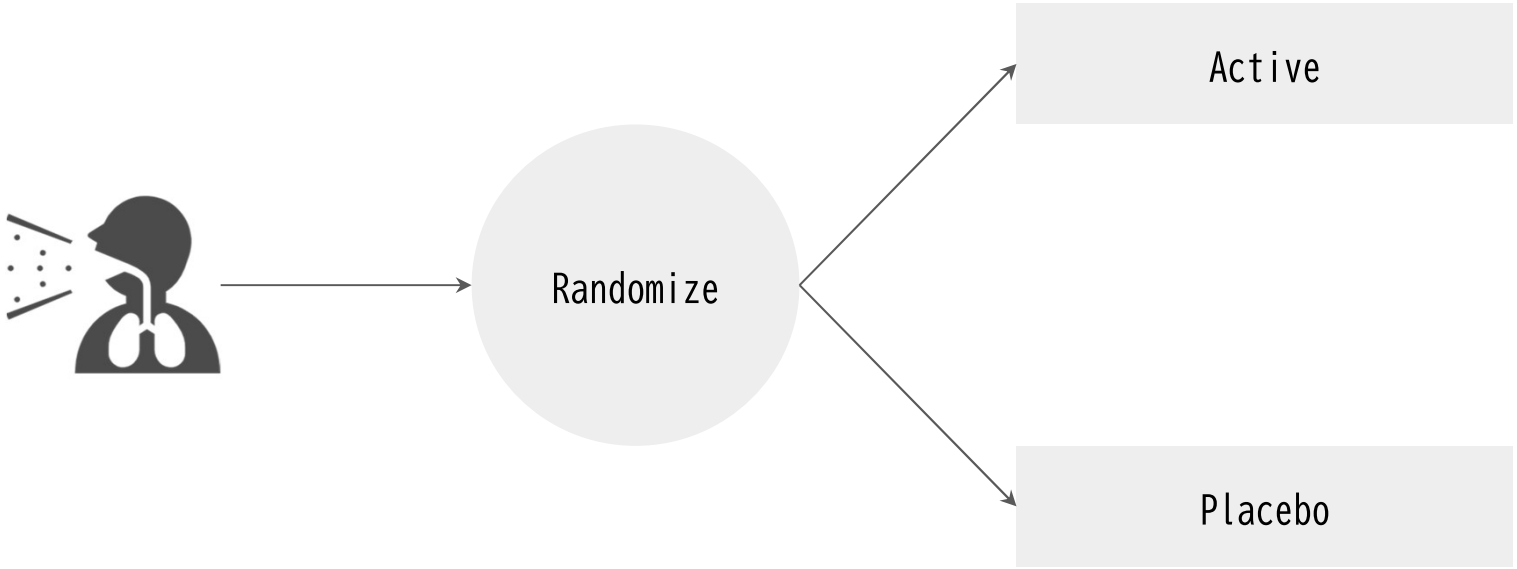
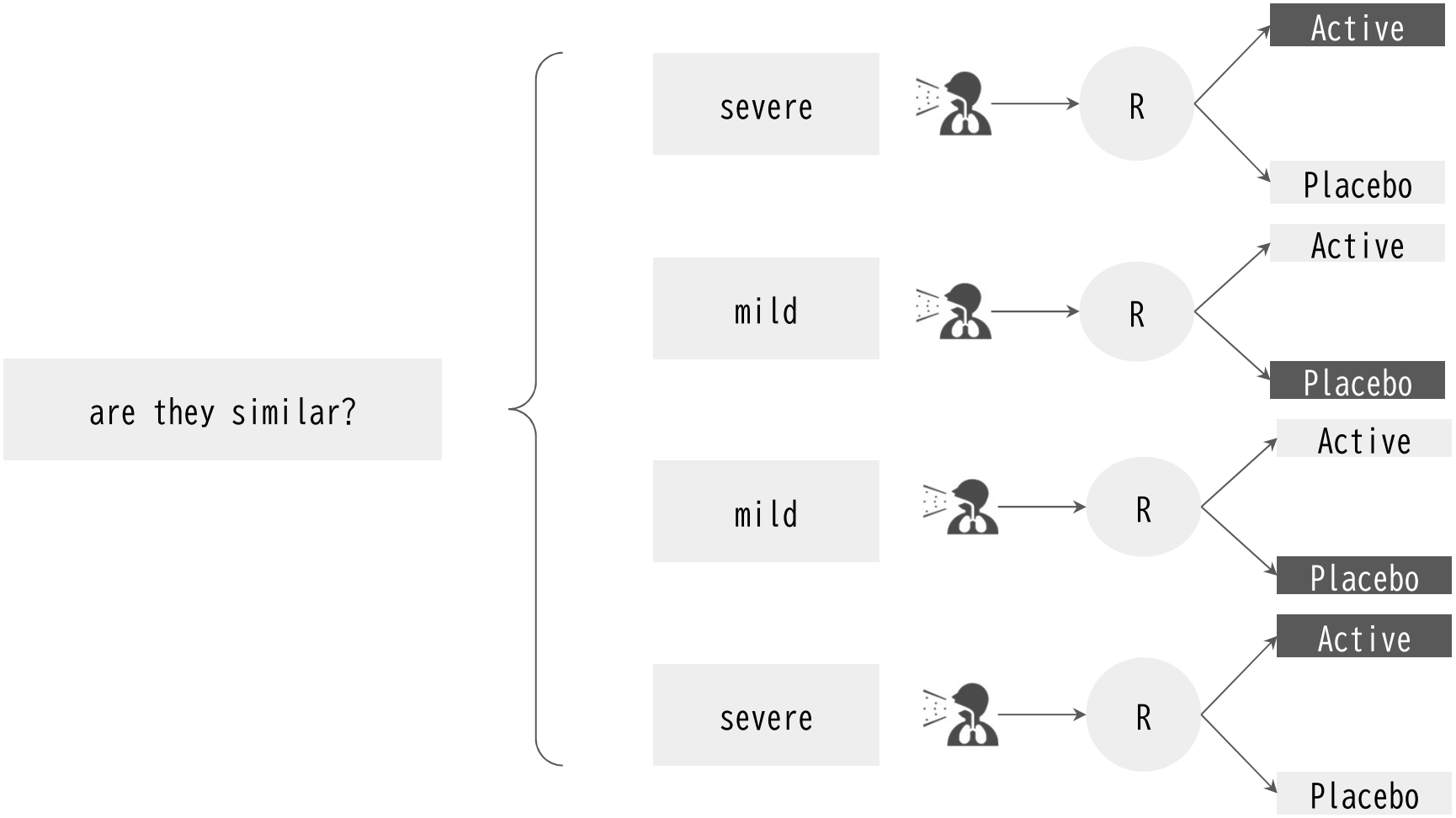
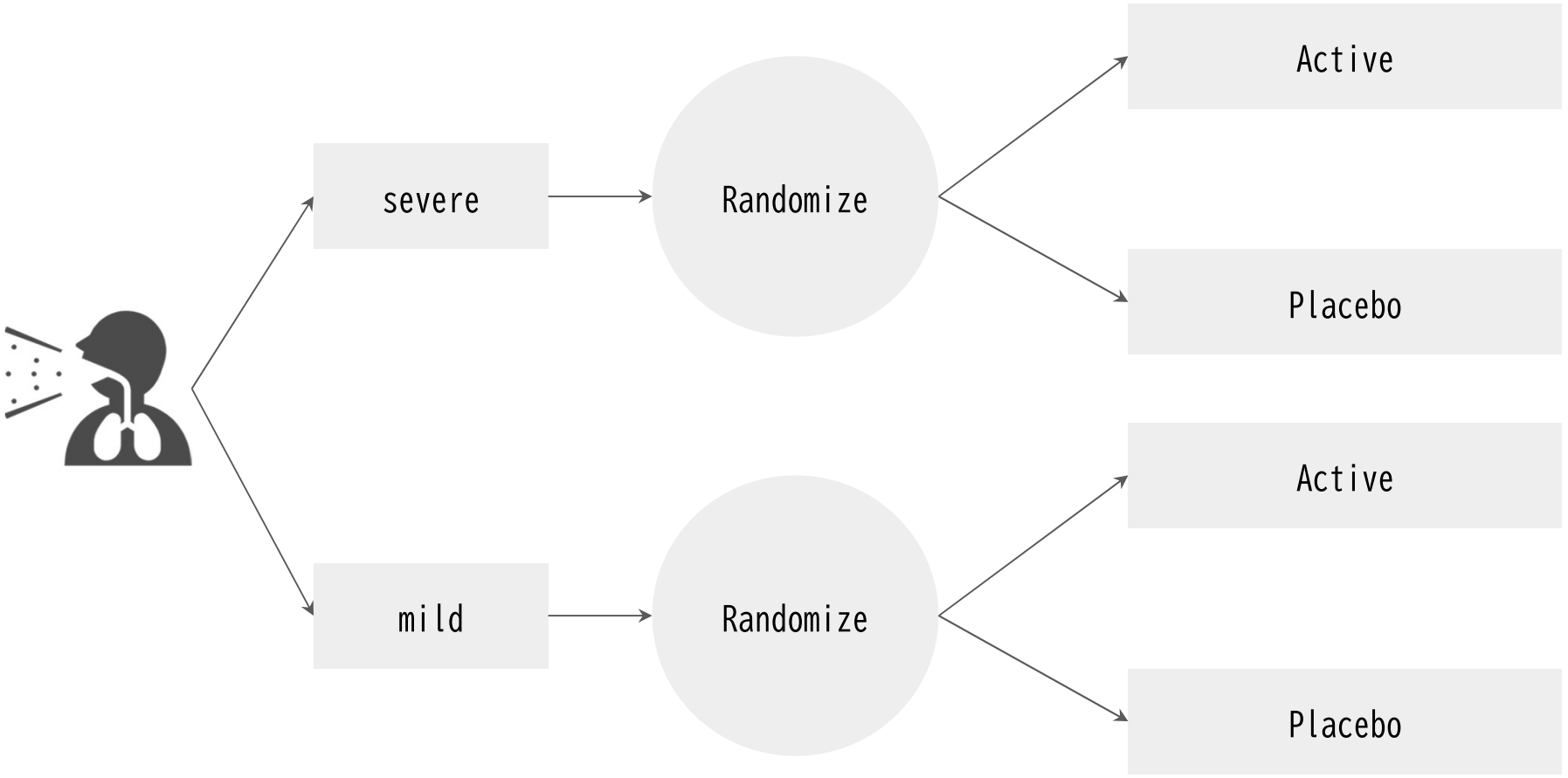
ICH-E9

3.1.1 Parallel Group Design

The most common clinical trial design for confirmatory trials is the parallel group design in which subjects are randomised to one of two or more arms, each arm being allocated a different treatment.
These treatments will include the investigational product at one or more doses, and one or more control treatments, such as placebo and/or an active comparator.

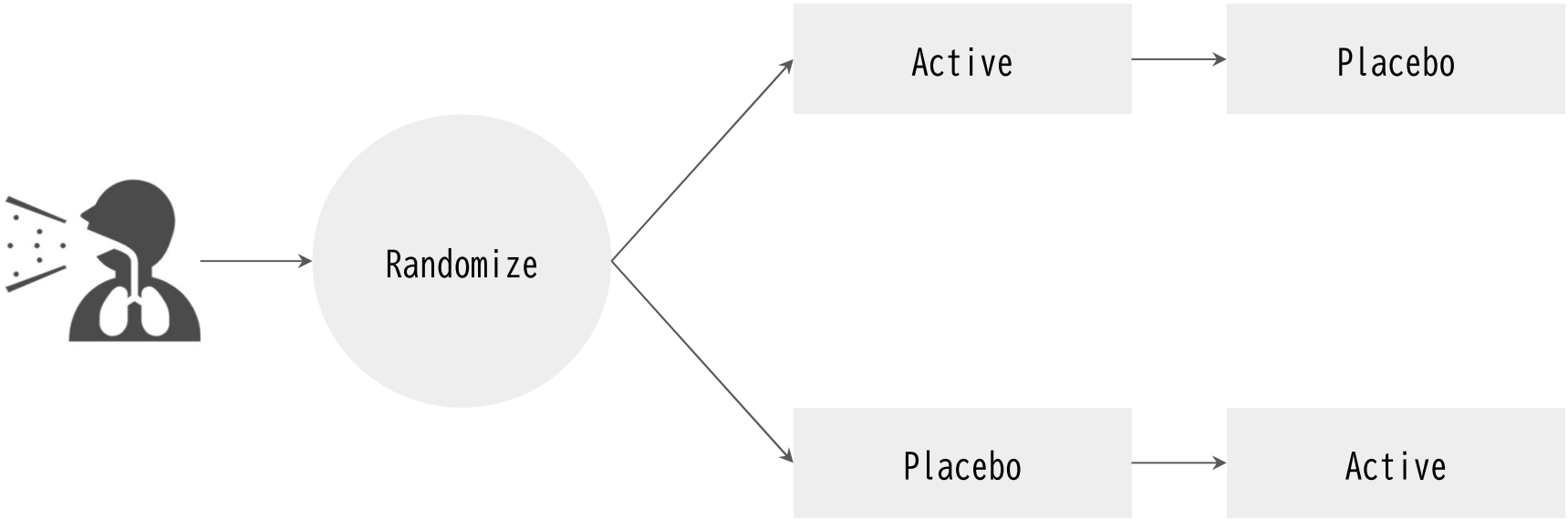

Active
Randomize
Placebo


are they similar?
severe
R
Active
Placebo
mild
R
Active
Placebo
mild
R
Active
Placebo
severe
R
Active
Placebo

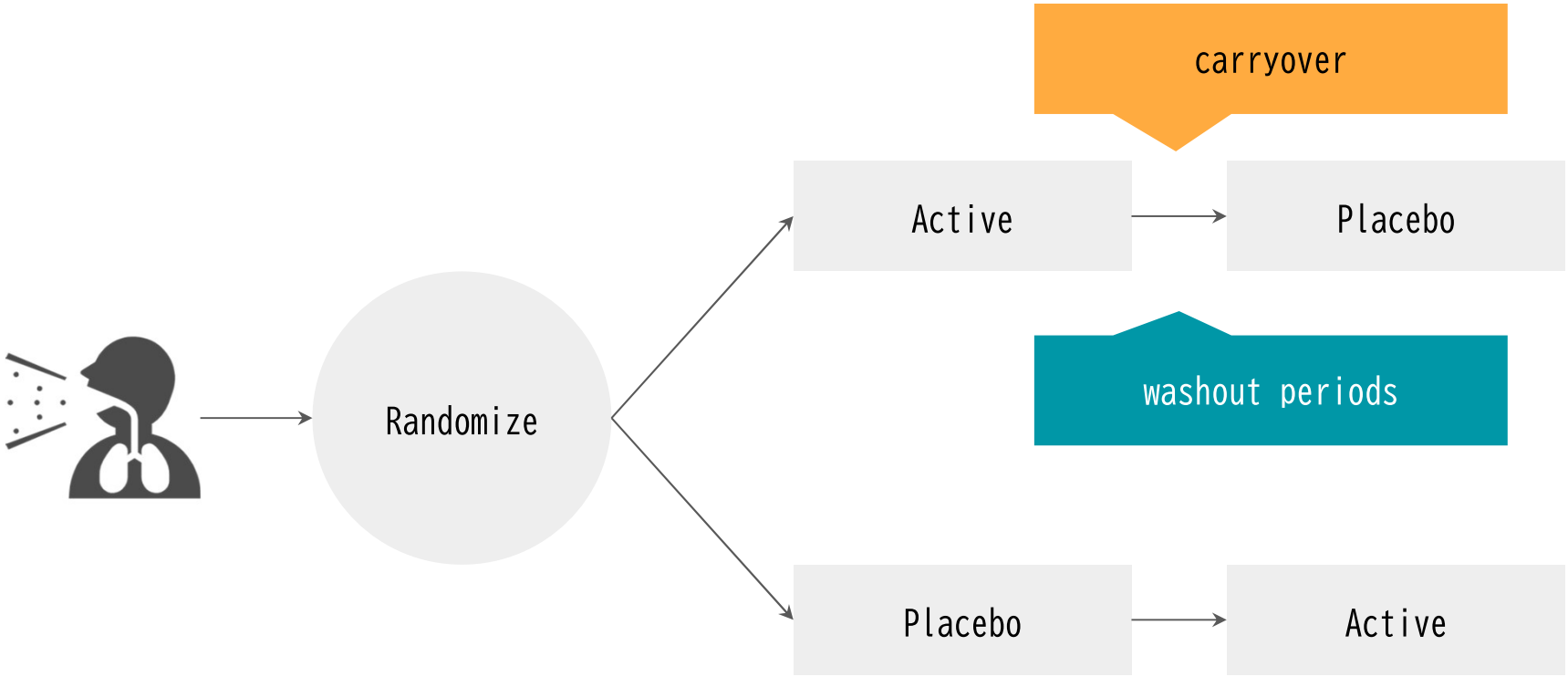

severe
mild
Randomize
Randomize
Active
Placebo
Active
Placebo

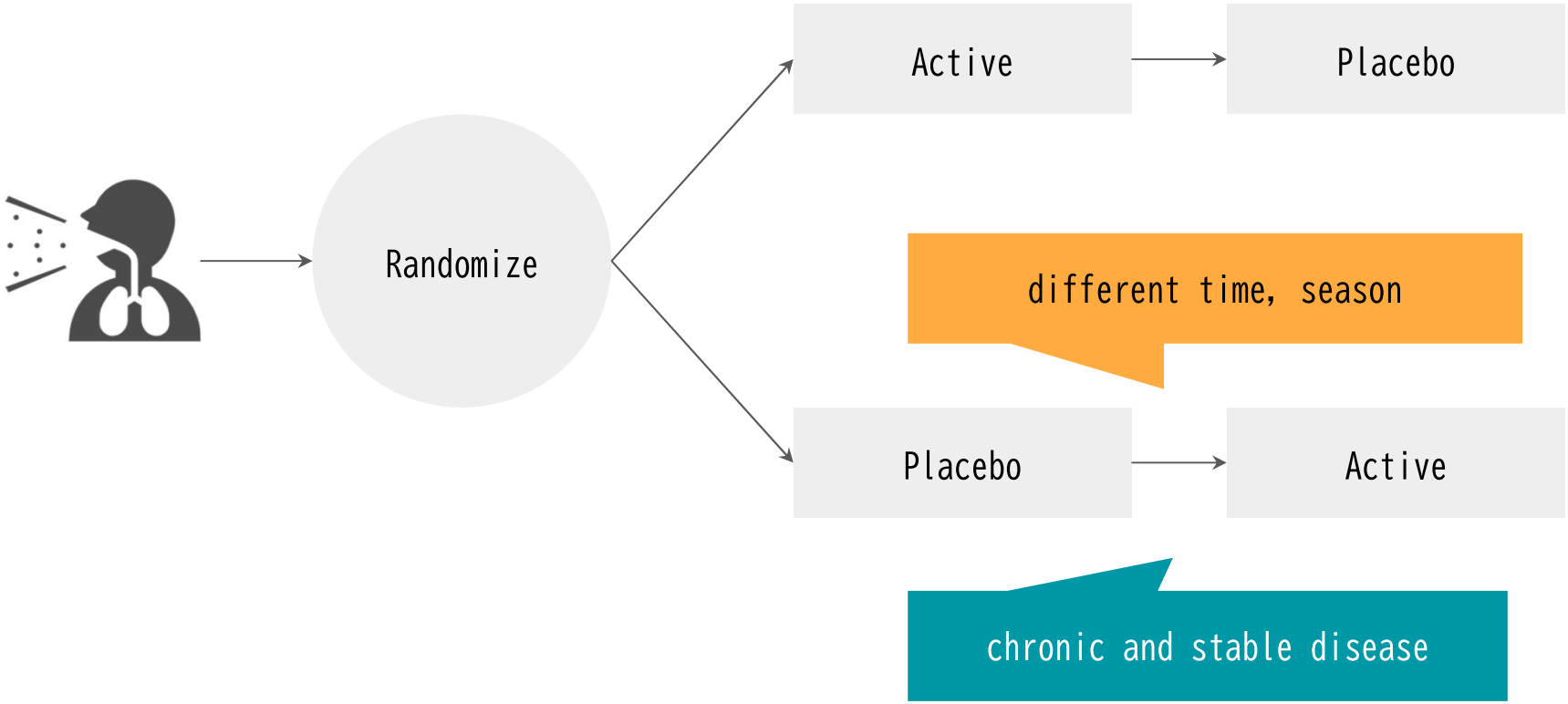
ICH-E9	3.1.2 Crossover Design

In the crossover design, each subject is randomised to a sequence of two or more treatments, and hence acts as his own control for treatment comparisons. This simple manoeuvre is attractive primarily because it reduces the number of subjects and usually the number of assessments needed to achieve a specific power, sometimes to a marked extent…



Crossover designs have a number of problems that can invalidate their results.


carryover
Active
Placebo
Randomize
washout periods
Placebo
Active


Active
Placebo
Randomize
different time, season
Placebo
Active
chronic and stable disease

ICH-E9	2.2.2 Primary and Secondary Variables

The primary variable (‘target’ variable, primary endpoint) should be the variable capable of providing the most clinically relevant and convincing evidence directly related to the primary objective of the trial.
There should generally be only one primary variable. This will usually be an efficacy variable, because the primary objective of most confirmatory trials is to provide strong scientific evidence regarding efficacy.

Why ”Only One” ?

In a research of an antihypertensive drug …

Efficacy on blood pressure was not demonstrated. but …

More people in the group taking the new drug had improved mood as the secondary end point.

Is this result evidence? or reference?

We have to be careful about “multiplicity”

Continue to next topic

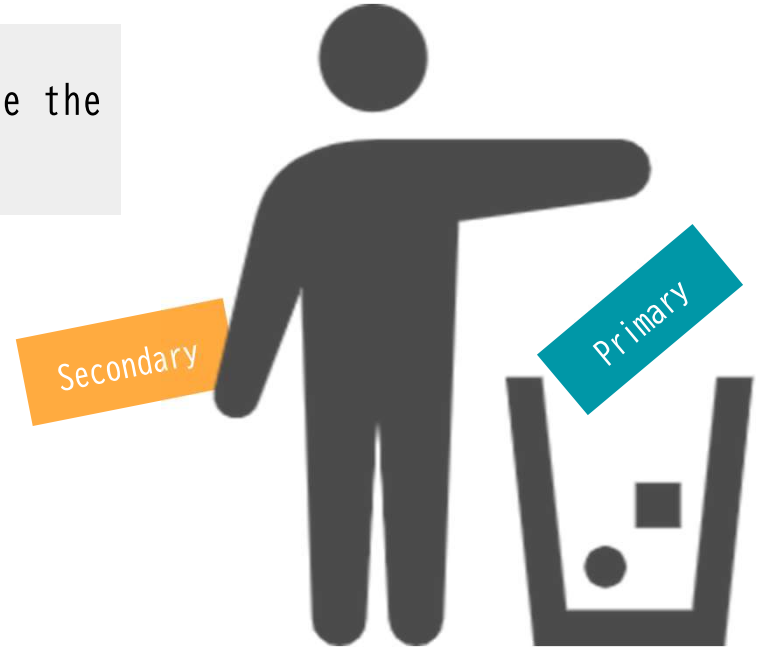
ICH-E9	3.5 Sample Size

The number of subjects in a clinical trial should always be large enough to provide a reliable answer to the questions addressed. This number is usually determined by the primary objective of the trial. If the sample size is determined on some other basis, then this should be made clear and justified.

Using the usual method for determining the appropriate sample size, the following items should be specified: a primary variable, the test statistic, the null hypothesis, the alternative hypothesis at the chosen dose(s), the probability of erroneously rejecting the null hypothesis (the type I error), and the probability of erroneously failing to reject the null hypothesis(the type II error), as well as the approach to dealing with treatment withdrawals and protocol violations.

Even if we get good results on the secondary endpoint, we can't translate that into the primary conclusion.

because the sample size was calculated to prove the primary endpoint.



people say "skim the cream!"

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5.2 Analysis Sets

Full Analysis Set

The intention-to-treat principle implies that the primary analysis should include all randomised subjects. Compliance with this principle would necessitate complete follow-up of all randomised subjects for study outcomes. In practice this ideal may be difficult to achieve, for reasons to be described. In this document the term 'full analysis set' is used to describe the analysis set which is as complete as possible and as close as possible to the intention-to-treat ideal of including all randomised subjects.

Per Protocol Set

The 'per protocol' set of subjects, sometimes described as the 'valid cases', the 'efficacy' sample or the 'evaluable subjects' sample, defines a subset of the subjects in the full analysis set who are more compliant with the protocol.

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5.2.3 Roles of the Different Analysis Sets

Full Analysis Set

In general, it is advantageous to demonstrate a lack of sensitivity of the principal trial results to alternative choices of the set of subjects analysed.

When the full analysis set and the per protocol set lead to essentially the same conclusions, confidence in the trial results is increased,

Per Protocol Set

5.3 Missing Values and Outliers

Missing values represent a potential source of bias in a clinical trial. Hence, every effort should be undertaken to fulfil all the requirements of the protocol concerning the collection and management of data.

5.8 Integrity of Data and Computer Software Validity

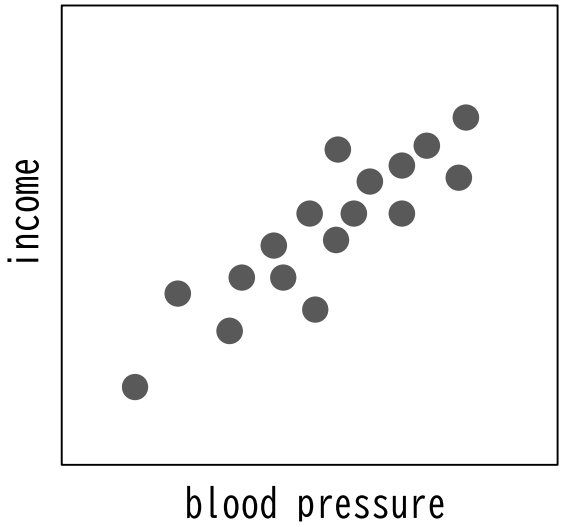
The credibility of the numerical results of the analysis depends on the quality and validity of the methods and software used both for data management (data entry, storage, verification, correction and retrieval) and also for processing the data statistically. Data management activities should therefore be based on thorough and effective standard operating procedures.

Continue to next session

appropriate interpretation is important

It was published in a magazine with an article
”There was a correlation between income and blood pressure.”

A businessman who read this article
started eating more salt the next day.



Statistical analysis requires not only aggregation and analysis techniques,
but also literacy to understand the results.

Discussion

Discussion 1

One investigator noticed a missing baseline (before initiation) primary endpoint measurement at week 4 in a 12-week dosing study.

The investigator consulted with you on what to do.

How would you answer?

Discussion 1

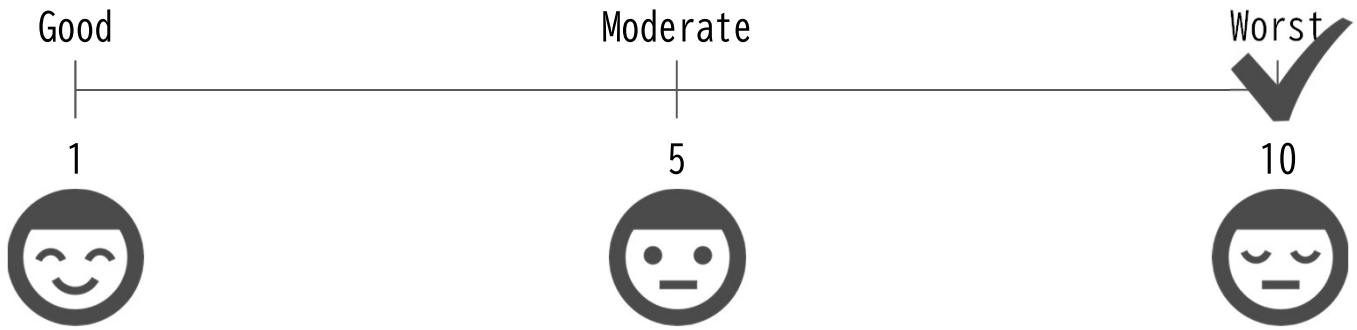
One investigator noticed a missing baseline (before initiation) primary endpoint measurement at week 4 in a 12-week dosing study.

What are you going to do with this subject for the remaining 8 weeks?

How will you handle this subject's data when analyzing it?

Discussion 2

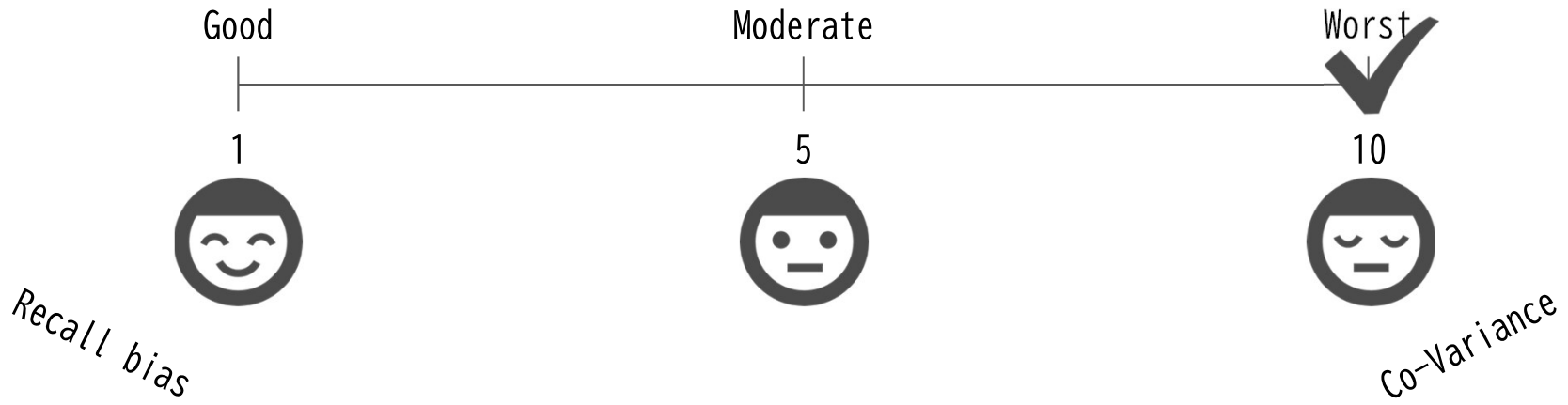
One study was collecting VAS(Visual Abalogue Scale) as a PRO(Patient Reported Outcomes)



A subject checked 10 points at baseline.

Discussion 2

At the next evaluation, the subject said,
”It has gotten worse and I would like to modify the baseline value.”



What would you do?

Today’ s contents

Introduction

Statistics in Clinical Research

Data Management in Clinical Research

Wrap up meeting

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