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

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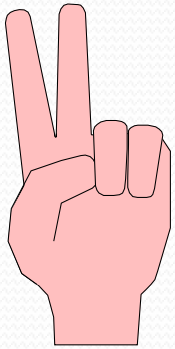
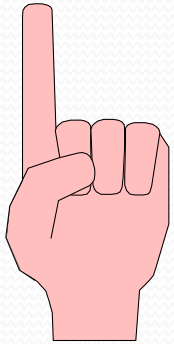
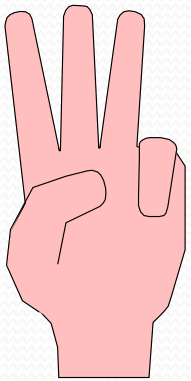
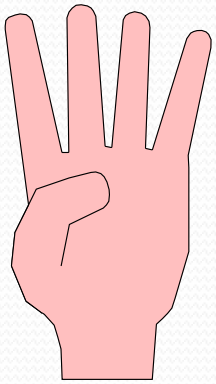
Clinical Development Phases





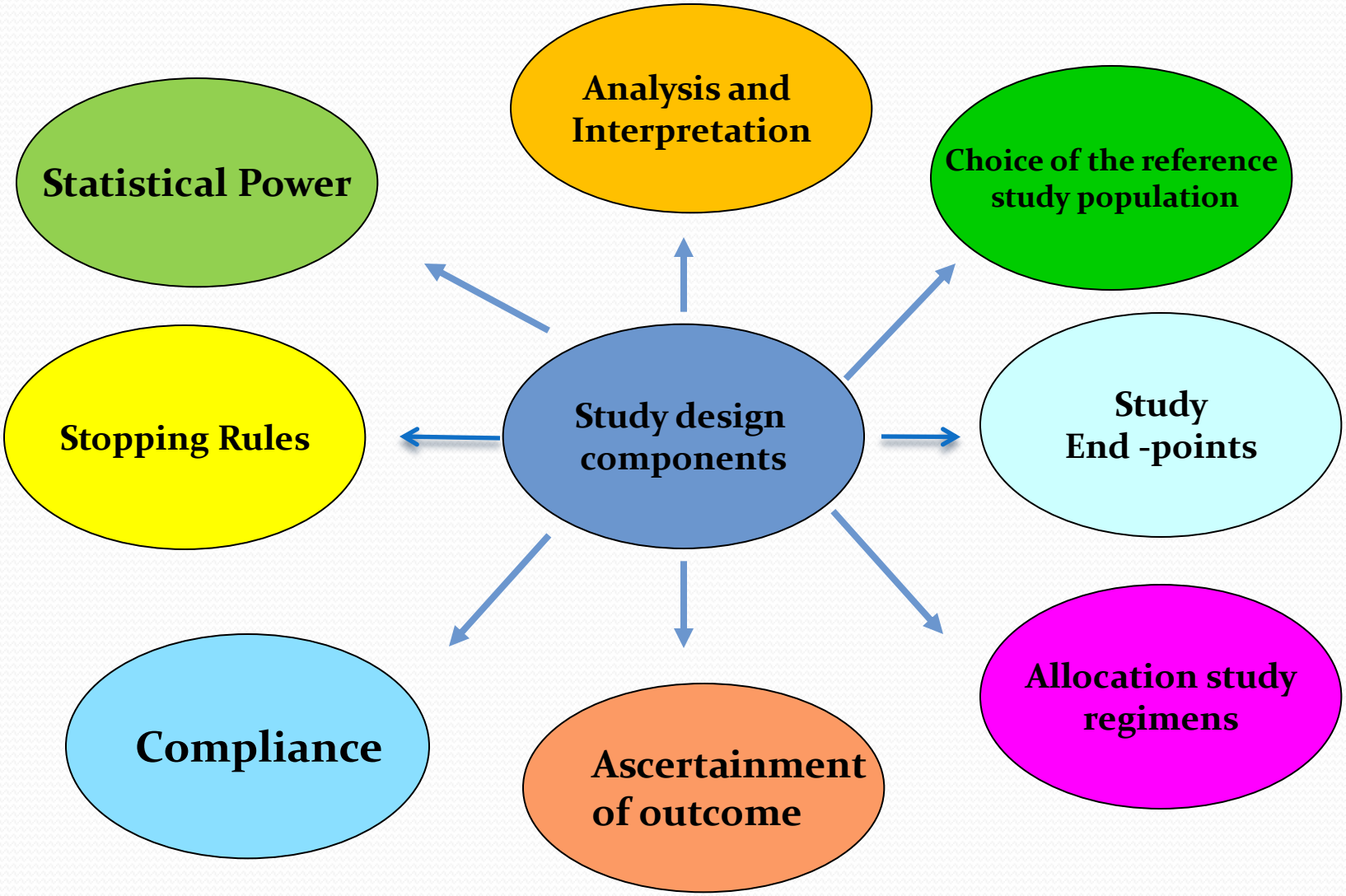


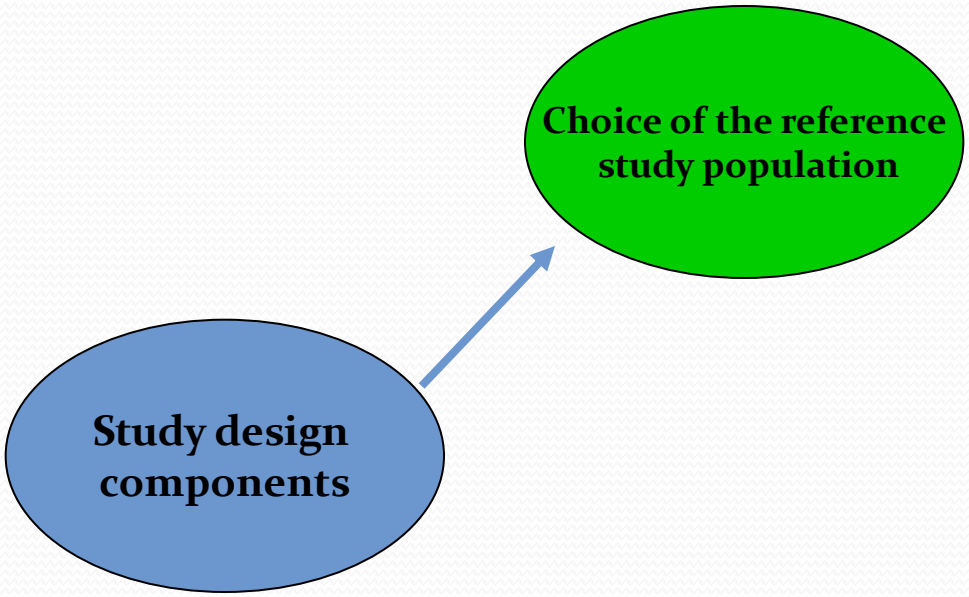


- Phase I: safety & immunogenicity
- Phase II: safety & immunogenicity
- Phase III: efficacy, safety
- Phase IV : post licensure, immunogenicity, effectiveness, safety

Clinical Study = Clinical Trial

Clinical Study (trial) design components




Choice of the reference study population
Study design components

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

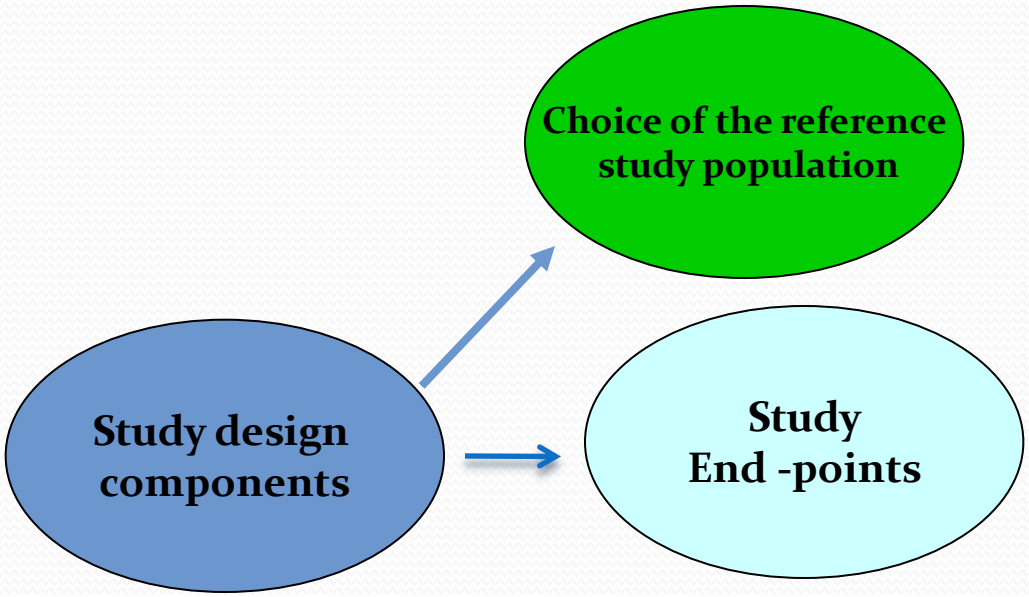
- Phase I : Healthy men and women aged between 18 and 45 years with no comorbidities were eligible for inclusion. (Ramsauer K et al. Immunogenicity, safety, and tolerability of a recombinant measles-virus-based chikungunya vaccine: a randomised, double-blind, placebo-controlled, active-comparator, first-in-man 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 AfricansN 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.

(Feng-Cai Zhu et al. Efficacy and safety of a recombinant hepatitis E vaccine in healthy adults: a large-scale, randomised, double-blind placebo-controlled, phase 3 trial. Lancet 2010; 376: 895–902)


Choice of the reference study population
Study design components
Study End -points

Establishement 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

Establishement 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

Samba O.Sow et al. Immunogenicity and Safety of a Meningococcal A Conjugate Vaccine in Africans N Engl J Med 2011;364:2293-304.

Establishement 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 end-points

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.

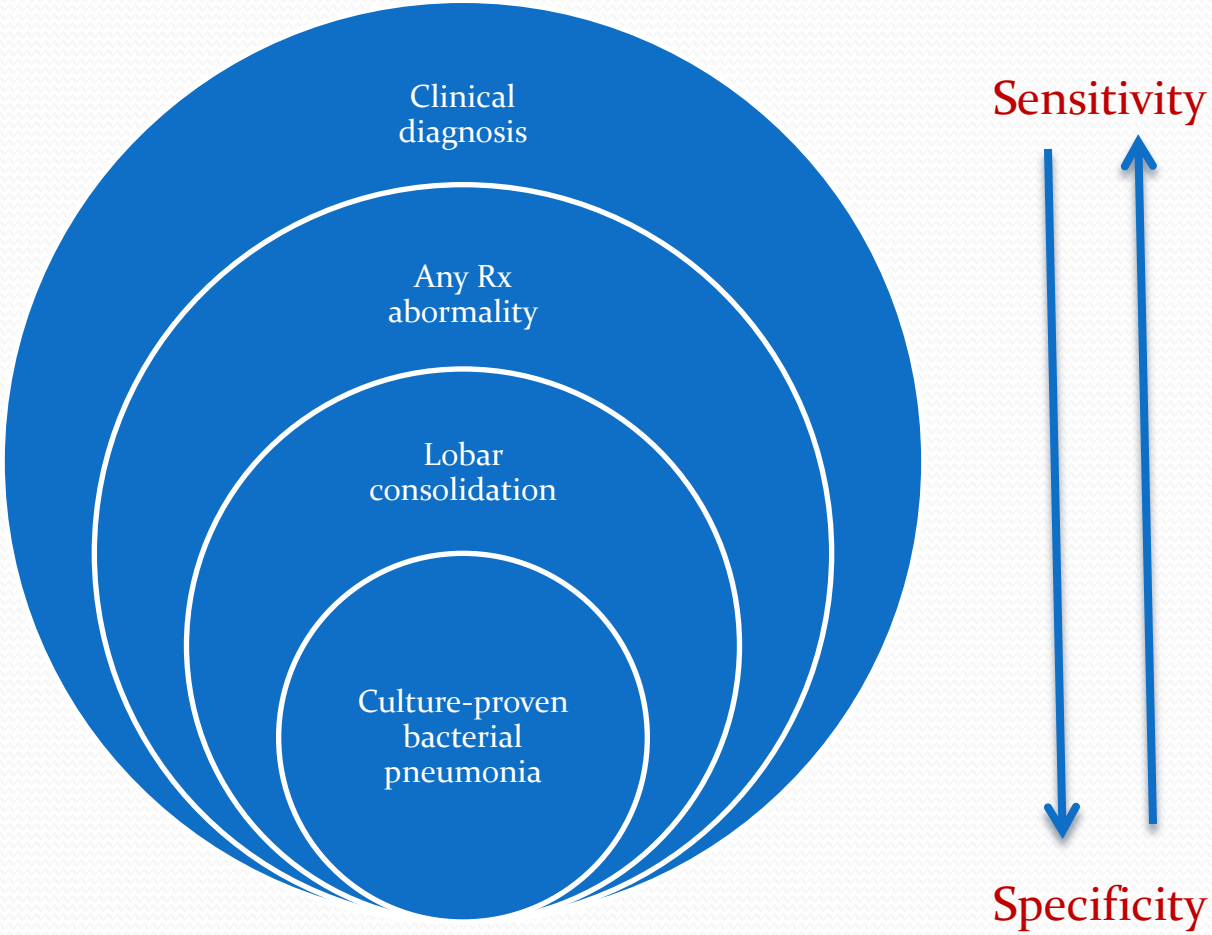
Feng-Cai Zhu et al. Efficacy and safety of a recombinant hepatitis E vaccine in healthy adults: a large-scale, randomised, double-blind placebo-controlled, phase 3 trial. Lancet 2010; 376: 895–902

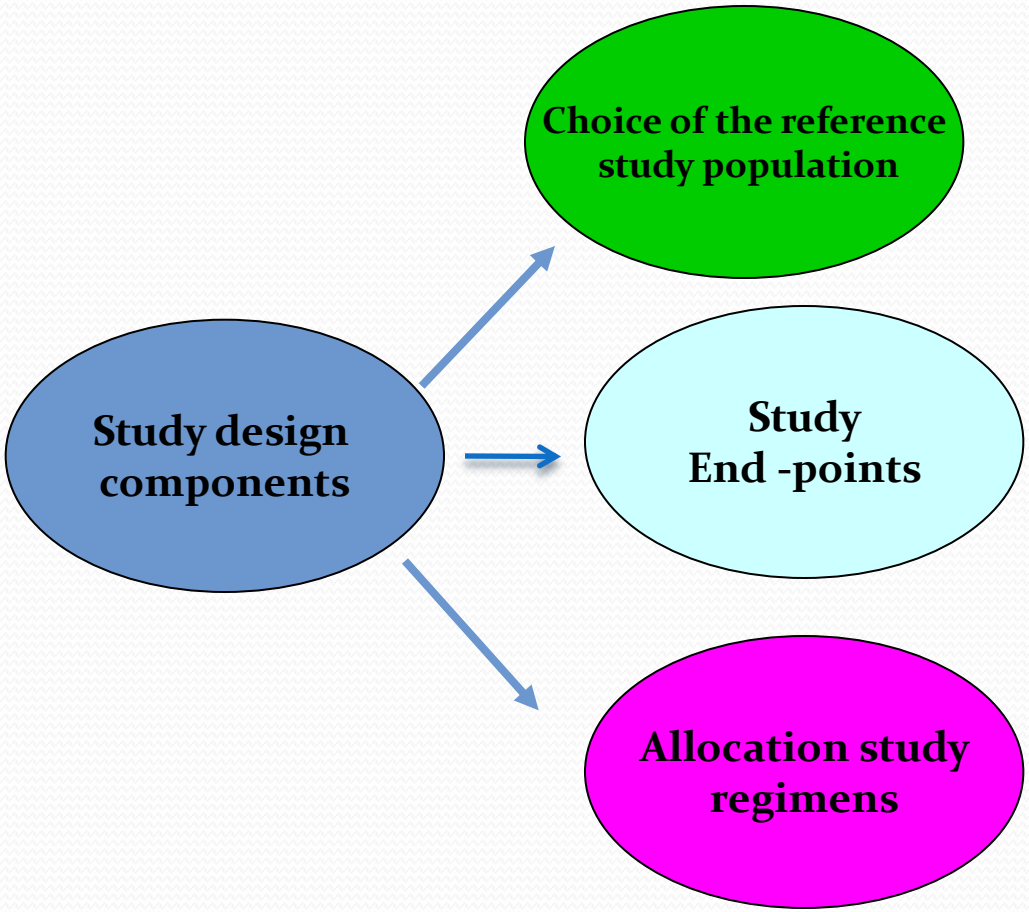
Sensitivity and specificity of case definition

- Case definition should be validate 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 the case definition if the disease is truly present
- Specificity:
  - Probability of a subject being negative according the case definition if the disease is truly absent

Diagnostic spectrum of pneumonia

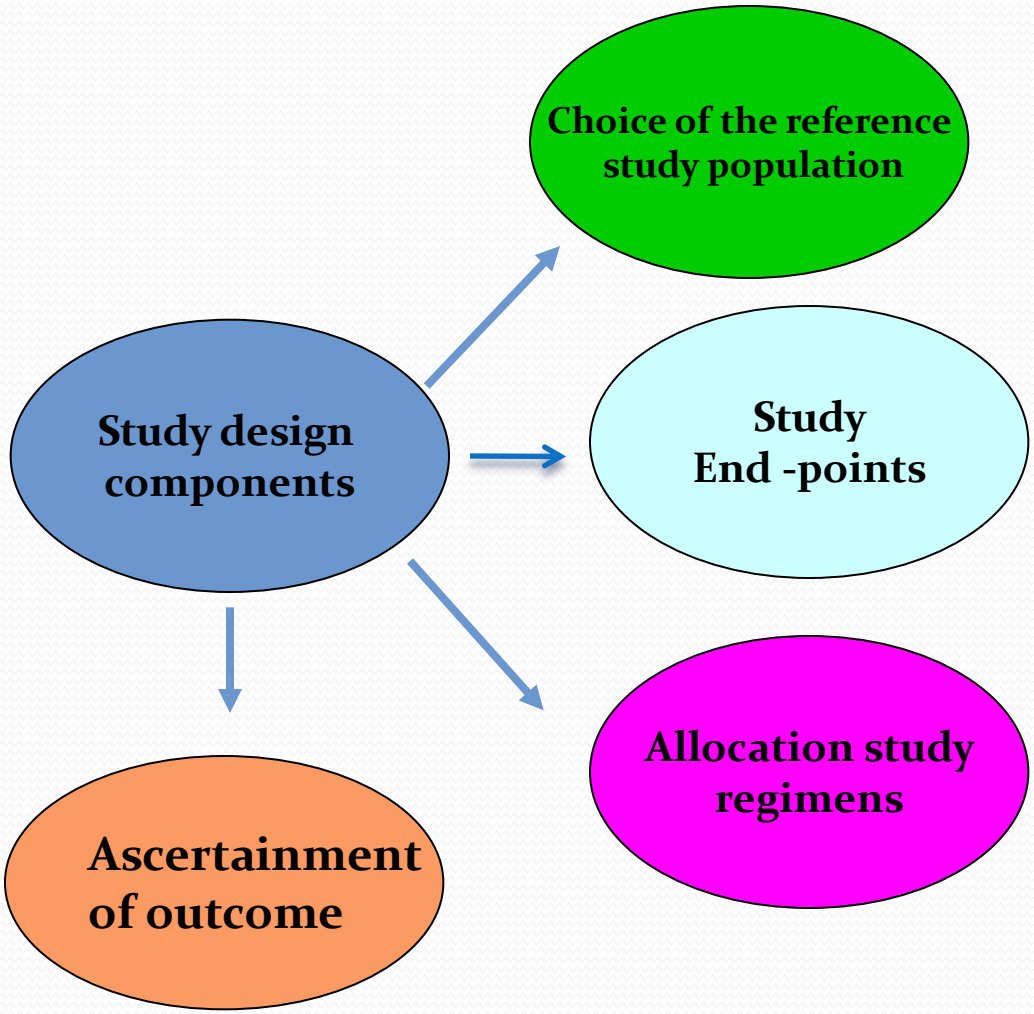
Expert Rev Vaccines 8(8) 1051-1061 (2009)




Choice of the reference study population
Study design components
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)


Choice of the reference study population
Study design components
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 heaptitis, 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**

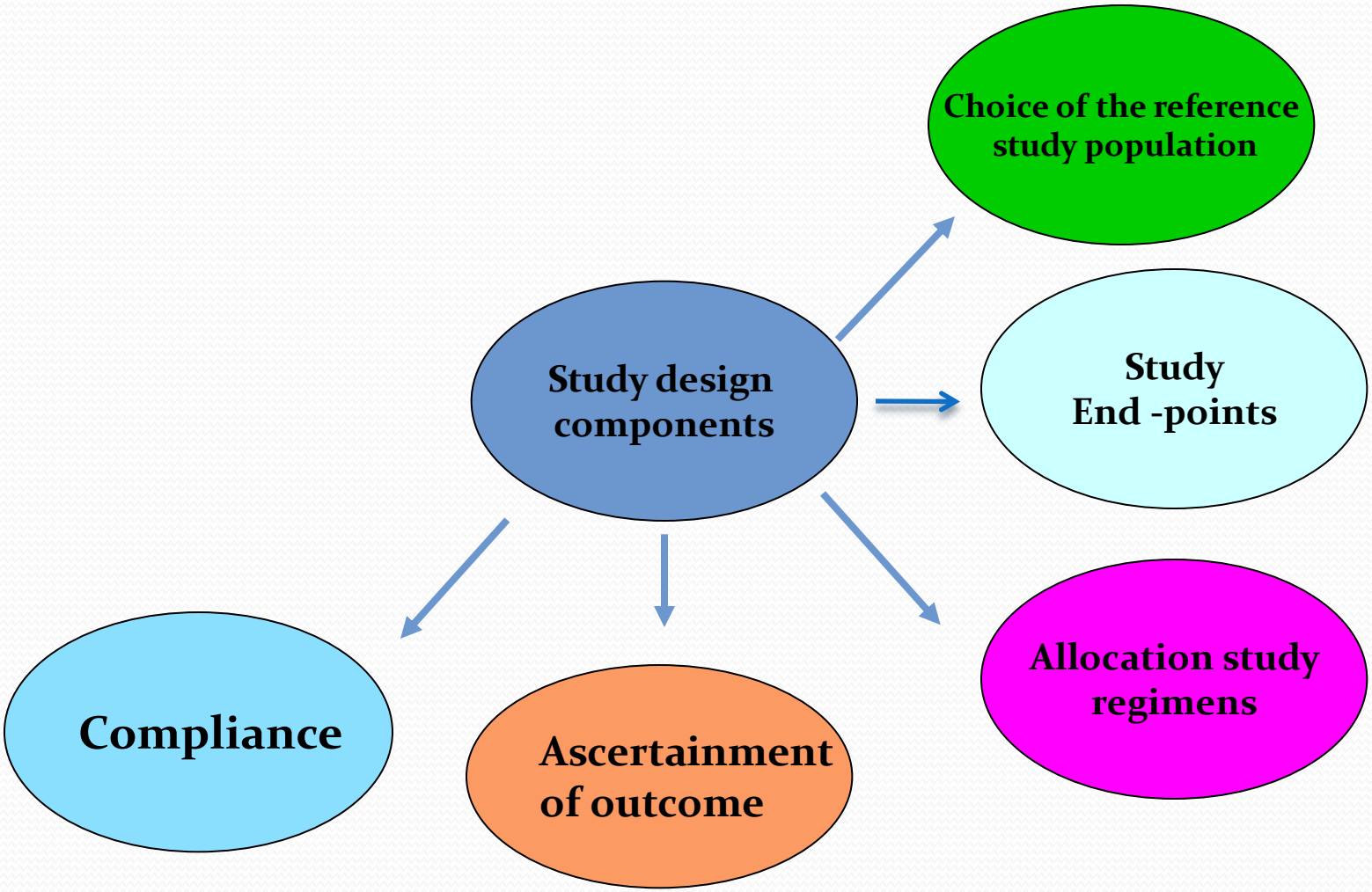
Blinding

- 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


Choice of the reference study population
Study design components
Study End -points
Compliance
Ascertainment of outcome
Allocation study regimens

Assess and mantain compliance

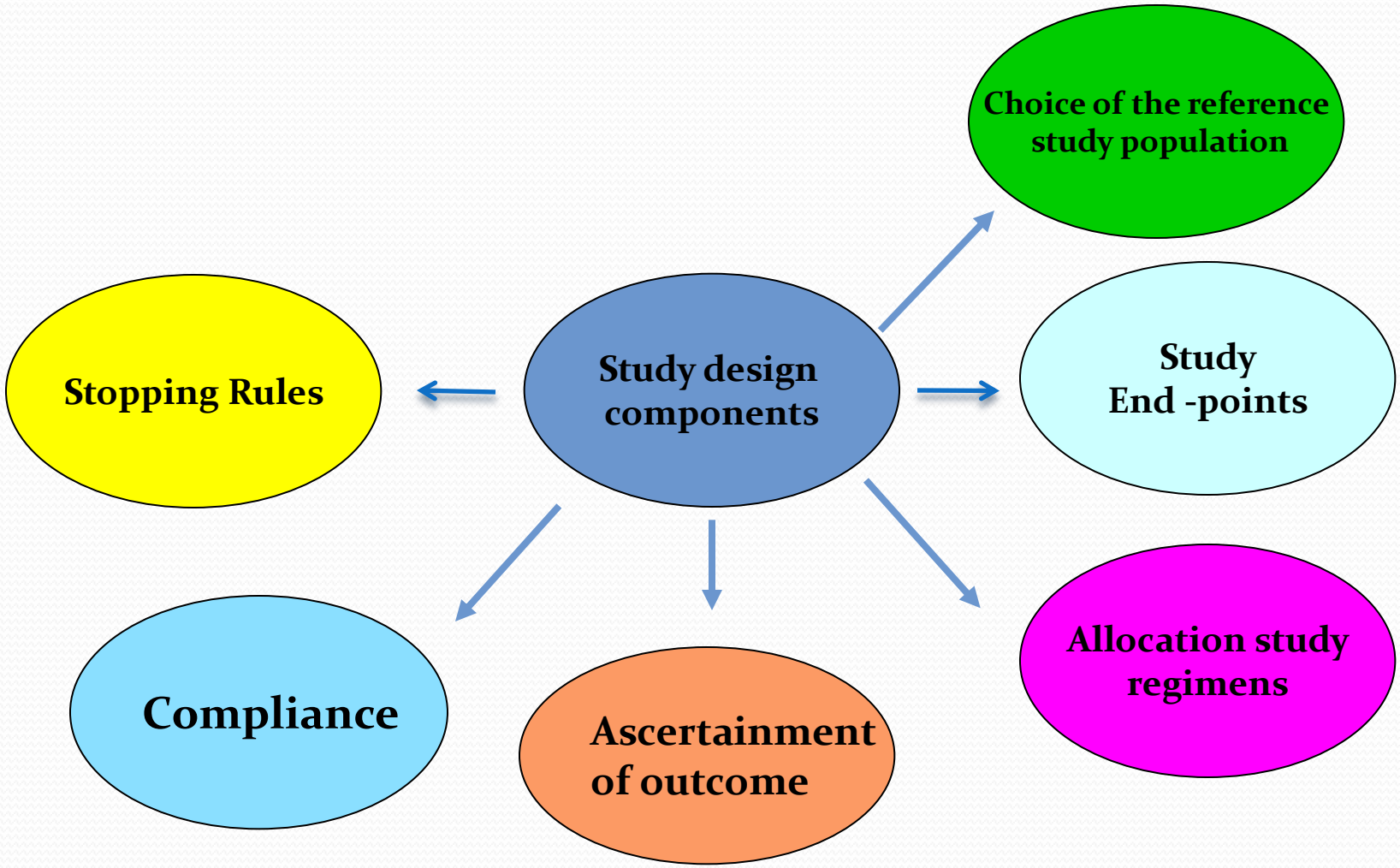
- Critical to keep the subjects lost-to-follow up at the minimum and ensure that they are compliant with study procedures: compliance may become a true operational challenge for even simple studies!
- Non compliance decrease the sample size and statistical power of the trial to detect any true effect of the study vaccine
- It is inevitable that some subjects will be non-compliant despite any resonable 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**".

Arunee Sabchareon et al. Protective efficacy of the recombinant, live-attenuated, CYD tetravalent dengue vaccine in Thai school children: a randomised, controlled phase IIb trial. The Lancet, Volume 380, Issue 9853, Pages 1559 - 1567, 3 November 2012.

VE randomized double-blind controlled study design



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 (ususally 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

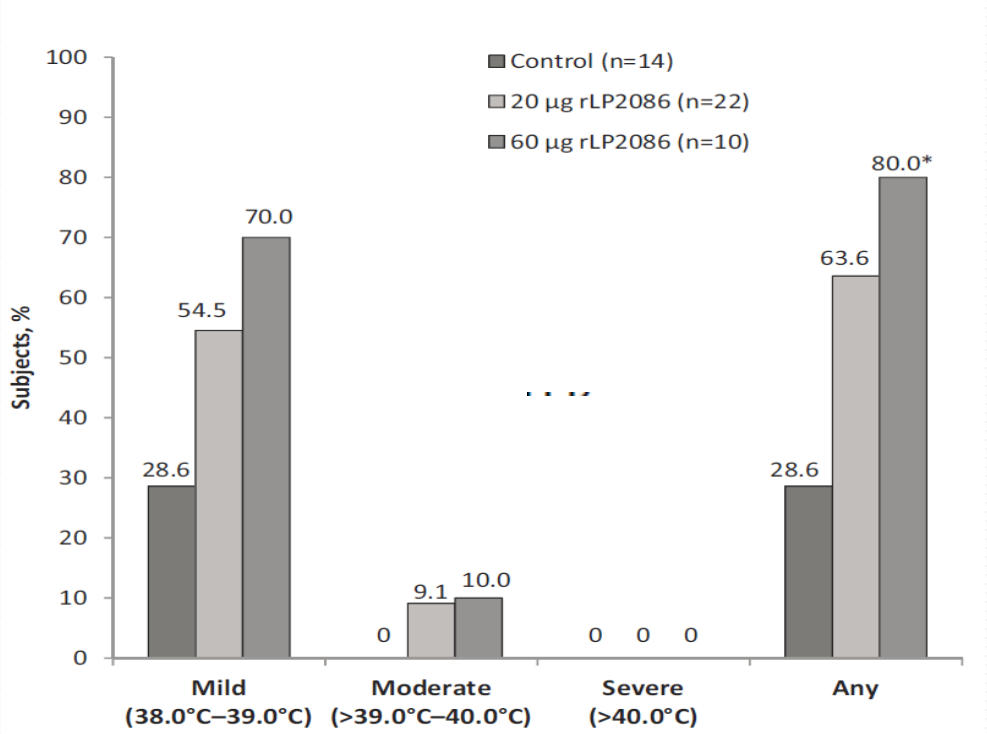
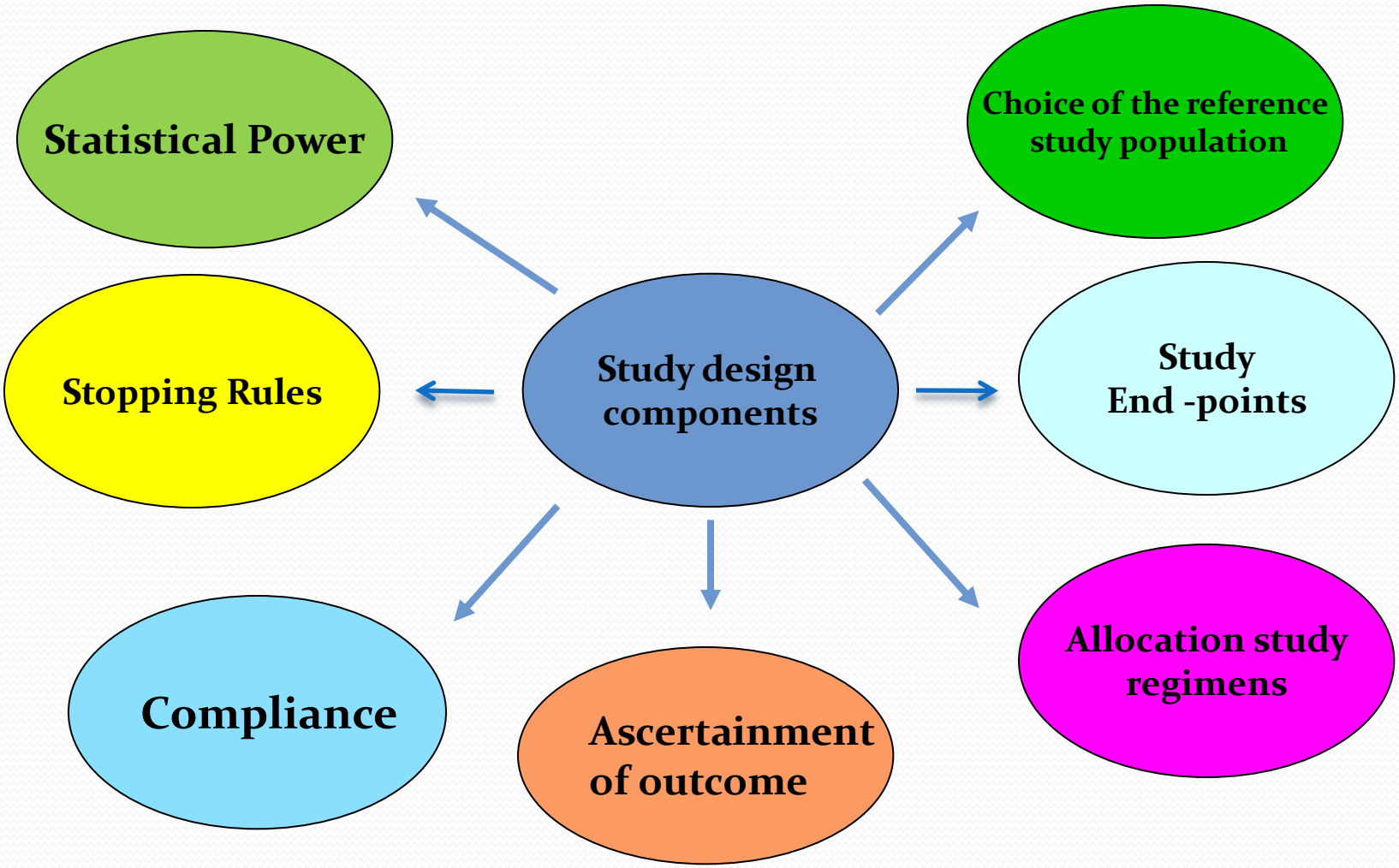


Fig. 2. Fever severity in subjects in the safety population. *Not including the case of aseptic meningitis.

Martinon-Torres F et al. **A randomized, phase 1/2 trial of the safety, tolerability, and immunogenicity of bivalent rLP2086meningococcal B vaccine in healthy infants**.Vaccine. 2014 Sep 8;32(40):5206-11.

VE randomized double-blind controlled study design



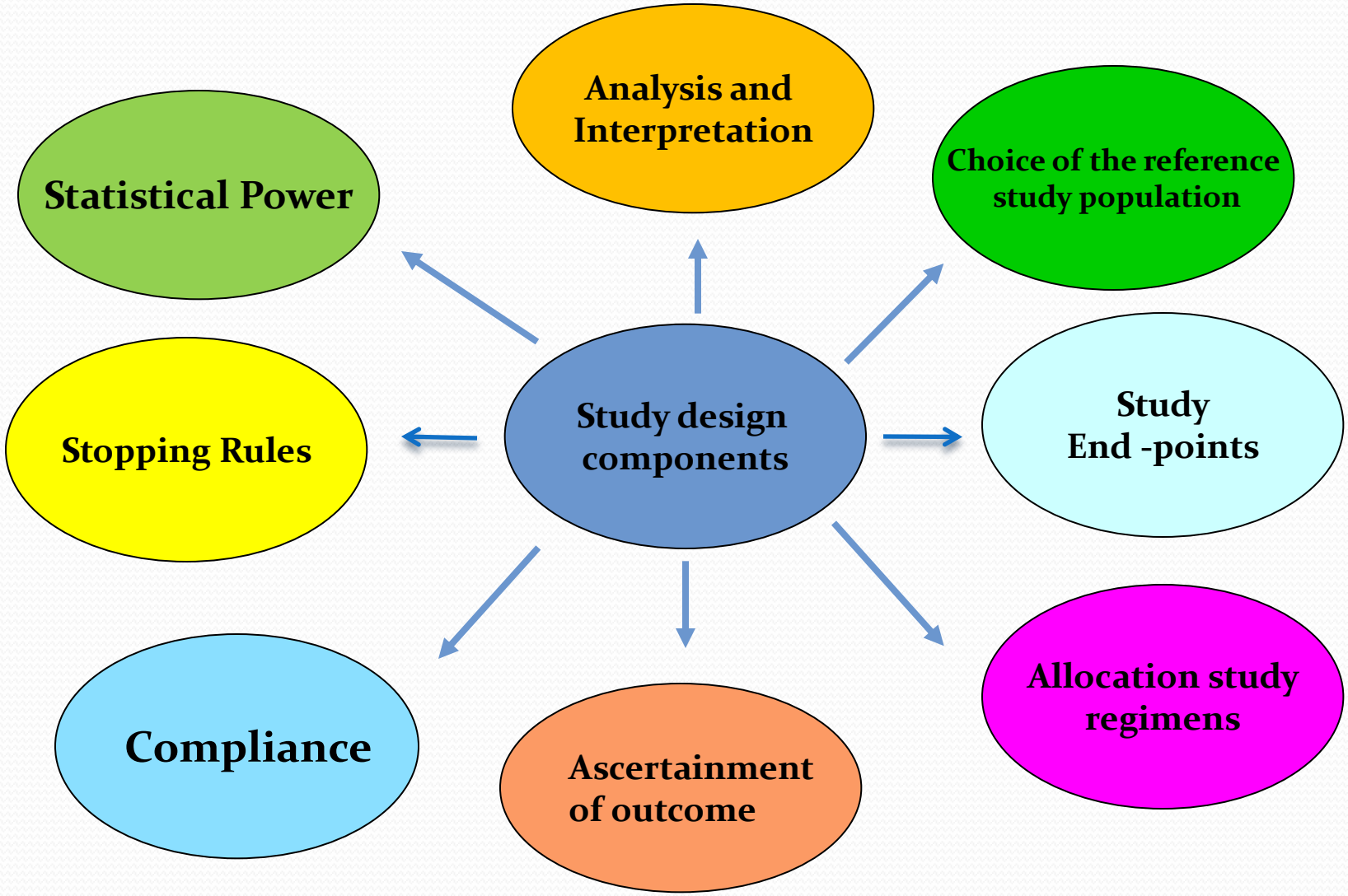
Statistical power

- Sample size determination must be adressed 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".

Arunee Sabchareon et al. Protective efficacy of the recombinant, live-attenuated, CYD tetravalent dengue vaccine in Thai school children: a randomised, controlled phase IIb trial. The Lancet, Volume 380, Issue 9853, Pages 1559 - 1567, 3 November 2012.


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

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 achievied
- ITT and PP population
- Analysis of primary outcome (endpoint)
- Analysis of secondary enpoints
- Interpretation

Analysis ITT and PP population

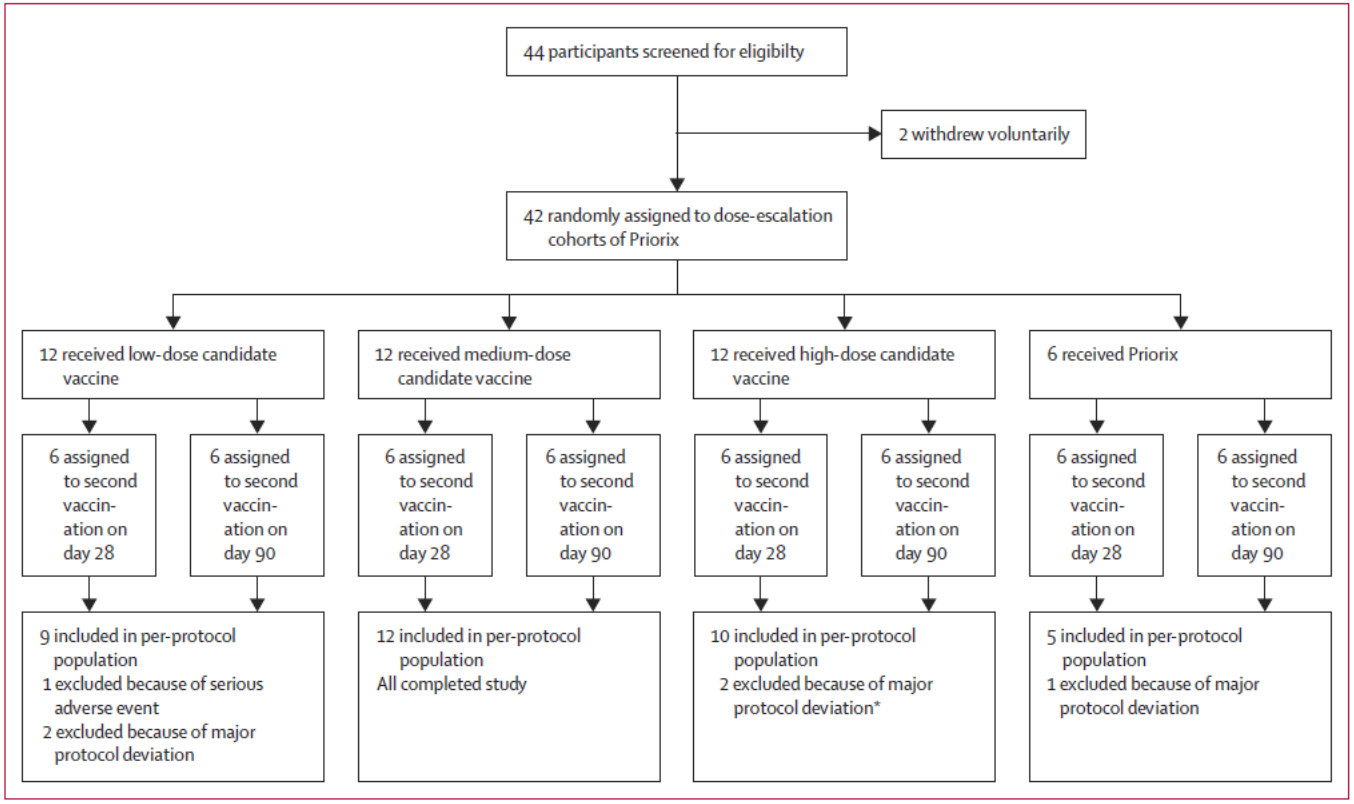


Figure 1: Trial profile
*Major protocol deviations were time-window deviations (n=3) and two voluntary withdrawals (for any reason) from further vaccinations.

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.

Analysis: Demographics Characteristics

	Dengue vaccine (n=2669)	Control (n=1333)
Per-protocol analysis set for efficacy		
n	2452	1221
Age (years)	8·18 (2·04)	8·23 (2·06)
Boys	1187 (48%)	583 (48%)
Full analysis set for immunogenicity		
n	197	99
Age (years)	8·26 (1·74)	8·12 (1·74)
Boys	84 (43%)	46 (46%)
Body-mass index (kg/m^2)	16·4 (3·4)	16·8 (3·7)
Anti-DENV or anti-JEV prevalence*	179 (91%)	91 (92%)
Anti-JEV prevalence*	157 (80%)	77 (78%)
Anti-DENV prevalence (≥1 serotype)*	138 (70%)	68 (69%)

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 ($PRNT_{50}$) titre of 10 or higher.

Table 1: **Baseline characteristics of participants**

Arunee Sabchareon et al. Protective efficacy of the recombinant, live-attenuated, CYD tetravalent dengue vaccine in Thai school children: a randomised, controlled phase IIb trial. The Lancet, Volume 380, Issue 9853, Pages 1559 - 1567, 3 November 2012

Analysis: Demographics Characteristics

Table 1. Demographic Characteristics of the Subjects (Intention-to-Treat Population).*

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

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding.

Salim Abdulla et al. Safety and Immunogenicity of RTS,S/AS02D Malaria Vaccine in Infants. N ENGL J Med 2008;359:2533-44.

Analysis: Primary Endpoint

	Dengue vaccine		Control		Efficacy	
	Person-years at risk	Cases or episodes*	Person-years at risk	Cases or episodes*	% (95% CI)	Heterogeneity p value†
>28 days after three injections (per-protocol analysis)						
Cases	2522	45	1251	32	30·2% (−13·4 to 56·6)	0·0340
Serotype 1 episodes	2536	9	1251	10	55·6% (−21·6 to 84·0)	..
Serotype 2 episodes	2510	31	1250	17	9·2% (−75·0 to 51·3)	0·0309
Serotype 3 episodes	2541	1	1257	2	75·3% (−375·0 to 99·6)	..
Serotype 4 episodes	2542	0	1263	4	100·0% (24·8 to 100·0)	..
NS1-antigen positive only episodes	2542	4	1265	0	ND	..
>28 days after two injections						
Cases	3824	61	1905	47	35·3% (3·3 to 56·5)	0·0057
Serotype 1 episodes	3855	10	1921	16	68·8% (27·0 to 87·4)	..
Serotype 2 episodes	3824	44	1918	22	−0·3% (−75·8 to 41·1)	0·0009
Serotype 3 episodes	3860	2	1924	6	83·4% (7·1 to 98·4)	..
Serotype 4 episodes	3864	1	1934	4	87·5% (−26·5 to 99·7)	..
NS1-antigen positive only episodes	3863	4	1936	1	−100·5% (−9771·8 to 80·2)	..
After at least one injection (intention-to-treat analysis)						
Cases	5292	76	2630	58	34·9% (6·7 to 54·3)	0·0027
Serotype 1 episodes	5343	14	2666	18	61·2% (17·4 to 82·1)	..
Serotype 2 episodes	5312	52	2662	27	3·5% (−59·8 to 40·5)	0·0007
Serotype 3 episodes	5348	4	2667	11	81·9% (38·8 to 95·8)	..
Serotype 4 episodes	5353	1	2679	5	90·0% (10·6 to 99·8)	..
NS1-antigen positive only episodes	5351	5	2681	1	−150·5% (−11748·3 to 72·0)	..

ND=not determined. *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 χ^2 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.

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

Arunee Sabchareon et al. Protective efficacy of the recombinant, live-attenuated, CYD tetravalent dengue vaccine in Thai school children: a randomised, controlled phase IIb trial. The Lancet, Volume 380, Issue 9853, Pages 1559 - 1567, 3 November 2012

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).*

Event	Hepatitis B Vaccine		RTS,S/AS02D Vaccine	
	No.	Percent (95% CI)	No.	Percent (95% CI)
Serious adverse event†				
Total no. of subjects	170		170	
No. of subjects with event				
Any	42	24.7 (18.4–31.9)	31	18.2 (12.7–24.9)
Plasmodium falciparum infection	7	4.1 (1.7–8.3)	2	1.2 (0.1–4.2)
In absence of *P. falciparum* infection	40	23.5 (17.4–30.6)	29	17.1 (11.7–23.6)
Pneumonia	28	16.5 (11.2–22.9)	10	5.9 (2.9–10.6)
Gastroenteritis	5	2.9 (1.0–6.7)	8	4.7 (2.1–9.1)
Anemia	8	4.7 (2.1–9.1)	2	1.2 (0.1–4.2)
Death‡	1	0.6 (0.0–3.2)	0	0 (0.0–2.1)
Unsolicited report of adverse event§				
No. of subjects with event				
Any	141	82.9 (76.4–88.3)	137	80.6 (73.8–86.2)
Cough	80	47.1 (39.4–54.9)	80	47.1 (39.4–54.9)
Pneumonia	54	31.8 (24.8–39.3)	49	28.8 (22.1–36.3)
Rhinorrhea	73	42.9 (35.4–50.7)	56	32.9 (25.9–40.6)
Severity grade 3	16	9.4 (5.5–14.8)	7	4.1 (1.7–8.3)
Related to vaccine	2	1.2 (0.1–4.2)	0	0 (0.0–2.1)

Salim Abdulla et al. Safety and Immunogenicity of RTS,S/AS02D Malaria Vaccine in Infants. N ENGL J Med 2008;359:2533-44.

Analysis and interpretation

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

THANK YOU