LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Statistical assessment and reporting of Phase 3 trials

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CONSORT (Consolidated Standards of Reporting Trials)

(www.consort-statement.org)

- Developed from 1993 to improve quality of reports of trials – driven by those conducting meta-analyses
- Updated version in 2010 comprises 25-item checklist and flow diagram for reporting RCTs (including vaccine trials) – adopted now by many journals
- Used by peer reviewers , editors and meta-analysts to identify reports with inadequate description and potentially biased results
- Extensions added for:

  - ✓ **Acupuncture trials (2001)**
  - ✓ **Cluster randomised trials (2004)**
  - ✓ **Reporting of Harms (2004)**
  - ✓ **Non-inferiority and equivalence trials (2006)**
  - ✓ **Herbal medicinal interventions (2006)**
  - ✓ **Non-pharmacological interventions (2008)**
  - ✓ **Abstracts (2008)**
  - ✓ **Pragmatic trials (2008)**
  - ✓ **Patient reported outcomes (2013)**

CONSORT Checklist of items to include in reporting of randomised trials

1	**TITLE & ABSTRACT**	Include how participants allocated to interventions. Structured summary of design, methods, results, conclusions
	INTRODUCTION	
2	**Background & objectives**	Scientific background and rationale. Specific objectives
	METHODS	
3	**Trial design**	e.g. Parallel group, factorial, group randomised, including allocation ratio
4	**Participants**	Eligibility criteria, trial location/setting
5	**Interventions**	Precise description (to allow replication) for all trial-arms, and how/when given
6	**Outcomes**	Primary and secondary and how and when measured. Any changes after start of trial and reasons for changes
7	**Sample size**	How determined and any planned interim analyses/stopping rules
8	**Randomisation**	How generated – and blocking or stratification

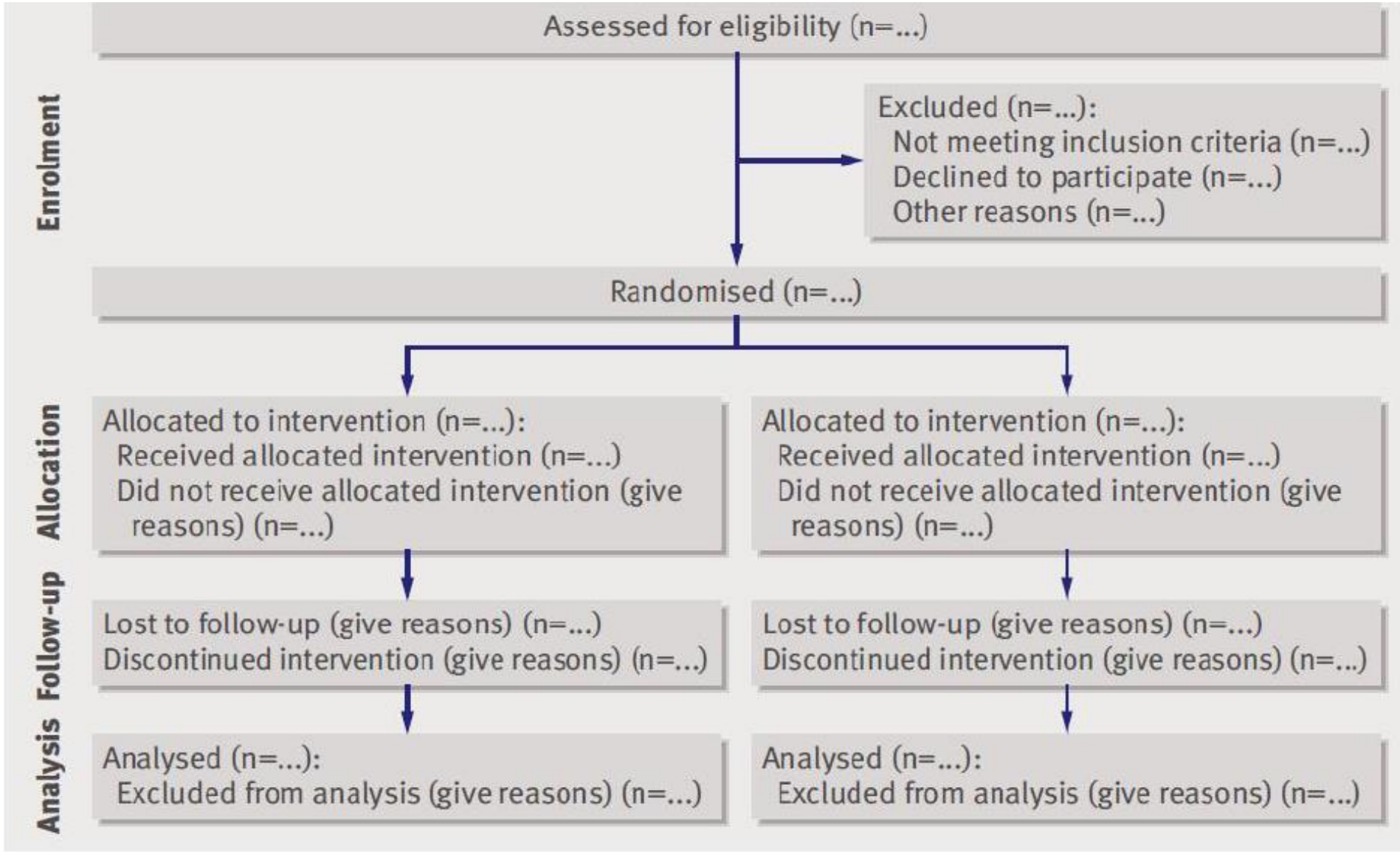
CONSORT Checklist of items to include in reporting of randomised trials

9	**Allocation concealment**	Treatment allocation not known until subject has entered study? How achieved (e.g. numbered envelopes)?
10	**Implementation**	Who randomised, enrolled, assigned participants to groups?
11	**Blinding**	Participants, vaccinators, outcome assessors – how achieved? Similarity of interventions (if relevant)
12	**Statistical methods**	Methods to compare groups for 1° and 2° outcomes, planned subgroup and adjusted analyses
	RESULTS	
13	**Participant flow**	Numbers of subjects: randomly assigned to each arm, receiving intended vaccine, completing protocol, analysed for primary outcome. Losses and exclusions after randomisation, and reasons.
14	**Recruitment**	Dates defining recruitment and follow-up. Why the trial ended or was stopped.
15	**Baseline data**	Table showing baseline demographics and clinical characteristics of each group
16	**Numbers analysed**	In each group – number included in each analysis and if analysis was by originally assigned groups (“intention to treat”) or to those receiving full intervention (“per protocol”)

CONSORT Checklist of items to include in reporting of randomised trials

17	**Outcomes & estimation**	For 1° and 2° outcomes, effect sizes and confidence intervals. For binary outcomes show both relative and absolute effects.
18	**Ancillary analyses**	Sub-group and adjusted analyses. Separate pre-specified and exploratory
19	**Harms**	All important harms or unintended effects in each group.
	DISCUSSION	
20	**Limitations**	Trial limitations - including potential biases, imprecision, multiple analyses.
21	**Generalisability**	External validity.
22	**Interpretation**	Interpretation consistent with results, benefits and harms, other relevant evidence
	OTHER INFORMATION	
23	**Registration**	Registration number and name of trial registry.
24	**Protocol**	Where the full trial protocol can be accessed, if available.
25	**Funding**	Sources of funding and other support (including vaccine donations). Role of funders.

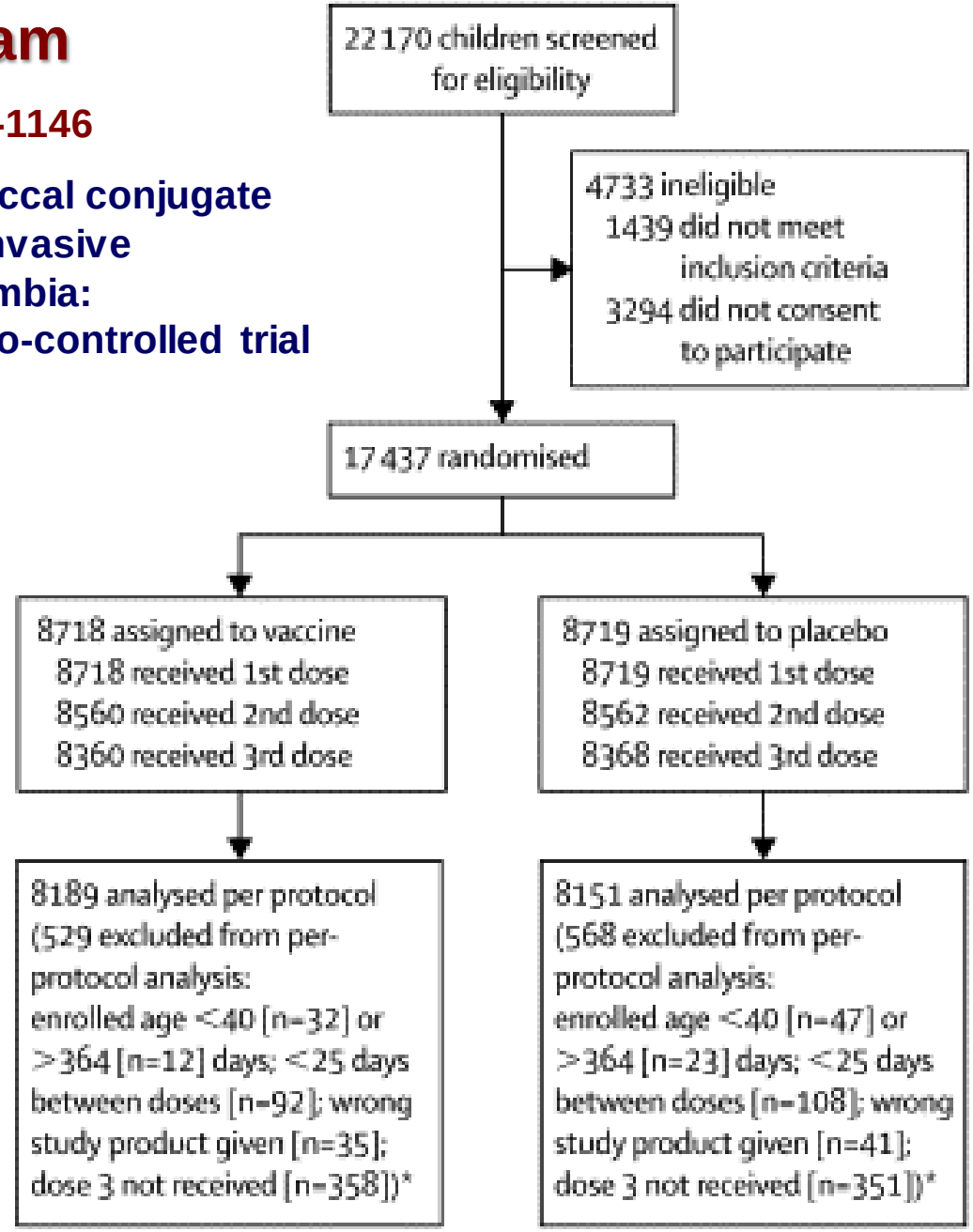
CONSORT 2010: Flow diagram of the progress through the phases of a parallel randomised trial of two groups



CONSORT Flow Diagram

Cutts et al. Lancet 2005,365, 1139-1146

Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial



STATISTICAL ANALYSIS PLAN

- Should be developed and finalised in advance of breaking code
- Approval by Steering Committee, DSMB, Regulatory Agency
- Unambiguous definition of
  - primary end-point and secondary endpoints
  - exclusion and inclusion criteria
  - entry and exit time for follow-up and analysis
  - methods of statistical assessment
  - any adjusted analyses and criteria for these
  - any sub-group analyses
- Good practice to conduct “dummy” analyses with arbitrary assignment of participants to intervention groups – speeds post code-breaking analysis
- Who will “frozen” set of data be lodged with in advance of breaking code (e.g. DSMB, Regulatory Agency)?

Analysis of an "idealised" vaccine trial

	Number randomised	Cases of disease in follow up period	Risk of disease
Control	N_0	c_0	$p_0=c_0/N_0$
Vaccinated	N_1	c_1	$p_1=c_1/N_1$

Vaccine Efficacy = $(p_0 - p_1)/ p_0$

= (1- Relative risk)

(multiply by 100 to express as percentage)

"Idealised" vaccine trial – derivation of confidence limits

	Number randomised	Cases of disease in follow up period	Risk of disease
Control	N_0	c_0	$p_0=c_0/N_0$
Vaccinated	N_1	c_1	$p_1=c_1/N_1$

VE = 1 – p_1/p_0 (expressed as a proportion) (x100 to express as %)

ln R = ln (p_1/p_0)

Standard Error (ln R) = $\sqrt{[(N_0-c_0)/c_0N_0 + (N_1-c_1)/c_1N_1]}$

95% confidence limits on ln R = ln R ± 1.96 SE

Hence 95% confidence limits on VE

Example of an idealised trial

	Number randomised	Cases of disease in follow up period	Risk of disease
Control	200 (N_0)	50 (c_0)	p_0=0.25
Vaccinated	200 (N_1)	30 (c_1)	p_1=0.15

VE = 1 - 0.15/0.25 = 0.4 (i.e. **40%**)

ln R = ln (p_1/p_0) = ln(0.15/0.25) =-0.511

Standard Error (ln R) = $\sqrt{[(N_0-c_0)/c_0N_0 + (N_1-c_1)/c_1N_1]}$

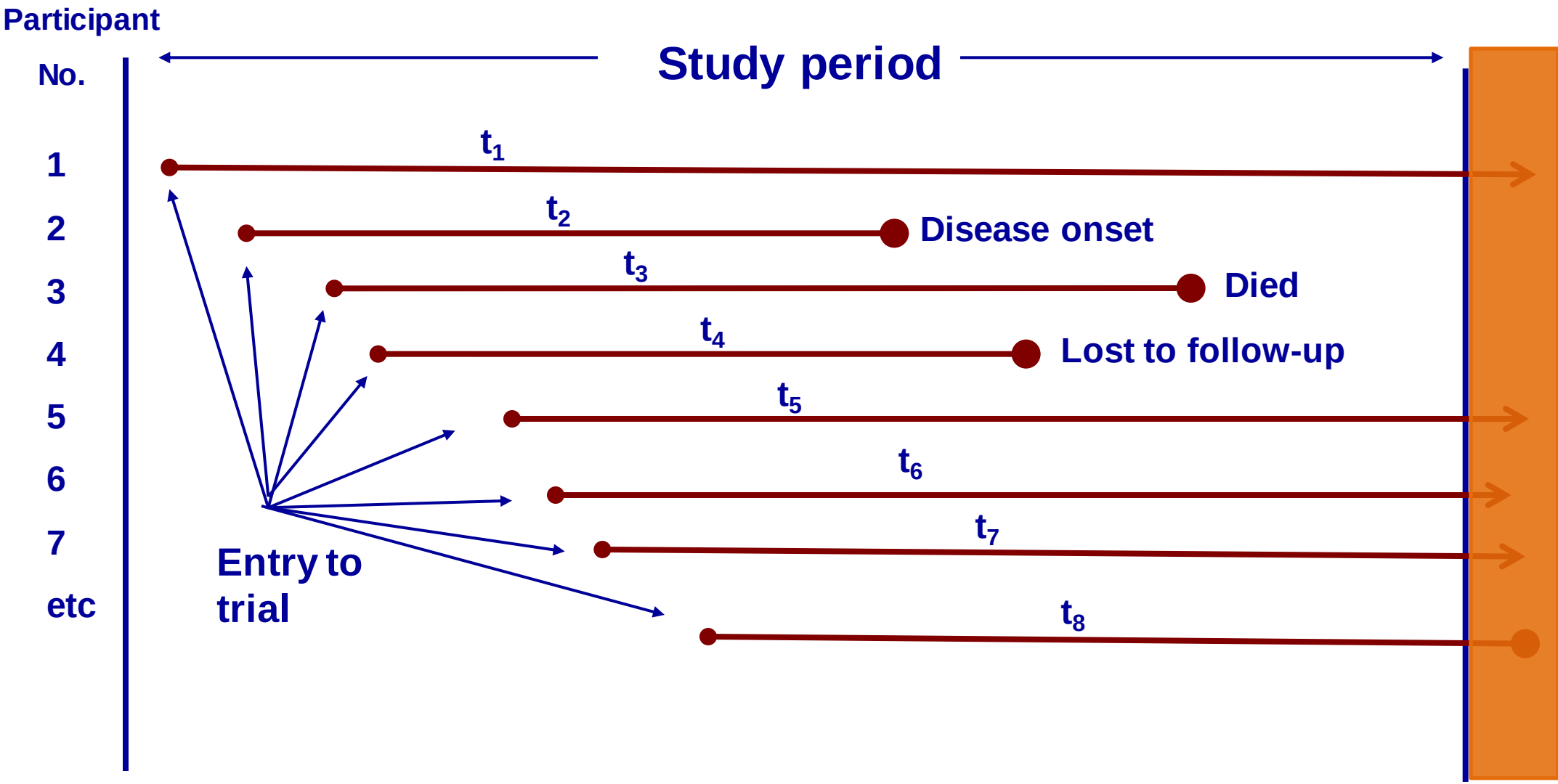
$= \sqrt{[150/(50x200) + 170/(30x200)]} = 0.208$

95% confidence limits on ln R = ln R ± 1.96 SE = -0.511 ± 1.96*0.208 = -0.919,-0.103

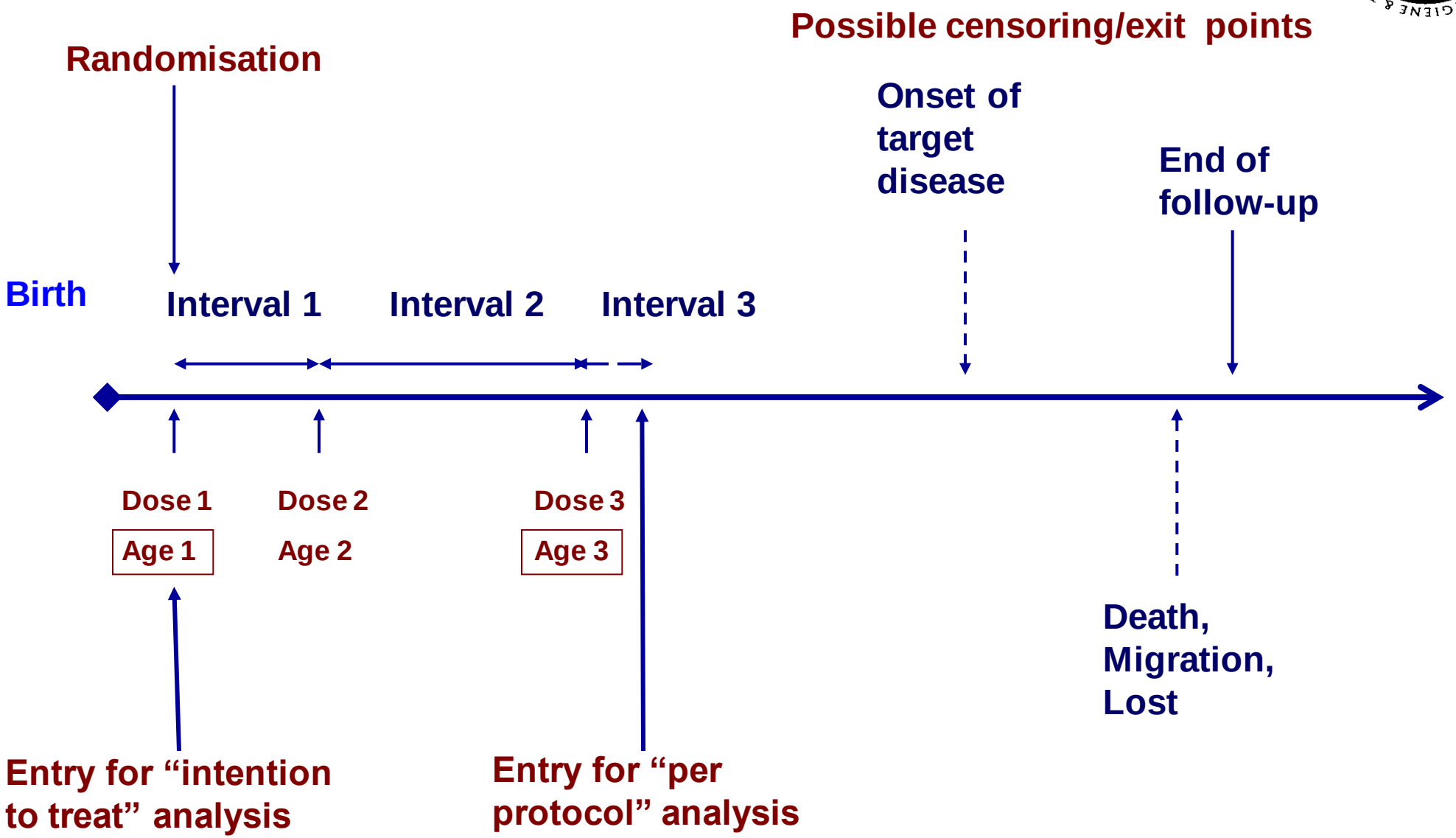
Hence 95% confidence limits on VE = $1 - e^{-0.103}$,$1 - e^{-0.919,}$ =1-0.90, 1-0.40

= 0.10, 0.60 (**10%, 60%**)

Follow-up in a “real life” trial



TIMELINE FOR PARTICIPANTS IN A VACCINE TRIAL



"Intention to treat" or "per protocol" analysis?

Intention to treat

- Participants enter trial as soon as they have been randomised (or received the first vaccine dose), irrespective of whether they subsequently receive subsequent dose at the correct time
  - Gives closer approximation of the impact the vaccine might have in public health practice – closer to a measure of "effectiveness" rather than "efficacy" – but often trial procedures are much more rigorous than is likely in public health practice (unless "pragmatic " trial)
  - Less susceptible to bias as randomisation respected, but may underestimate "full" effect of the vaccine

Per protocol

- Participants are included only if they receive the full course of vaccinations at the correct time and correct ages (and an interval left after the final dose for the full immune response to develop).
  - Measures the "maximum" impact of the vaccine – protection if given as on the label.
  - Possibility of bias, as not all those randomised included in analysis – particular concern if different numbers drop out from different arms

"Intention to treat" or "per protocol" analysis?

- Ideally both kinds of analysis give similar results and not many participants excluded from the *per protocol* analysis
- Difficult to interpret *per protocol* analyses if different numbers of persons excluded, or different reasons for exclusion, in vaccine and placebo groups

Analysis of an "real life" vaccine trial

	Number randomised	Person-time follow-up	Cases of disease in follow up period	Rate of disease
Control	N_0	T_0	c_0	$r_0=c_0/T_0$
Vaccinated	N_1	T_1	c_1	$r_1=c_1/T_1$

Vaccine Efficacy (%) = $100\ (r_0 - r_1)/\ r_0$

= 100(1- Relative rate)

SE ln R = $\sqrt{(1/c_0 + 1/c_1)}$

Trial of 9-valent pneumococcal vaccine in The Gambia – efficacy against radiological pneumonia

	Number randomised	Person-time follow-up	Cases of disease in follow up period	Rate of disease (/1000 child years
Placebo	8151	12,543	513	40.9
Vaccinated	8189	12,808	333	26.0

Vaccine Efficacy (%) = 100[(40.9-26.0)/40.9] = 37%

95% confidence interval 27% to 45%

Cutts et al, Lancet 2005

Computation of confidence interval on VE

Relative rate (R) = 26.0/40.9

ln R = -0.453

SE (ln R) = $\sqrt{}$(1/333 +1/513) = 0.0704

1.96*SE = 1.96 *0.0704 = 0.138

95% confidence interval on ln R = -0.453 ± 0.138 = -0.591, -0.315

95% confidence interval on R = $e^{-0.315}$, $e^{-0.591}$ = 0.73, 0.55

95% confidence interval on VE = 100(1-0.73, 1-0.55) = 27% to 45%

Subgroup analysis in pneumococcal vaccine trial

	Vaccine (n=8189)		Placebo (n=8151)		Vaccine efficacy (%) (95% CI)
	Number	Rate per 1000 child-years (95% CI)	Number	Rate per 1000 child-years (95% CI)	
Season of receipt of all three doses					
July–Nov	67	36·4 (28·7–46·2)	72	39·7 (31·5–50·0)	8 (–30 to 35)
Dec–June	116	28·1 (23·4–33·7)	176	43·0 (37·1–49·8)	35 (1 to 49)
Mixed	150	21·9 (18·7–25·7)	265	40·0 (35·5–45·2)	45 (33 to 56)

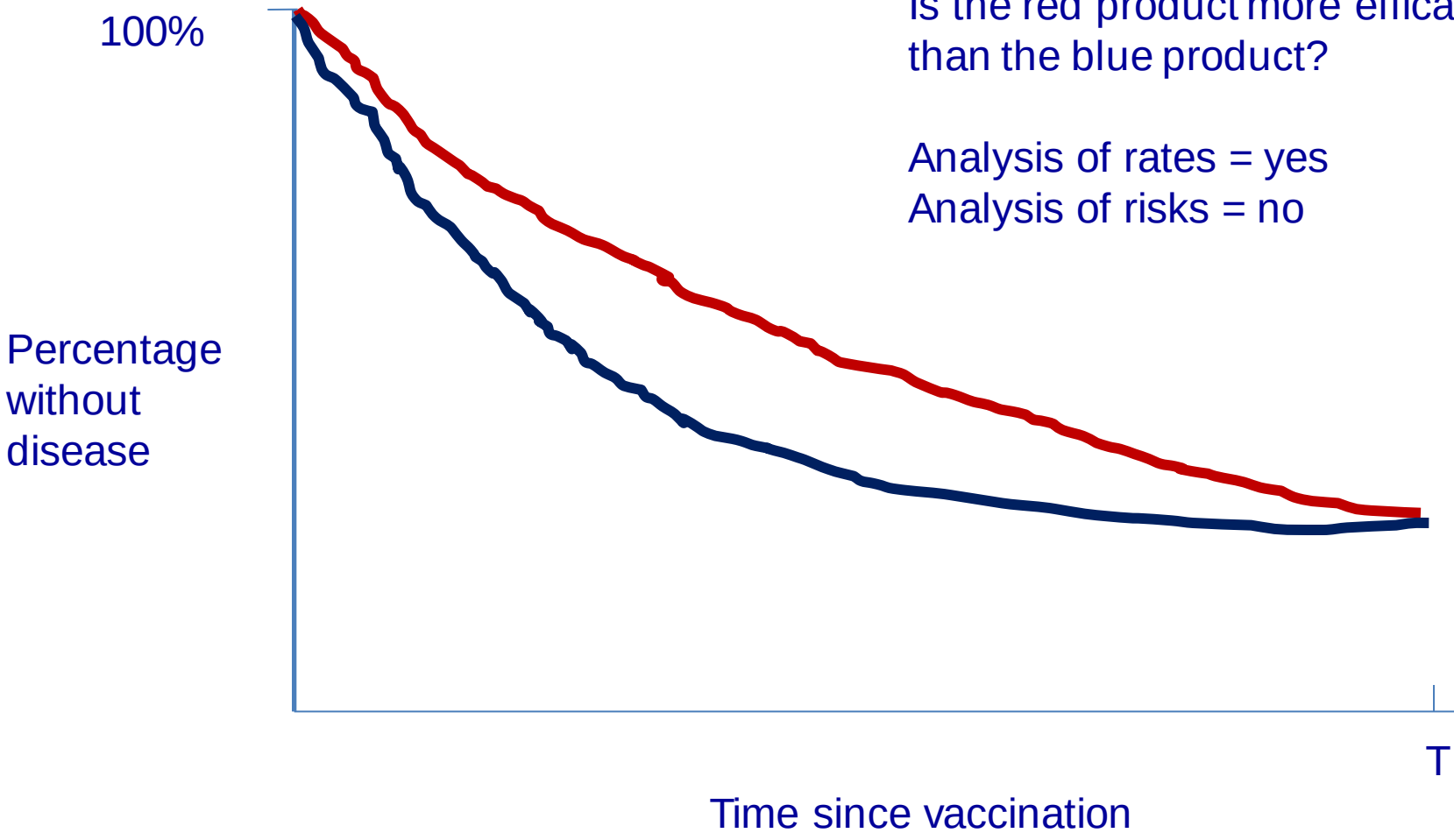
Test for heterogeneity of VE: P=0.10

In subgroup analyses it is important to perform **a statistical test for heterogeneity** of VE. A "significant effect in one sub-group and no significant effect in another does not establish that there is a difference in protection in the different subgroups.

Adjusting for potential confounding variables

- In a large properly randomised trial known and unknown confounding variables should be evenly balanced between vaccine and placebo groups – therefore adjustment for imbalance unnecessary.
- In smaller trials there may, by chance, be difference between the two groups with respect to known confounding variables (it will be unknown if there is also imbalance with respect to unknown confounding variables!)
- In such circumstances it may be appropriate to allow for such imbalance in the analysis either by stratification or using multivariate analysis.
- However, the criteria to be used to identify which variables to adjust for should be specified in the analytic plan in advance of breaking the code
- Marked different results in adjusted and unadjusted analyses in an RCT are liable to reduce the credibility of the trial results!

VE = ratio of risks or ratio of rates?



Is the red product more efficacious than the blue product?

Analysis of rates = yes
Analysis of risks = no

References

- Cutts FT, Zaman SMA, Enwere G, et al (2005). Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial. Lancet 365, 1139-1146.
- Cutts FT, Enwere G, Zaman SM, Yallop FG. Operational challenges in large clinical trials: examples and lessons learned from the Gambia pneumococcal vaccine trial. PLoS Clin Trials 2006;1:e16
- Schulz KF, Altman DG, Moher D, for the CONSORT Group (2010). CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMC Medicine 2010, 8:18 (http://www.biomedcentral.com/1741-7015/8/18)
- Smith PG, Morrow RH (Eds) (1996). Field Trials of Health Interventions in Developing Countries: A Toolbox (2nd Edition). MacMillan, London (3rd edition expected in late 2014)

LSHTM Short Course: Epidemiological evaluation of vaccines: efficacy, safety and policy 7-18 July 2014

Course Content

- Epidemiological principles of vaccine evaluation
- Immunological basis for vaccination
- Pre-licensure epidemiological issues:
  - Phase I, II and III trials
  - Practical and ethical considerations
  - Clinical trials: sample size and analysis issues
  - Good clinical practice and adverse event monitoring during vaccine trials
- Post-licensure epidemiological issues:
  - Vaccine efficacy and effectiveness
  - Impact studies
  - Burden of disease assessment
  - Surveillance of disease and infection
  - Adverse events monitoring
- Using immunology in vaccine evaluation
- Infectious disease modelling in assessing vaccine impact
- Economic evaluation of vaccination programmes
- Key issues in vaccination schedules and policy
- Long term implications of vaccination programmes
- Topical issues in the epidemiology of vaccine preventable disease

http://www.lshtm.ac.uk/study/cpd/seev.html