**!
- Non compliance decrease the sample size and statistical power of the trial to detect any **true effect** of the study vaccine
- It is inevitable that some subjects will be non-compliant despite any reasonable effort
  - Follow-up operational methodology has to be detailed, uniform and feasible
  - **Investigator, Site and Field evaluation** are very important
  - **Population characteristics**: urban, rural, migration
  - **Resources**: affordability and sustainability

**Feasibility! Feasibility! Feasibility!**
“The study was done at Ratchaburi Regional Hospital (RRH), and involved 35 schools in the district. We enrolled schoolchildren aged 4–11 years and actively followed up all children to detect acute febrile illness based on daily surveillance of school registers during school terms for absenteeism, followed by phone calls or home visits to absentees, and on phone calls twice per week, mobile phone text-messages, or home visits throughout school holidays. In case of febrile illness at anytime (defined as illness with two temperature readings of 37 • 5°C or higher at least 4 h apart), parents were asked to take their child to RRH for diagnosis and treatment. The surveillance system also captured spontaneous consultations at RRH…………….Active surveillance was maintained until each participant had been followed up for at least 13 months after the third vaccination”.

VE randomized double-blind controlled study design

Study design components

- Choice of the reference study population
- Study End-points
- Allocation study regimens
- Ascertainment of outcome
- Compliance
- Stopping Rules
Stopping Rules: decision for early termination of the trial

- Complex issue with an underlying Hippocratic principle to follow: “Primum non nŏcēre” or «First do no harm»
- When during the trial there is persistent evidence (usually statistically significant) of vaccinated individuals exposed to high risk than unvaccinated control (or placebo) group
  - Higher disease rate (lack of VE)
  - Higher mortality
  - Higher Adverse Events rates
Early termination of a trial

VE randomized double-blind controlled study design

- Statistical Power
- Stopping Rules
- Compliance
- Ascertainment of outcome
- Choice of the reference study population
- Study End-points
- Allocation study regimens

Study design components
Statistical power

- Sample size determination must be addressed earlier in the planning of clinical trials.

- Sample size has to be sufficient (statistical power) to detect differences between the two groups.
  - Non-inferiority
  - Safety outcome
  - Disease incidence/prevalence (VE)

- The required sample size is a function of the desired width of the confidence interval, the assumed VE (or events frequency), and the assumed disease attack rate (or event frequency) in the controls, and dropout rate.
Sample size and statistical power

«With an assumed disease incidence of 1 • 3%, a true VE of 70%, a minimum follow-up of 1 year after the third vaccination, and a subject attrition rate of 7 • 5% per year, 4002 participants assigned with a 2:1 ratio to dengue vaccine or control were needed to show, with more than 80% power, and 95% confidence, that VE was not null”.

Study design components

- Analysis and Interpretation
- Choice of the reference study population
- Study End-points
- Allocation study regimens
- Ascertainment of outcome
- Compliance
- Stopping Rules
- Statistical Power
Analysis and Interpretation

- **All randomized subjects** have to be included in the analysis “once randomized, always analyzed”

- **First step** is to compare relevant baseline subjects characteristics between vaccine and comparison group to show that balance is achieved

- ITT and PP population

- Analysis of primary outcome (endpoint)

- Analysis of secondary endpoints

- Interpretation
### Analysis: Demographics Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Dengue vaccine (n=2669)</th>
<th>Control (n=1333)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Per-protocol analysis set for efficacy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>2452</td>
<td>1221</td>
</tr>
<tr>
<td>Age (years)</td>
<td>8.18 (2.04)</td>
<td>8.23 (2.06)</td>
</tr>
<tr>
<td>Boys</td>
<td>1187 (48%)</td>
<td>583 (48%)</td>
</tr>
<tr>
<td><strong>Full analysis set for immunogenicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>197</td>
<td>99</td>
</tr>
<tr>
<td>Age (years)</td>
<td>8.26 (1.74)</td>
<td>8.12 (1.74)</td>
</tr>
<tr>
<td>Boys</td>
<td>84 (43%)</td>
<td>46 (46%)</td>
</tr>
<tr>
<td>Body-mass index (kg/m²)</td>
<td>16.4 (3.4)</td>
<td>16.8 (3.7)</td>
</tr>
<tr>
<td>Anti-DENV or anti-JEV prevalence*</td>
<td>179 (91%)</td>
<td>91 (92%)</td>
</tr>
<tr>
<td>Anti-JEV prevalence*</td>
<td>157 (80%)</td>
<td>77 (78%)</td>
</tr>
<tr>
<td>Anti-DENV prevalence (≥1 serotype)*</td>
<td>138 (70%)</td>
<td>68 (69%)</td>
</tr>
</tbody>
</table>

Data are n, mean (SD), or n (%). DENV=dengue virus. JEV=Japanese encephalitis virus. *Anti-DENV and anti-JEV seroprevalence defined as the percentage of participants with a plaque-reduction neutralisation test (PRNT<sub>50</sub>) titre of 10 or higher.

**Table 1: Baseline characteristics of participants**
### Table 1. Demographic Characteristics of the Subjects (Intention-to-Treat Population).*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hepatitis B Vaccine (N=170)</th>
<th>RTS,S/AS02D Vaccine (N=170)</th>
<th>All Subjects (N=340)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at the time of first dose of vaccine — wk</td>
<td>7.9±0.8</td>
<td>7.8±0.8</td>
<td>7.8±0.8</td>
</tr>
<tr>
<td>Sex — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>85 (50.0)</td>
<td>91 (53.5)</td>
<td>176 (51.8)</td>
</tr>
<tr>
<td>Male</td>
<td>85 (50.0)</td>
<td>79 (46.5)</td>
<td>164 (48.2)</td>
</tr>
<tr>
<td>Distance from hospital to home — km</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5.0</td>
<td>59 (34.7)</td>
<td>45 (26.5)</td>
<td>104 (30.6)</td>
</tr>
<tr>
<td>5.0–9.9</td>
<td>16 (9.4)</td>
<td>20 (11.8)</td>
<td>36 (10.6)</td>
</tr>
<tr>
<td>10.0–14.9</td>
<td>42 (24.7)</td>
<td>51 (30.0)</td>
<td>93 (27.4)</td>
</tr>
<tr>
<td>≥15.0</td>
<td>53 (31.2)</td>
<td>54 (31.8)</td>
<td>107 (31.5)</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding.
### Analysis: Primary Endpoint

#### Table 2: Serotype-specific and overall efficacy of CYD tetravalent dengue vaccine against virologically confirmed dengue disease

<table>
<thead>
<tr>
<th></th>
<th>Dengue vaccine</th>
<th>Control</th>
<th>Efficacy (95% CI)</th>
<th>Heterogeneity p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;28 days after 3 injections (per-protocol analysis)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td>2522</td>
<td>1251</td>
<td>30.2% (13.4 to 56.6)</td>
<td>0.0340</td>
</tr>
<tr>
<td>Serotype 1 episodes</td>
<td>2536</td>
<td>1259</td>
<td>55.6% (21.6 to 84.0)</td>
<td>--</td>
</tr>
<tr>
<td>Serotype 2 episodes</td>
<td>2510</td>
<td>1259</td>
<td>9.2% (75.0 to 51.3)</td>
<td>0.0309</td>
</tr>
<tr>
<td>Serotype 3 episodes</td>
<td>2541</td>
<td>1257</td>
<td>75.3% (37.0 to 99.6)</td>
<td>--</td>
</tr>
<tr>
<td>Serotype 4 episodes</td>
<td>2542</td>
<td>1263</td>
<td>100.0% (24.8 to 100.0)</td>
<td>--</td>
</tr>
<tr>
<td>NS1-antigen positive only episodes</td>
<td>2542</td>
<td>1265</td>
<td>ND</td>
<td>--</td>
</tr>
<tr>
<td>&gt;28 days after 2 injections</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td>3824</td>
<td>1905</td>
<td>35.3% (3.3 to 56.5)</td>
<td>0.0057</td>
</tr>
<tr>
<td>Serotype 1 episodes</td>
<td>3855</td>
<td>1921</td>
<td>68.8% (27.0 to 87.4)</td>
<td>--</td>
</tr>
<tr>
<td>Serotype 2 episodes</td>
<td>3824</td>
<td>1918</td>
<td>-0.3% (75.0 to 41.1)</td>
<td>0.0009</td>
</tr>
<tr>
<td>Serotype 3 episodes</td>
<td>3860</td>
<td>1924</td>
<td>83.4% (7.1 to 98.4)</td>
<td>--</td>
</tr>
<tr>
<td>Serotype 4 episodes</td>
<td>3864</td>
<td>1934</td>
<td>87.5% (26.5 to 99.7)</td>
<td>--</td>
</tr>
<tr>
<td>NS1-antigen positive only episodes</td>
<td>3863</td>
<td>1936</td>
<td>-100.5% (97.1 to 80.2)</td>
<td>--</td>
</tr>
<tr>
<td>After at least one injection (intention-to-treat analysis)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td>5292</td>
<td>2630</td>
<td>34.9% (6.7 to 54.3)</td>
<td>0.0027</td>
</tr>
<tr>
<td>Serotype 1 episodes</td>
<td>5343</td>
<td>2666</td>
<td>61.2% (17.4 to 82.1)</td>
<td>--</td>
</tr>
<tr>
<td>Serotype 2 episodes</td>
<td>5312</td>
<td>2662</td>
<td>3.5% (59.8 to 40.5)</td>
<td>0.0007</td>
</tr>
<tr>
<td>Serotype 3 episodes</td>
<td>5348</td>
<td>2667</td>
<td>81.9% (38.8 to 95.8)</td>
<td>--</td>
</tr>
<tr>
<td>Serotype 4 episodes</td>
<td>5353</td>
<td>2679</td>
<td>90.0% (10.6 to 99.8)</td>
<td>--</td>
</tr>
<tr>
<td>NS1-antigen positive only episodes</td>
<td>5351</td>
<td>2681</td>
<td>-150.5% (73.7 to 32.2)</td>
<td>--</td>
</tr>
</tbody>
</table>

Note: A case was defined as a first episode of virologically confirmed dengue by either serotype-specific PCR, or NS1-antigen ELISA. Serotype-specific efficacy was calculated including all episodes of that serotype. Four children with two virologically confirmed dengue episodes during the study were therefore included once in each of the two serotype-specific analyses concerned. Fisher’s exact test was used to test heterogeneity of serotype distribution between groups among the four serotypes and Kruskal-Wallis was used to test the distribution between groups of serotype 2 versus the other three serotypes, NS1-antigen positive only cases (ie, RT-PCR negative cases) were excluded from heterogeneity testing.

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### Analysis: Secondary Endpoints

#### Table 2. Incidence of Serious Adverse Events, Unsolicited Reports of Adverse Events, and Solicited Reports of Injection-Site and General Adverse Events (Intention-to-Treat Population). *

<table>
<thead>
<tr>
<th>Event</th>
<th>Hepatitis B Vaccine</th>
<th>RTS, S/AS02D Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serious adverse event</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total no. of subjects</td>
<td>170</td>
<td>170</td>
</tr>
<tr>
<td>No. of subjects with event</td>
<td>170</td>
<td>170</td>
</tr>
<tr>
<td>Any</td>
<td>42</td>
<td>31</td>
</tr>
<tr>
<td><em>Plasmodium falciparum</em> infection</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>In absence of <em>P. falciparum</em> infection</td>
<td>40</td>
<td>29</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>28</td>
<td>10</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Anemia</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Death</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Unsolicited report of adverse event</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of subjects with event</td>
<td>141</td>
<td>137</td>
</tr>
<tr>
<td>Any</td>
<td>82.9 (76.4–88.3)</td>
<td>80.6 (73.8–86.2)</td>
</tr>
<tr>
<td>Cough</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>54</td>
<td>49</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>73</td>
<td>56</td>
</tr>
<tr>
<td>Severity grade 3</td>
<td>16</td>
<td>7</td>
</tr>
<tr>
<td>Related to vaccine</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

*Percent (95% CI)*

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Analysis and interpretation

Always dedicated as much time as needed to examine the data (i.e. tables, figures, diagrams) and to interpret your results
THANK YOU