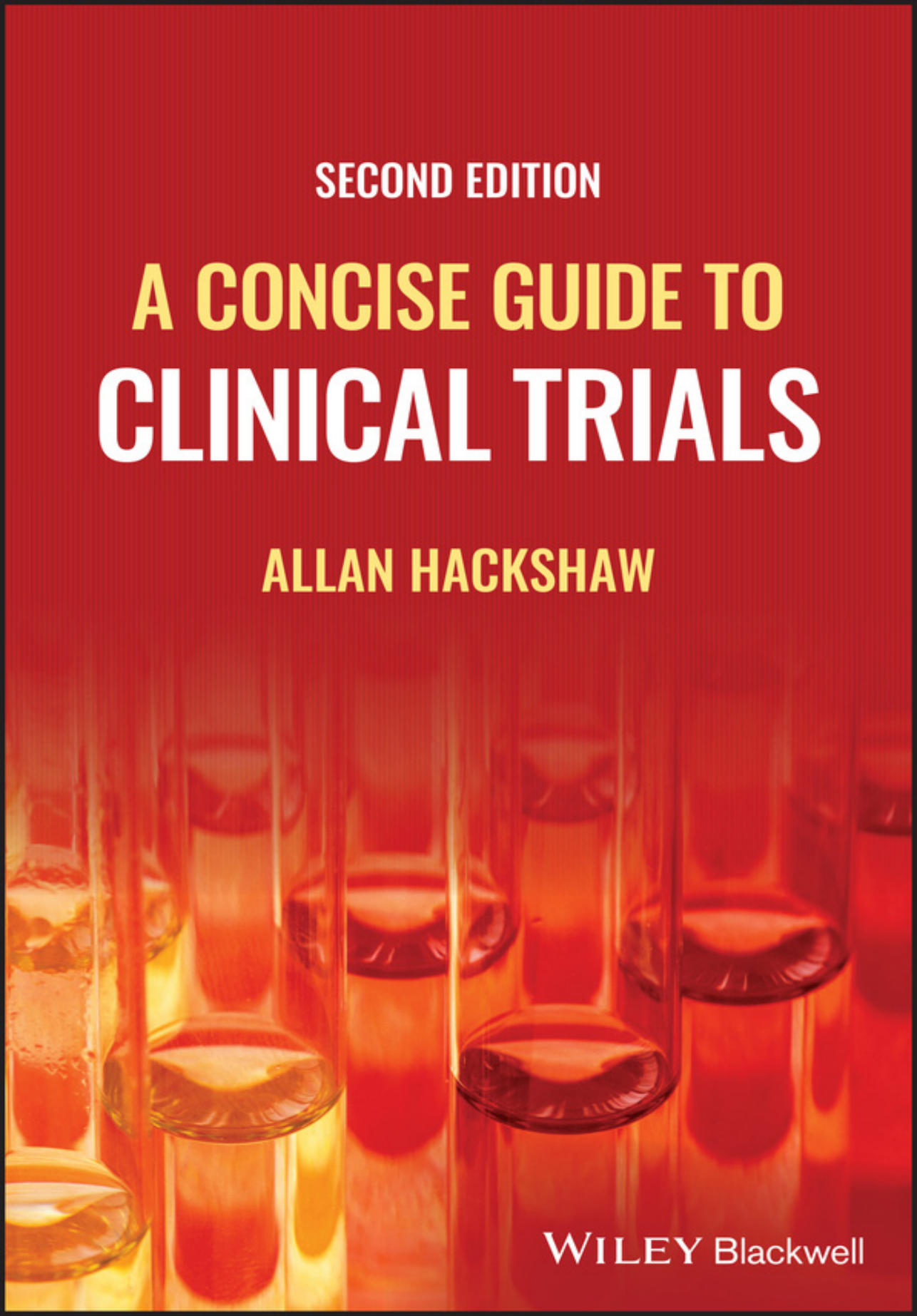
SECOND EDITION

A CONCISE GUIDE TO CLINICAL TRIALS

ALLAN HACKSHAW



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Preface

Clinical trials are essential for evaluating ways of preventing, detecting or treating disorders, or preventing early death. They are central to the work of many research departments including those in universities, hospitals, governmental organisations and pharmaceutical/medical device companies.

Health professionals conduct their own trials or engage in trials by recruiting participants, and others are involved in decision-making for grant funding, drug/medical device approval or developing clinical guidelines. There also many trial managers and those who analyse trials (research staff, statisticians and co-ordinators). All need to understand how new interventions are evaluated for themselves, and especially to be able to explain the benefits and harms to patients or the public. This book provides an overview of the design, conduct and interpretation of trials. No prior knowledge is required.

This is a significantly revised second edition, in which many new items have been added, including modern phase I to III study designs, trial designs for licencing and market access, translational research and precision medicine (incorporating biomarkers), and indirect treatment comparisons and real-world data as supporting evidence. There is also greater clarification of non-inferiority trials, health-related quality of life and subgroup analyses. Many examples used throughout the book are based on medicinal products (drugs) as these represent a substantial number of trials in practice. However, their design and analysis features can easily be applied to other interventions, and specific aspects of these are provided in Chapter 8.

I have spent over 32 years designing, conducting, analysing and publishing numerous clinical studies for various disorders (prevention, screening and treatment), from prenatal to the elderly. The book contains many practical tips that are not readily available in the literature. Much of this book has been based on successful courses on clinical trials delivered to a wide range of people: undergraduates, postgraduates and clinical and non-clinical health professionals in many academic institutions and pharmaceutical companies. The topics raised by them and how they have been taught and discussed have influenced the presentation of many concepts throughout the book

The book should be an easy-to-read guide that can be used as an introduction to clinical trials and as a teaching aid. It also contains enough information for those who wish to know more about a topic, and as a helpful reference guide to those already working in clinical trials.

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Foreword

No one would doubt the importance of clinical trials in the progress and practice of medicine today. They have developed enormously over the past 80 years and have made significant contributions to our knowledge about the efficacy of new treatments, particularly in quantifying the magnitude of their effects. Clinical trials have become highly sophisticated, in their design, conduct, statistical analysis and the processes required before new medicines can be legally sold. They have become expensive and require large teams of experts covering pharmacology, statistics, computing, health economics and epidemiology, to mention only a few. The systematic combination of the results from many trials to provide clearer results, in the form of meta-analyses, have themselves developed their own sophistication and importance.

In all this panoply of activity and complexity, it is easy to lose sight of the elements that form the basis of good science and practice in the conduct of clinical trials. Allan Hackshaw, in this book, achieves this with great skill. He informs the general reader of the essential elements of clinical trials: the different forms of trial design and analyses and how trials are conducted.

As well as dealing with scientific issues, this book is useful in describing the terminology and procedures used in connection with clinical trials, including explanations of phase I, II and III trials, and real-world data. The book outlines the regulations governing the conduct of clinical trials and those that relate to the approval of new medicines – an area that has become complicated.

This book educates the general medical and scientific reader on clinical trials without requiring detailed knowledge in any particular area. It provides an up-to-date overview of clinical trials with commendable clarity.

Professor Sir Nicholas Wald FRS
Formerly, Director, Wolfson Institute of Environmental & Preventive Medicine
Barts and The London School of Medicine & Dentistry

CHAPTER 1

Fundamental concepts

This chapter provides a summary of the main types of trials and their key design features. A checklist for critical appraisal of trial reports is on page 199, and a glossary of common abbreviations is on page 201.

1.1 What is a clinical trial?

The two distinct study designs used in health research are **observational** and **experimental**. Observational studies (usually cross-sectional, retrospective case-control or prospective cohort) do not intentionally involve intervening in the way individuals live their lives or how they are treated.[1] However, clinical trials (experimental) are specifically designed to intervene, and then evaluate health-related outcomes, with the following objectives:

- To diagnose or detect a disease
- To prevent a disease or early death (prolong life)
- To treat or cure an existing disorder, including reducing or managing symptoms
- To change behaviour or lifestyle habits, including reducing risk factors.

Countries (low, middle and high income areas) can successfully conduct clinical trials that reflect local health issues. The fundamental features of design and analysis are similar but the conduct and delivery will vary (especially how interventions are administered and how follow-up and outcome data are collected).

An intervention could be a single therapy involving a substance that is injected, infused, swallowed, inhaled or absorbed through the skin; medical device; surgical procedure; radiotherapy; behavioural or psychological therapy; something to improve health service delivery or promote health education; or an alternative or complementary therapy.

A new generation of **biological and targeted therapies** (small molecules, monoclonal antibodies, immunotherapies and genetic and cell therapies) has revolutionised the treatment of several disorders, in which the choice of a therapy is influenced by the presence (or absence) of a biomarker, genetic abnormality or imaging marker. There are also **vaccines** that can be used for disease prevention or to reduce the risk of disease progression.

A combination of interventions can be referred to as a **regimen**, such as chemotherapy and surgery in treating cancer.

Any drug or micronutrient that is examined in a clinical trial with the specific purpose of treating, preventing or diagnosing disease is usually referred to as an **Investigational Medicinal Product (IMP)** or **Investigational New Drug (IND)**.[#] Most clinical trial regulations cover studies using an IMP and several medical devices.

[#] IMP in the UK and European Union, and IND in the United States, Canada and Japan.

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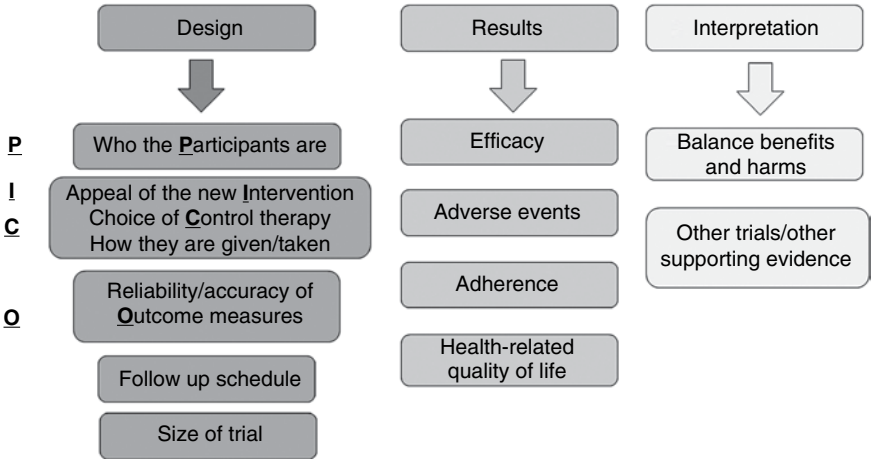

Figure 1.1 Overall view of trial design, types of results and interpretation. The acronym PICO (Participants/Population, Intervention, Control and Outcome) focuses on the four key design elements that must always be clearly defined (examples of trials in later chapters use the PICO list). Translational research (bio- and imaging markers) can also be examined.

New drugs and some medical devices usually require a **licence** or **marketing authorisation** for human use from a national regulatory authority. They can then be made available to the target population after review by a **health technology assessment (HTA)** or **payer/reimbursement** organisation through a process referred to as **market access**.

Throughout this book, the terms **intervention**, **treatment** and **therapy** are used interchangeably. People who take part in a trial are referred to as **participants** if they are healthy individuals or **patients** if they are already ill with the disorder of interest.

Figure 1.1 is an overall view of trial design and types of results (covered in more detail in other chapters).

Patient and Public Involvement and Engagement (PPIE) is a key activity in which lay members (e.g. past patients, carers and members of the public) can help with trial design (e.g. agree that the new therapy is appealing), conduct (create the participant-facing information materials) and interpret trials in a way that can be easily understood.

Artificial intelligence is also expected to be used, for example in identifying eligible participants from electronic medical records and analysing clinical data and multiple biomarkers.

Decentralised trials may be increasingly used where many or all of the processes from participant selection and eligibility, allocation of treatments (usually licensed products already in use), through to data and outcome collection are done electronically including remote assessments of participants.

1.2 Early trials

James Lind, a Scottish naval physician, is regarded as conducting the first clinical trial.[2] During a sea voyage in 1747, he chose 12 sailors with *similarly* severe cases of scurvy and examined 6 treatments, each given to 2 sailors: cider, diluted sulphuric acid, vinegar, seawater, a mixture of foods including nutmeg and garlic, and oranges and lemons. These sailors were made to live in the *same* part of the ship and given the *same* basic diet. Lind understood the importance of standardising their living conditions to ensure that any

change in their disease would unlikely be influenced by other factors. After about a week, both sailors given fruit had almost completely recovered unlike the other sailors. This dramatic effect led to the conclusion that eating fruit cured scurvy, without knowing that it was due to vitamin C.

Two important features of his trial were a **comparison** between two or more interventions and an attempt to ensure that the participants had **similar characteristics** (see confounding below). The requirement for these two features has not changed for more than 270 years, indicating how essential they are to evaluating interventions.

One key element missing from Lind's trial was the process of **randomisation**. The Medical Research Council trial of streptomycin and tuberculosis in 1948 is regarded as the first to use random allocation.[3]

1.3 Why clinical trials are needed

Statin therapy is effective in treating coronary heart disease. However, why do some patients who have had a heart attack and been given statin therapy have a second attack, while others do not? The answer is that people *vary*. People have different body characteristics (e.g., weight, blood pressure and blood measurements), genetic make-up and lifestyles (e.g., diet, exercise, and smoking and alcohol consumption habits). These lead to **variability** or **natural variation.** People respond to the same exposure or treatment in different ways. When a new intervention is evaluated, it is essential to consider whether the observed responses are consistent with natural variation (i.e. chance) or whether there really is a treatment effect. This is a principal concern of medical statistics.

1.4 Alternatives to clinical trials

Examining interventions can be done using a clinical trial and in particular a randomised controlled trial (RCT), observational study or trial with historical controls. They have fundamentally different designs. Some observational studies are used as supporting evidence for the effectiveness and safety of an intervention under the topic **real-world evidence** (RWE) or **real-world data** (RWD); see Chapter 9.

Although studies other than RCTs can provide useful information about an intervention, care is needed over their interpretation. Observational studies, for example, can give the same or conflicting conclusion to RCTs:

- A review of 20 observational studies indicated that giving the influenza vaccine to the elderly could halve the risk of developing respiratory and flu-like symptoms.[4] Practically the same effect was found in a large double-blind RCT.[5]
- A review of 6 observational studies indicated that people with a high β-carotene intake, by eating lots of fruit and vegetables, had a 31% reduction in the risk of cardiovascular death than those with a low intake.[6] However, 4 RCTs together showed that a high intake increases the risk by 12%.[6]

Observational (non-randomised) studies

Observational studies may be useful in evaluating treatments with large effects, although there may still be uncertainty over the actual size of the effec.[7, 8] They can have a larger number of participants than RCTs and therefore provide more evidence on side effects,

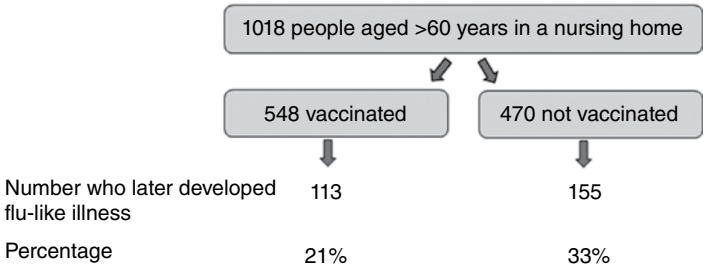

Figure 1.2 Example of an observational study of the flu vaccine. Source: Adapted from[9].

particularly uncommon ones. However, when the treatment effect is small or moderate, the potential design limitations of observational studies can make it difficult to establish whether a new intervention is truly effective. These limitations are called **confounding** and **bias**.

Several observational studies have examined the effect of the influenza vaccine in preventing flu and respiratory disease in elderly individuals. Such a study would involve taking a group of people aged over 60 years, then ascertaining whether each participant had had the influenza vaccine or not, and who subsequently developed flu or flu-like illnesses. An example is given in Figure 1.2.[9] The chance of developing flu-like illness was lower in the vaccine group than in the unvaccinated group: 21 versus 33%. However, did the flu vaccine really work?

Assume that vitamin C protects against acquiring influenza. People who choose to have the vaccine might also happen to eat more fruit than those who are unvaccinated (Table 1.1). The difference in flu rates of 5 versus 10% could be due to the vaccine only, the difference in fruit intake (80 vs 15%) only or both together. But we are not interested in fruit intake. If fruit intake had not been measured, it could be incorrectly concluded that the difference in flu rates is due to the vaccination.

When the association between an intervention (e.g. flu vaccine) and a disorder (e.g. flu) is examined, a spurious relationship could be created through a third factor, called a **confounding factor** (e.g. eating fruit). A confounder needs to be correlated with both the intervention *and* the disorder of interest. Even though there are methods of design and analysis that can allow for their effects, there could exist unknown confounders for which no adjustment can be made because they were not measured. There is also **residual confounding** which occurs when the statistical adjustment for a confounder has been insufficient.

There may also be **bias**, where the actions of participants or researchers produce a value of the trial endpoint that is *systematically* under- or over-reported in one trial group. In the flu example, the clinician or carer could deliberately choose fitter people to be vaccinated,

Table 1.1 Hypothetical observational study of the flu vaccine.

	1000 people aged ≥60 years	
	Vaccinated N = 200	*Not vaccinated N = 800*
Eat fruit regularly	160 (80%)	120 (15%)
Developed flu	10 (5%)	80 (10%)

Box 1.1 Confounding and bias

Confounding represents the natural relationships between the physical and biochemical characteristics, genetic make-up and lifestyle/behavioural habits that may affect how an individual responds to a treatment.

- It cannot be removed from a research study, but known confounders can be measured and therefore allowed for in a statistical analysis.

Bias is a study design feature that affects how participants are selected, treated, managed or assessed, which systematically distorts the results in one trial group more than another.

- It can be prevented, but human nature sometimes makes this difficult.
- It is difficult to allow for bias in statistical analyses because it often cannot be measured.

Randomisation within a clinical trial minimises the effect of confounding and some biases.

believing they would benefit the most. Also, the vaccinated group may be people who chose to go to their family doctor and request the vaccine. It is therefore possible that people who were vaccinated had different lifestyles and characteristics than unvaccinated people. The effect of the vaccine could be over-estimated if the vaccinated people are less likely to acquire the flu than the unvaccinated ones.

When designing trials, it is a useful exercise to imagine being a participant, someone who allocates/administers the trial interventions, or someone who assesses outcome measures, and consider whether there is anything that can be done that can distort the results. Then consider how this could be minimised or avoided by the trial design and conduct.

Confounding is sometimes called a form of bias because both affect the results. However, it is useful to distinguish them (Box 1.1).

1.5 Types of clinical trials

Clinical trials are broadly categorised into four types (Phase I, II, III and IV), largely depending on the main aim (Box 1.2).

Phase I	*Phase II*	*Phase III*	*Phase IV (real-world data)*
Safety/toxicity	*Efficacy*	*Efficacy*	Effectiveness
Pharmacology	Safety	Safety	Long term safety
	Adherence	Adherence	Uncommon side effects
		Quality of life	New indications
		Health economics	

Words in italics indicate the common primary focus.

Efficacy and effectiveness are used interchangeably. However, efficacy is sometimes used in a clinical trial setting where the participants could be a select (often motivated) group with high adherence to the trial intervention. Effectiveness applies to routine practice, which better reflects the use of the treatment in the target group and the extent

of adherence among them. The magnitude of benefit associated with a new therapy is sometimes higher when using efficacy than effectiveness.

Traditionally, there has been a sequence from phase I to phase III involving separate trials, particularly for pharmaceutical drugs. To reduce the entire evaluation period, phases can be combined within the same protocol (for example, phase I/II or phase II/III).

Box 1.2 Types of trials

Phase I

- First time a new drug or regimen is examined in humans ('first-in-human' studies), and also used to examine a licenced drug for a new indication (disorder) or a new combination of therapies.
- Few participants (often <50 but can sometimes be >100 if covering multiple disease subtypes).
- Primary aims: check that the toxicity profile is acceptable; find a dose (e.g. drug or radiotherapy) that is tolerable; examine the biological and pharmacological effects.
- Patients or healthy volunteers are monitored closely.

Phase II

Often 30–100 people (but may be larger in common disorders).
- Aims to obtain a *preliminary* estimate of efficacy and further evidence of harms.
- May be single group or randomised (multiple groups), including a control therapy.
- Results are used to help design a confirmatory phase III trial; or the efficacy evidence is good enough to change practice for rare disorders or when there is clear unmet need

Phase III

- Should (must) be randomised and with a comparison (control) group.
- Relatively large (usually several hundred or thousand people).
- Aims to provide a *definitive* answer on whether a new treatment is better than the control group (**superiority**), or similarly effective (**equivalence**) or not materially worse (**non-inferiority**) but with other advantages
- Used to obtain a marketing authorisation from a regulatory agency or for market access for a new drug or medical device (pivotal trial).

Phase IV (post-marketing, surveillance or real-world studies).

- Relatively large (usually several hundred or thousand people).
- Used to continue to monitor efficacy and safety in the population once the new treatment has been adopted into routine practice.
- Not usually randomised, but there are pragmatic randomised phase IV studies that compare currently used interventions.
- Based on participants in the general target population, rather than the selected group who agreed to participate in a phase III trial.

1.6 Key design features

Clinical trials have common fundamental design characteristics (Figure 1.3).

Inclusion and exclusion criteria

Specifying which participants are recruited is done using an **eligibility list**: a set of **inclusion and exclusion** criteria which each participant has to fulfil before they can take part. Common criteria include age range, having no serious co-morbid conditions, the ability to give consent, having no known contraindications to the therapy, and no previous or recent exposure to the trial treatment or others that are similar to it. They should have unambiguous definitions to make recruiting participants easier.

Having many criteria produces a homogenous group that is more likely to respond to the treatment in a similar manner, making it easier to detect an effect if it exists, particularly small or moderate effects. However, the trial results might not be easily generalisable. A trial with few criteria will have greater generalisability but more variability, perhaps making it more difficult to show that the treatment is effective and sometimes only large effects can be detected easily.

Studies increasingly use biomarkers or molecular/genetic testing (profiling) of blood, urine or tissue samples to select only patients who are more likely to benefit from a new treatment that has been developed specifically for that type of patient (**precision/personalised medicine**).

Experimental/investigational treatment group

The new intervention could have been developed using prior studies or laboratory research. Importantly, its description and delivery should be clear enough for other people to replicate it. Investigators expect to show that a new intervention is more effective than the control group (**superiority**), or it has an effect that is similar (**equivalence**) or 'not much worse' (**non-inferiority**).

Control (comparator) group

The outcome of participants given the new intervention can be compared with that in a control group. A **control** group normally receives the current standard of care, no intervention or placebo (see Blinding below). Treatment effects from RCTs are therefore always comparative. The choice of the control intervention depends on the availability of alternative treatments, what is recommended in local or national clinical guidelines, or the requirements of regulatory agencies or organisations responsible for market access. When an established treatment exists, it can be unethical to give a placebo instead because this deprives some participants of a known benefit.

Randomisation and allocating participants

The randomisation process ensures that each participant has the same chance of being allocated to a group as everyone else (Box 1.3). Neither the participant or research team can influence which intervention is given. This minimises the effect of both known *and unknown* confounders, and thus has a distinct advantage over observational studies in which statistical adjustments can only be made for known confounders that have been measured. Randomisation does not produce *identical* groups; there will always be small differences because of chance variation.

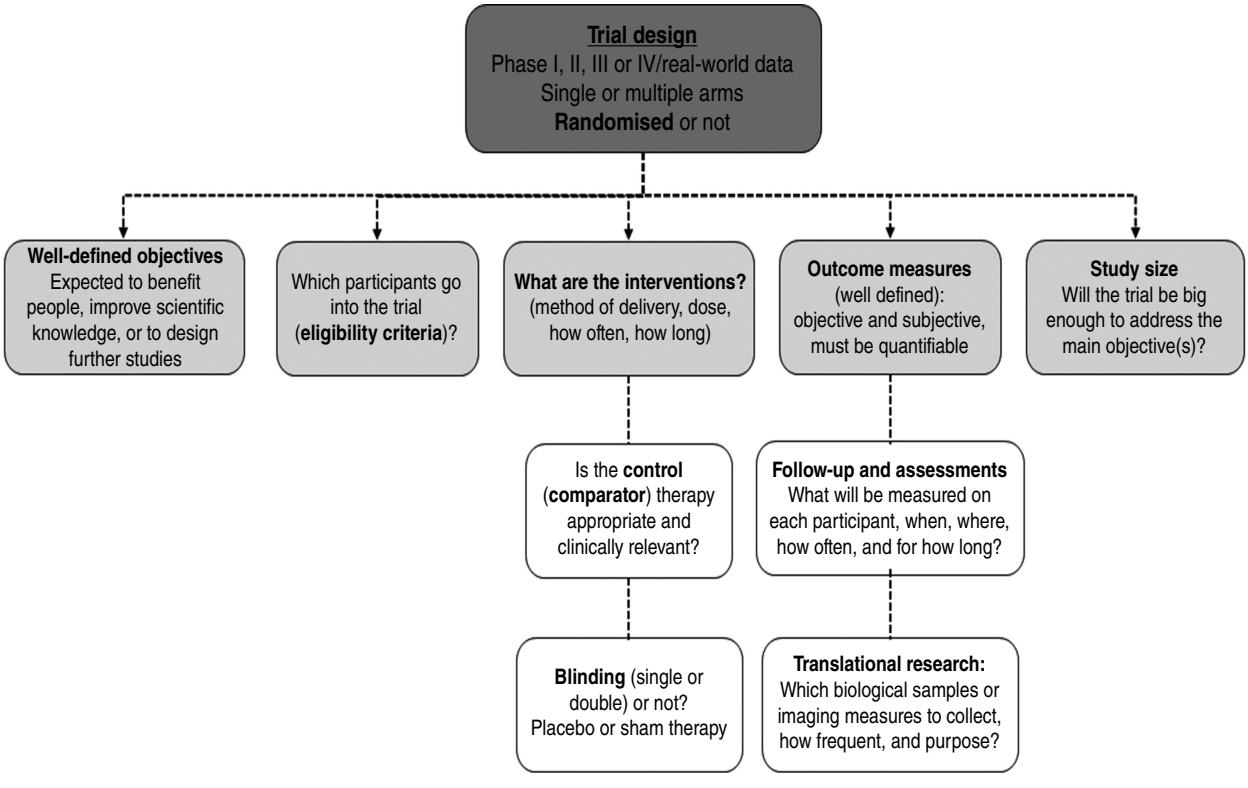

Figure 1.3 Overview of trial design features. Examples of objectives are: "To determine whether Intervention A reduces the risk of dying among people who have had a stroke"; "To evaluate whether Therapy B is non-inferior to standard of care in people with chronic lung disease"; "To investigate whether Drug A has potential efficacy and acceptable toxicities in patients with multiple sclerosis".