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Clinical trials:
a community guide to HIV research

i-Base treatment training manual for advocates

March 2009

Contents

This booklet is one section of the i-Base training manual for advocates, available online (www.i-Base.info). Other sections include: The immune system and CD4 count; Virology, HIV and viral load; Introduction to ARVs; Side effects of ARVs; OIs and co-infections; HIV and pregnancy; Drug users and ARVs and Learning resources: science support modules.

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Introduction to this resource

This booklet is one chapter from the i-Base advocacy manual which is available free online:

www.i-Base.info

The format is very simple.

It is written by and for people who do not have a formal scientific background or medical training.

Even if you are not very academic, and this training is difficult, you can still be a very effective advocate and activist. This training will help you understand the background to treatment issues.

The training material has been written in a way that makes it easier for you to then explain the information again to other people who do not have a medical background.

As community advocates and trainers, it is important to understand and explain things that people may not have a great interested in at first, and explain them in a way that makes the new information relevant to them getting better care.

Most people don't want to know about science - they just want to get on with their lives.

You will need to explain, however, the science behind how things work. It means getting people to believe in things that they can't see with their own eyes, and getting them to trust in these things.

We can't see a virus, or a CD4 cell or any of the things that are tested in blood with the naked eye. We can't see whether one pill or another will work better or at all.

However, understanding a little about how treatment works can empower people to have more control over their treatment choices.

This course is written by treatment advocates who have had no formal medical training and who are mostly HIV-positive. We have tried to remember the biggest surprises that we found as we developed our own treatment knowledge.

Sometimes it's the surprises that keep you learning – because they show how things can in reality be very different to how you imagined them.

Hopefully, some of these will be helpful in developing your own treatment interest – once you start, you realise there is always more to learn.

8.1 Introduction

Section 8 of the i-Base manual provides information about clinical trials and research.

- It provides a key grounding for advocates interested in this subject.
- It also includes information about how research is presented and how to analyse and interpret trial results.

Community involvement in HIV research is important. Advocates have always argued for active patient and community representation and involvement at all stages of our health care, including research.

This includes being involved on the type of research and the design of trials. It helps make sure that:

- Trials are run properly
- All patients receive at least the current standard-of-care treatment
- We are able to follow both enrolment and how the trial is run
- We are able to monitor and follow early results
- As patients and advocates we have a good idea on how latest treatment advances may affect the standard of care in the future.

This will make sure that patients are treated at the current standard of care throughout the whole duration of the study, and that, if appropriate, the study is changed as new information becomes available.

Even after a study design is finalised, it will often take a year or longer before any patients are enrolled, and then several years for the study to run. Trials therefore need to be designed based on what we expect the standard of care to be for the duration of the study.

Most advocates will need training and support to be actively involved, if they are not just included to show good clinical practice, or to get a grant approved.

This involves us learning about the work and the responsibilities of being involved in research.

8.2 Aims for this section

After reading section 8, you should have an understanding of:

- How trials are designed to produce reliable and accurate information
- Why research is needed to inform treatment choices
- The basic concepts used in trials
- The main types of trials and quality of different types of studies
- Advantages and disadvantages of different studies
- Common features of all studies
- Informed consent and patient care
- Interpreting study results
- The different roles advocates can take

8.3 Why trials are important

Modern medicine is often called 'evidence-based medicine'. This is because it is based on treatments or strategies that have been **proven** to show an advantage compared to other approaches.

Well-designed research can produce detailed results, that could be repeated in similar trials.

Without trial results, treatment decisions would only be based on a mixture of:

- guesswork or intuition
- on the hope that a treatment works
- on untypical results, or
- on commercial marketing.

Hard evidence is needed to know how to improve care.

Trials can show which drugs are better than others. For example, the higher risk of side effects when using d4T compared to tenofovir in first-line therapy.

Research can show which strategies are better than others. For example, that combinations that include three drugs to treat HIV are better that combinations with two drugs.

8.4 Developing a new treatment: Phase I, II, III and IV studies

When a new drug is being developed, there are four main 'phases' of clinical research in humans. These studies are run in order - you have to start with Phase I, then II etc.

Pre-clinical research is a term used to describe earlier studies, including test-tube and animal studies, that are carried out before a drug enters human trials.

Phase I studies

Phase I studies are the first human studies.

This includes single-dose studies that are often called Phase Ia trials. A small group of patients (5-10) will take one single dose and be carefully monitored. 1-2 patients will usually get a placebo.

Short-term multi-dose studies, perhaps for 1-2 weeks, are called Phase Ib. This is where a slightly larger group (perhaps 10-20 patients) will take multiple doses and be carefully followed.

These studies are usually in 'healthy volunteers' - ie for an HIV drug, the first people to take it are HIV-negative.

Phase II studies

Phase II studies are usually the first study to look at whether the investigational compound is actually active. They are run in HIV-positve people.

These can last one day, a week or two or several months. Phase IIa studies usually enrol 20-50 people.

Phase IIb studies also look at different doses of a drug - called 'dose-finding' studies. In which case they may enrol 200-300 people.

Phase III studies

Phase III studies are the large trials that are used by regulatory agencies like the EMEA in Europe or the FDA in the U.S. to decide whether a drug will be approved.

For an HIV drug this is usually 1,000 - 2,000 patients.

If the same people from the Phase II study, continue to be followed in the Phase III study, the study is sometimes called Phase II/III.

If one study leads into another study, it is called a 'roll-over' study.

8.5 Hypotheses and endpoints

Phase IV studies

Phase IV studies are usually referred to as 'post-marketing' studies.

They involve longer follow-up of patients looking at side effects and other safety concerns. Sometimes a rare side effect, or a side effect that takes years to develop, may not be seen in a Phase III or earlier study.

Phase IV studies are usually recommended by a regulatory agencies at the same time that a drug is approved.

Although, in the past, the European regulatory agency had very little power to make sure companies followed through on these commitments, recent legislation has strengthened their authority.

Phase IV studies are now compulsory and the EMEA can withdraw a medication if safety commitments are not followed.

Several key concepts are important in research.

Trial question - the hypothesis

This is the idea or theory that the trial aims to either prove or disprove.

Every trial or study needs to start with a question. For example:

- Is something happening? ie does smoking/diet/exercise affect health? or Do our bones get more brittle as we age?
- Can doing something improve health?
- Is one treatment better than (or as good as) another?

Primary endpoint

The primary endpoint is the main way that the results of a trial will be assessed. It should be decided in the study design before any patients are enrolled.

A primary endpoint decides what level of evidence or results will be accepted to prove or disprove the study question. The choice of endpoints can determine whether the final results are going to be useful.

For example, with a new drug, the primary endpoint is often the percentage of people who have an

undetectable viral load at a certain point. This could be 8 weeks for an early effect or 48 weeks for a longer effect.

But it could also be the average drop in viral load or the average increase in CD4 count; or a direct measure of health in how many people see improved or reduced health.

Secondary endpoints

Secondary endpoints can look at everything else.

- Safety of a drug, side effects
- Impact on CD4 count
- Impact on quality of life
- Cost-effectiveness of treatment and many other factors

Community involvement in trial design can help ensure that important secondary endpoints are included when the study is first planned.

8.6 Main types of trial design

There are three main ways to categorise research. Each type of study has specific advantages and disadvantages They each provide different types of information.

Observational vs experimental (or interventional)

An observational study either looks for evidence that something has happened, or follows people to see whether something happens. The trial does not involve a specific intervention other than normal standard care.

Examples of an observational study include looking at:

- How many people have lipodystrophy at one time, or
- How many people develop lipodystrophy over time

An experimental (or interventional) study is where something specific is done in the study - ie using a treatment, strategy, or other intervention, that is recorded and analysed.

Examples of an experimental study include:

- Comparing whether switching one drug for another improves diarrhoea or another side effect

- Seeing whether diet or exercise can improve fat accumulation

Cross-sectional vs longitudinal

A cross-sectional study collects information at one point in time.

Examples of a cross-sectional study include:

- Looking at a group of patients to see how many people have osteoporosis (bone disease), or
- Finding out what percentage of HIV-positive patients are smokers

A longitudinal study follows individuals to see how things change over time.

Examples of a longitudinal study include:

- Following a group of patients to see how many develop lipodystrophy
- Following a group of patients to see whether an intervention to quit smoking could reduce the percentage of patients at risk of heart disease

Retrospective vs prospective

A retrospective study looks backwards in time.

Examples of a retrospective study include:

- Analysing a database to find out what percentage of patients failed their first combination, or
- Looking at medical records to see whether a recently reported side effect occured in other patients

A prospective study decides on what is going to be studied and then follows people over time to see what happens.

Examples of a prospective study include:

- Comparing a new HIV drug to an existing drug, or
- Following a group of patients to see whether heart disease is linked to HIV treatment

In describing a study one of each of these three terms should be included, for example:

- An observational, longitudinal, prospective study
- An interventional, longitudinal, prospective study

etc...

8.7 Randomised, double-blind, placebo-controlled trials

The most reliable evidence - often referred to as the 'gold standard' - comes from 'prospective randomised, double-blind, placebo-controlled study.

Randomisation

Randomising patients in a study is the best proven way to allow for the fact that some things in a trial - and in life - can happen by chance.

Patients in a study are often randomised when two or more groups are studied.

Randomisation is designed to balance factors in each group that could affect the study results. This includes known factors, such as sex, smoking status or social differences, and unknown factors such as genetic differences that we may not know anything about.

Randomising people, if done correctly, and especially with larger groups, should normally result in an approximate balance of all these factors.

This is a very difficult concept, but it is one of the most important things to understand.

Randomisation also stops bias and confounding.

For example, it prevents a doctor putting patients who are most ill and in need of treatment into the group that receives an active drug rather than a placebo (dummy pill). If this happened, although this may sound more 'fair', the two groups would be different at the start, so you couldn't compare the results accurately at the end.

Clinical research, by definition, involves different people getting different treatment. Often the people to get first access to a treatment in a trial, may not get the best results compared to people who use the drug after it is approved.

This is a balance of advantages and disadvantages. Disadvantages for the first people using drugs may mean they do not use the best dose, or that they risk resistance if other newer drugs aren't allowed in the study. The advantages may be that despite these problems, the drugs have still been life-saving, and the person is still alive to benefit from the next drugs in the pipeline.

Randomisation has to be done in a way that doesn't select a certain group over another.

The most common example for randomising a patient to one of two groups is to toss a coin for each patient - heads they join one group and tails they join the other.

This is because tossing a coin is random and can't be predicted.

Over time, the more a coin is tossed, the more likely that approximately 50% will be heads and 50% will be tails.

An example of bad randomisation would be assigning patients who come to clinic on a Monday to one group and patients who come on a Tuesday to another. In this example, people who come on Mondays may be different from people who come on a Tuesday, for social reasons. They may be more organised, or less likely to have a hangover from the weekend! This could represent important differences between the two groups - ie alcohol use - and this could affect the study results.

Study results always should include the characteristics of the people being studied. Sometimes, even with randomisation, you may see that one group may have different characteristics.

When this happens it can sometimes be adjusted for in the final analysis, and it needs to be considered when interpreting the study results.

Blind and double-blind studies

Blinding (sometimes called 'masking') is the term to describe a doctor, patient or researcher not knowing which study group a patient has been assigned to.

A blinded study is where the patient doesn't know which group they are in, or which treatment they are getting.

A double-blinded study is where neither the doctor nor the patient know which group the patient is in.

Blinding prevents different care or treatment being given based on the personal beliefs of either the doctor or patient.

An example of why blinding is important is that if someone know they are getting an active drug, both doctors and patients may be more likely to report side effects.

It could also affect how often a patient takes the treatment.

Placebo

A placebo is the term for a dummy drug, ie something that looks, smells and tastes like the compound or intervention that is being studied, but which has no active ingredient.

Using a placebo helps find out whether the active drug is really active. It also helps interpret side effects.

If 10% of people in the active drug group report having a headache and 2% of people in the placebo group report a headache, then it is reasonable to think that the active drug can cause headaches.

If 10% of the placebo group also reported a headache, then it is reasonable to think that the active drug doesn't cause a headache.

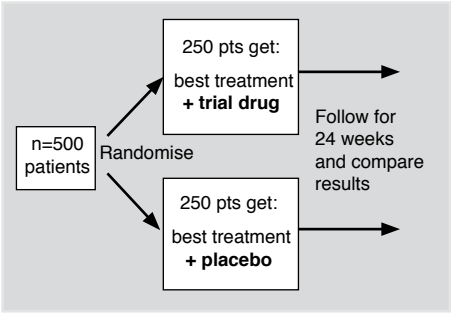
An example of why placebo studies are still important was shown in the development of capravirine (an NNRTI). In a Phase IIb study people using capravirie plus a background combination did no better than people using the same regimen plus a placebo.

This stopped further development of the study drug. It protected other patients being put at risk from using an ineffective treatment in later trials.

Control group

A control group refers to a group of patients in a study, that any intervention group is compared to. This helps to show that the intervention actually caused what was seen and that it wouldn't have happened anyway.

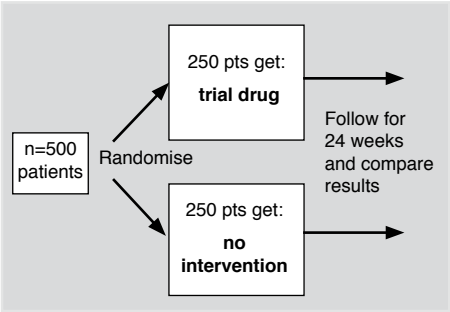
One common type of control group is to use a placebo.



In the example above, all patients get the best treatment with or without the new drug.

If, for example, this is a new HIV drug and the best treatment already includes 3 active drugs, then it could be difficult to see any difference between the new drug and the placebo, because both groups will already do very well.

Another type of control group is a group where no intervention takes place.

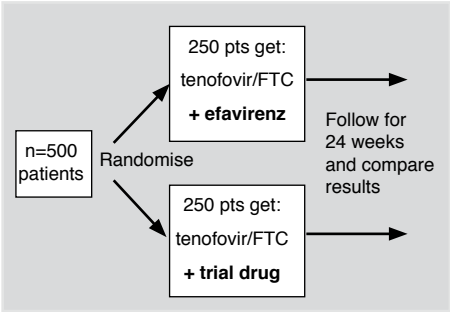


This example might be used where there is something about the trial drug that makes using a placebo difficult - perhaps because it is given by injection.

The difficulty of not randomising the control group to having a placebo is that you can never be sure whether some of the things (both good and bad) that happened to patients in the active drug arm, are not due to chance.

More importantly, people in each arm may behave differently because they know they are getting active drug, for example, by reporting more side effects.

The example below uses a drug or combination that has already been studied as a control group.



This is still generally the type of trial design used for studying a new HIV drug in people who have not yet used HIV treatment. This is generally okay, so long as the new drug turns out to be better than, or at least as good as, the current standard of care.

For this reason, early trials with this design should not enrol people who have advanced HIV (for example with CD4 counts less than 100 cells/mm^3) as these people will need to rely on a proven treatment.

Randomising patients should mean that important factors - both known and unknown - are likely to be distributed between each group. For example, having the similar numbers of women, Caucasians, smokers, CD4 counts etc in each group.

8.8 Other types of studies

We refer to randomised, double-blind, placebo-controlled studies as the gold standard, but other types of studies are very common, and are often needed first in order to justify the expense of running a randomised controlled study.

Randomised controlled trial (RCT)

These are usually experimental and prospective, and compare two or more groups.

Randomisation is the most important factor, as it should make sure each group is similar at the start. The control group helps confirm whether a real effect is seen, rather than just happening by chance, or from other external factors.

All potential new drugs have to be studied in RCTs before they can be approved.

Cohort study

Cohort studies are usually observational and longitudinal.

They can either follow a group of people prospectively to see the incidence of whatever is being looked for or look backwards (retrospectively) to look for an effect.

They can also look at other related factors.

Cohort studies may include all patients at one or more hospitals (such as the MACS or WIHS cohorts in the US), or patients in one country (such as the UK-CHIC cohort), or can include international collaborations of national cohorts, such as the EuroSIDA or D:A:D studies in Europe.

Cohort studies can provide different types of results to an RCT. They can report on what happens in a regular clinic setting and in a wider group of patients than are usually selected for clinical trials.

People can be followed for longer, and they can look at more than one or two options.

However, because patients are not randomised to different treatments and know which treatment they receive (ie are not blinded), results have to be interpreted carefully to try to rule out other things that might explain the results (called 'confounding factors').

Case-control study

These studies are usually observational and retrospective.

A group of patients with a symptom (cases) is compared to similar patients without the symptom (controls) in order to try and identify

what factors either caused the symptom or protected against it.

A case-control study could look at a group of people with lipodystrophy compared to a similar group (similar age, gender, duration of HIV infection, smoking status, etc) and see whether there was a pattern in different HIV drug use; or look to see whether genetic factors could be identified.

Cross-sectional study

These studies are usually quick studies to look at the scale of a problem. For example, what percentage of a population are HIV-positive; or what percentage of people have lipodystrophy etc.

They can identify prevalence of an illness (how many people have a disease at any one point in time) but not the incidence of an illness (how many people will develop an illness over time).

The results from cross-sectional studies are limited by not being followed in time. We can see what is seen at and analyse what factors are related or associated to what is seen.

They cannot prove that one thing causes another or whether an intervention improves health.

Case study and case-note review

This is not a strong type of evidence, but can be used to collect data that might lead to other types of studies.

A case study is where an individual patient report is included as evidence.

Even though all sorts of other factors could have caused what was seen, case studies can alert researchers, doctors and patients to something new.

A case-note review is where a group of patient notes are reviewed retrospectively. The quality of the results are dependent on the quality of the data that was recorded.

Literature review and systematic literature review

A literature review can report collected results from selected studies. A systematic review has to include all relevant studies in the area being looked at.

Meta analysis

This refers to comparing collected results from several studies.

These results have to be carefully interpreted as different studies usually involve different types of patients and it is not straightforward to just compare a final study result.

Both literature reviews and meta analysis are reliant on the types of studies that are published. For the results to be reliable you need to see the range of studies that were included in the analysis.

One problem is that studies that do not find a postive effect are often never published. This is an example of 'publication bias'.

8.9 Grading of recommendations and levels of evidence

Different types of trials are given a different weight when making recommendations in treatment guidelines.

UK Treatment guidelines use the system below in Table 1 to rate the different importance of different types of evidence.

For example, a recommendation that is rated AI should be followed as standard-of-care and is supported by substantial clinical research.

Table 1: Grading of recommendations and levels of evidence

Recommendation	Quality of evidence for recommendation
A: Required, should always be followed	(I) At least one randomised trial with clinical endpoints
B: Recommended, should usually be followed	(II) At least one randomised trial with surrogate markers
C: Optional	(III) Observational cohort data
	(IV) Expert opinion based on other evidence

Source:

www.bhiva.org

8.10 How studies are reported

Most studies are reported using a similar format or structure.

This involves five main sections:

Background - the context for the study - what is already known about this area of research and why the study is being run.

Method - the study design - what exactly was studied and how it was preformed.

Results - what was seen or demonstrated.

Discussion - this can include a discussion about the strengths and weaknesses of the study: cautions about interpretation, what could have been done better, and the implications for clinical practice, treatment guidelines or for further research.

Conclusion - the final summary results - what was learned and how it can affect care. Sometimes researchers jump from their results to conclusions that are not supported by their evidence. This is important to look out for.

Abstract

A study abstract is a reduced summary of the main points of a study and is usually limited to around 500 words. There is not usually enough information in the abstract to be able to discuss the quality and significance of the findings.

Poster

A poster is a presentation at a medical conference that includes more details than the abstract.

Peer-reviewed publication

A peer-reviewed publication is a most detailed presentation of a study, where other experts in the field have examined the methods, results, and conclusions in order to verify that the study was conducted properly and that the results stand up to scrutiny.

Peer-reviewed publication takes time. Many studies presented at conferences are never followed through to publication.

Study results vs real life

Results seen in a study are often different to the results you would expect to see routinely in a clinic after a drug has been approved.

Results are often better, because people in studies may be more organised and committed to treatment, and because they receive more care and time at the hospital.

Conflicts of interest

When looking at a study it is important to look at the authors, where they work and if they have a conflict of interest and whether this is declared.

8.11 Patient involvement in clinical studies and research

Clearly, studies need patients. But patients are real people, not just the subjects of research.

Any clinical study should follow guidelines to ensure that the trial is ethical.

People are willing to be part of the research and consent to this.

This is why non-technical information about any study has to be available for discussions with doctors and researchers AND as written material in a patients' first language. Community advocates should be involved in writing and approving this material.

People understand the risks and benefits of a study.

This is why every patient needs to sign an 'informed consent' form before entering a study. In theory, it should mean that every patient understands the risk and benefits of the study, and voluntarily agrees to take part in the research.

In practice, informed consent forms can be difficult to understand, and many patients are happy to sign whatever their doctor recommends.

Informed consent can be withdrawn by a patient at any time, and this should not affect his or her future health care

Patients are not knowingly harmed as part of the research.

- This involves all patients receiving at least the minimum standard of care when the trial is designed, and that the trial is changed to reflect any changes in the standard of care over the duration of the study.
- This means that a study may need to be discontinued early if one arm is found to be much better than another.
- This mean that a study design is changed or amended if results from other research have an impact on the current trial.
- Studies should have pre-planned reviews of study results (either blinded or unblinded), preferably by independent experts who are not connected with running the study. This group is called the DSMB (Data and Safety Monitoring Board).

  These are reasons why patient advocates need to be included in following the conduct and early results from a trial, and included in trial steering committees and at investigator meetings.

Patients taking part in a study will be able to benefit from the results of a study.

For example, a company can not save money by running cheaper trials in poor countries without ensuring that the drug will made available at an affordable cost for people in these countries afterwards

A study answers a relevant medical question.

- This includes making sure that new studies are not designed, for which we already know the answer.
- With randomised studies, it involves making sure at the start that each group in the study has the potential to be the best option. The study should have been approved by an ethics committee linked to that research centre.

  People in the ethics committee should understand the current standard of HIV care.

8.12 Confidentiality for advocates involved in research

For advocates to be actively involved in research usually requires understanding the importance of confidentiality in relation to study results, especially if you are seeing early trial results before they are made public.

This can sometimes include formally signing a confidentiality agreement.

Most studies will result in one group in a trial doing better than another. As an advocate you may get to see these results before they are presented in public.

Often the early results though are not the same as the results seen at the end of the study.

As long as the study continues to be run ethically and as long as the study question hasn't been answered, it is important that early results remain confidential.

Publicising early results could cause an important study to never reach a final result.

For example, participants may stop or change treatment based on preliminary results, or on word-of-mouth, which may not in fact be reliable.

Research into AZT is an important historical example of where the first short-term results lead to stopping a trial and then widely prescribing the drug. Only with results from a longer 2-year study did it become clear that there was no long-term benefit for most patients.

This does not stop you raising any serious concerns you have on the safety of a study, with:

- the researchers involved in the study, or
- other community colleagues that agree to the same level of confidentiality.

Only in exceptional circumstances and as a last resort should confidential results from an ongoing study be taken to the wider community.

8.13 Summary of different advocacy roles

Advocates can be involved in many different roles.

These include being involved in:

- Trial design before the study is finalised.
- Wording of patient information sheets and informed consent.
- Publicising good research to help study enrolment.
- Highlighting poor or inappropriate research.
- Taking an educational role to explain benefits and risks of a study to community groups.
- Being an independent advisor for whether a trial is appropriate for an individual patient.
- Joining a trial steering committee and following enrolment, trial practice and early results.
- Joining a Data and Safety Monitoring Board (DSMB).
- Reporting and critically commenting on results after they are publicly presented at medical meetings or published.
- Suggesting additional analysis of study results.
- Ensuring results are presented and published publicly and in time while they are still relevant.
- Ensuring study participants are informed of the results of the research that they have been involved in.

8.14 Glossary of other terms

Intent-to-treat (ITT) vs Observed/ on-treatment (OT). These are two important ways that drug trial results are analysed. ITT includes all patients when calculating the response rates. OT only calculates the response rates for people still on the randomised treatment. For example:

- 100 people use a trial drug in one arm of a study
- 25 stop treatment before the end of the study for various reasons
- 50 have an undetectable viral load after 48 weeks
- 25 have a detectable viral load after 48 weeks

In an ITT analysis 50% of people got an undetectable viral load using the study drug (50 out of 100 patients).

In an OT analysis, 66% of people got an undetectable viral load using the study drug (50 out of 75 patients).

ITT analyses are more conservative but arguably are most important when looking at overall effectiveness and safety. OT analyses always make a drug look more effective, so you need to check which analysis is being presented.

In-vitro - A study in a test tube.

In-vivo - A study in humans.

Matched sample - ie each group has similar age, gender, ethnicity, etc

Null hypothesis - this sometimes just refers to the hypothesis in a study, but more specifically it refers to the idea that any difference between 2 study groups has only occurred by chance.

Open label - where a patient in a trial knows which treatment they are taking.

Publication bias - refers the tendency for published results to be different to other trials. For example, trials that show a positive effect are more likely to be reported and published, than trials that find no effect.

Qualitative - where what is being measured either fits one of several categories, or includes descriptive results.

Quantitative - where what is being measured has a numerical value or fits a pre-defined scale or range of responses.

Roll-over study - when patients in one study 'roll-over' to a second related study. For example, this can be after a fixed period or after another event (for example, not having a treatment response).

Study population - the group of people studied. What happens to the study population is not guaranteed to happen in every person.

Section 8.15 Multiple choice questions and answers

For each question you can tick more than one answer.Please tick/check all that you think apply.

1. Community advocates should be involved in research because…

A It can help with grant applications.

B Advocates need jobs too.

C Advocates can help design a study today that will still be providing good treatment in a years time.

D Advocates can independently represent patient interests if a study isn't running well.

E If advocates understand the research they can give independent information about the risks and benefits to individual patients who may want to join the study.

2. Why is research important for advocates?

A Because if designed well, it can provide reliable information about how effective and/or harmful a treatment or drug may be.

B Because it will help a company sell more drugs.

C Because it can prove a new treatment may be better than an older treatment.

D Because without evidence, you can only guess at whether something works.

E Because without evidence people are vulnerable to false claims about miracle drugs.

3. Which of these statements about different trials in drug development are true?

A Phase IV studies are run to get a drug approved.

B Phase II studies are run before Phase I studies.

C Phase I studies are run in animals.

D Phase III studies are the main large studies that a company runs to get a new drug approved.

E Phase II studies look at different doses of a drug to try to find the best one.

4. Which of these statements about a trial hypothesis are true?

A Every trial needs to start with a question, which is called a 'hypothesis'.

B The hypothesis is a question that a study is designed to either prove or disprove.

C The hypothesis has to be true from the start of the study.

D A hypothesis has to say that one thing is better than another.

E Some trials do not need a hypothesis.

5. Which of these statements about a trial design are true?

A A primary endpoint of a study is always seen in the group that does the best.

B A primary endpoint is decided before the study starts.

C A secondary endpoint is only used for studies in older children.

D A primary endpoint decides what level of evidence or results will be acceptable to prove or disprove the study question.

E Secondary endpoints can look at a wide range of important things like side-effects and quality of life.

6. Which of these statements about studies are true?

A A prospective study looks backwards in time to see what happened in the past.

B A new drug is tested in an interventional study.

C A retrospective study look backwards in time.

D A cross-sectional study looks at something happening at one point in time.

E A longitudinal study looks at how tall people are.

7. Which of the following statements describe a study that randomises patients to receive a new drug or a placebo and then follows them over time?

A A prospective, observational study.

B A prospective, interventional study.

C A retrospective, cross-sectional study.

D A prospective, longitudinal study.

E A cross-sectional, longitudinal study.

8. Which of the following describes a cross-sectional, retrospective study?

A A study that give people a new drug to see if it has less side effects.

B A study that decides to see how many people have lipodystrophy at their next clinic appointment.

C A study that looks at hospital records to see how many patients are current smokers.

D A study that looks at hospital records to see how many patients had a heart attack last year.

E A study to see whether combination therapy with 4 drugs in young children was better than starting with three drugs.

9. Which of the following statements about randomisation are true?

A Randomisation helps make sure that people who are more ill stand a better chance of getting a new active drug.

B Randomisation will help make sure that each arm has the same proportion of women, with similar ages and CD4 counts.

C Randomisation will help make sure that equal proportion of Gemini, Aries, and Librans are in each arm.

D Randomisation is likely to be effective if people are chosen by tossing a coin.

E Randomisation is likely to be effective if people are chosen by the day that they visit the clinic.

10. Which of the following statements about terms used in trials are true?

A A placebo is a drug that works well but has no taste.

B A placebo has no active drug and is used to compare results to an investigational drug.

C Blinding makes sure that a patient knows which drug they get.

D Double-blinding means that neither the doctor nor patients know which arm they are in.

E A control group is the name for study arm that is used to compare the results of a new intervention.

11. Which statements about these different types of trial are true?

A A cohort study is usually an observational study that follows a group of people over time.

B A cohort study is the best way to see if a new drug works.

C Prospective, randomised, placebo-controlled, studies are the 'gold-standard' for getting the most reliable evidence about an intervention.

D A cross-sectional study can give you a quick answer to whether a new side effect is being seen in a clinic.

E A meta-analysis compares results from different studies.

12. Which of the following five terms relates to each of the longer descriptions below?

1 - results

2 - method

3 - discussion

4 - background

5 - conclusion

A The final summary results - what was learned and how it can affect care.

B The strengths and weaknesses of the study: cautions about interpretation, what could have been done better, and the implications for clinical practice, treatment guidelines or for further research.

C What exactly was studied and how it was performed.

D What is already known about this area of research and why the study is being run.

E What was seen or demonstrated.

13. Which of these statements about informed consent are true

A The 'main' reason for informed consent is to protect a researcher from legal claims in the future

B The 'main' reason for informed consent is to make sure patients understand the potential risks and benefits of a study before they agree to take part

C Informed consent should be written in simple language and carefully explain any technical terms

D Informed consent should be in a language that a patient understands

E Even after someone has signed an informed consent form, they can with draw from the study at any time

14. Advocates can be involved in the following roles in research...

A Following study recruitment and seeing early results with investigators

B Suggesting additional analysis of study results

C Being an independent advisor for whether a trial is appropriate for an individual patient

D Helping design the trial

E Highlighting poor or inappropriate research

Answers

Question 1: C, D, E

Question 2: A, C, D, E

Question 3: D, E

Question 4: A, B

Question 5: B, D, E

Question 6: B, C, D

Question 7: B, D

Question 8: D, E

Question 9: B, C, D

Question 10: B, D, E

Question 11: A, C, D, E

Question 12: 1-E, 2-C, 3-B, 4-D, 5-A

Question 13: B, C, D, E

Question 14: A, B, C, D,

If you have questions about the answers, please email:

questions@i-Base.org.uk

8.16 Course evaluation of Section 8

Please take a few minutes to complete this evaluation. Any comments are appreciated, including on the usefulness of the evaluation as we can develop this into an online resource.

1. How much of the information was new?

   None 1 2 3 4 5 All

2. How useful was the information?

   Very 1 2 3 4 5 Not at all

3. Has the booklet helped you to understand new research concepts?

   A lot 1 2 3 4 5 Not at all

4. Has the booklet increased your interest in research?

   A lot 1 2 3 4 5 Not at all

5. Did the information relate to questions you already had about research?

   A lot 1 2 3 4 5 Not at all

6. What was your pass rate? ____ / 14 or ____ / 70

Easy marking: One point for each completely correct answer

Maximum total = 14

Detailed marking: Give yourself one point for every paragraph that was correctly assigned minus one point for each paragraph missed or that was wrongly assigned.

Maximum total = 14 x 5 = 70

7. Now sit the test again in one week to see how much you remember.
8. Did your pass rate improve? YES NO

If you have questions about the answers, please email:

questions@i-Base.org.uk

8.17 Further information and links

HIV i-Base

www.i-Base.info

An intenrational HIV advocacy and treatment information organisation based in the UK.

UK Community Advisory Board

www.ukcab.net

UK-CAB is a network for community HIV treatment advocates in the UK.

The CAB aims to develop, strengthen and support:

- A network of treatment advocates
- Expert training on current treatment issues and opportunities to meet with doctors, researchers and pharmaceutical companies
- Community representation in clinical trials and setting the standard of care

The UK-CAB is free to join and connects over 200 members from over 100 community organisations.

Please see the website for further details.

ECAB (European CAB)

www.eatg.org

The ECAB is a working group of the European AIDS Treatment Group. It has been running for over ten years to support community involvement in trials across Europe.

Medical Research Council (MRC)

www.mrc.ac.uk

The national orgnaisation for research across all disease areas in the UK.

The MRC Clinical Trials Unit is responsible for running many national and international HIV trials in the UK.

US Clinical Trial Database

www.clinicaltrials.gov

Important site that lists US and international studies.

Regulatory agencies

The following agencies are responsible for evaluating the safety of medicines in the UK (MHRA), Europe (EMEA) and the US (FDA).

http://www.mhra.gov.uk

www.emea.europa.eu

http://www.fda.gov/

British HIV Association (BHIVA)

www.bhiva.org

BHIVA produces an important range of clincal guidelines and organises annual conferences.

8.18 Key studies in HIV research

Links to a few important examples of different types of research.

1. First reports

Masur H et al. NEJM, Vol 305:1431-1438. Dec 10, 1981. Number 24.

http://content.nejm.org/cgi/content/abstract/305/24/1431

One of 3 papers and an editorial from the New England Journal of Medicine in December 1981.

An example of why case reports from insightful doctors can be so important.

2. AZT: ACTG019 and Concorde

Learn the history of the first approved drug. In 1989, the first AZT study was stopped early and everyone started treatment. Four years later, Concorde showed no clinical benefit for all but the most ill. Concorde began in 1988 but 'preliminary results' were only reported in a letter to the Lancet in April 1993.

Volberding et al. NEJM

http://content.nejm.org/cgi/content/abstract/322/14/941

Concorde Trial. Lancet. 1993 Apr 3;341(8849):889-90. Not available online .

As these papers are not online, see:

NEJM editorial on ACTG 019:

http://content.nejm.org/cgi/content/full/329/5/351

After Concorde article in BMJ, 1993:

http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1677009

3. PI-based triple combination

Gulick RM et al. World AIDS Conference, 1996. Abstract Th.B.931.

http://www.aegis.org/conferences/iac/1996/thb931.html

The first triple-combination protease-based studies showed:

i) 3 drugs were essential

ii) viral load could measure the effect of treatment

Despite this, numerous studies after 1996 still included treatment groups using one (monotherapy) or two (dual therapy) arms.

An example of how early results, presented at a conference rather than in a medical journal, changed clinical practice and guidelines.

4. Resistance, replication and viral load

Richmann D et al. Full text publication form Journal of Virology.

http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=109542

Reducing viral load to undetectable (less than 50 copies/mL) stops HIV from developing and mutating, and makes the likelihood of developing resistance very low.

A key paper to understand how treatment works.

5. Combination therapy in pregnancy - transmission approaching zero

Beckerman K et al. World AIDS Conference, Geneva, 1998. Abstract 459.

www.aegis.org/conferences/iac/1998/459.html

This was probably the most important study at the World AIDS Conference in Geneva in 1998, yet it received hardly any press coverage.

Using combination therapy during pregnancy went against the mainstream caution to only use AZT, yet it reduced transmission to near zero. It still took years for this to become standard-of-care in Western countries.

6. New standards of care: efavirenz

K. Tashima et al.

www.retroconference.org/1999/Abstracts/LB16.htm

This study was presented at the World AIDS Conference six months earlier, but didn't include the results in the abstract. A similar abstract is therefore included here from a meeting a few months later.

This study was important for comparing a new drug to the best standard-of-care, for looking at results at high viral load (over 100,000 copies/mL) and the first use of Intention-To-Treat analysis (ITT).

7. Biopsy studies showing d4T and AZT cause changes in fat cells

Hammond et al. 7th Lipodystrophy Workshop, Dublin, 2005. Abstract 2.

www.aegis.org/conferences/lipo/2005/2.html

This careful fat biopsy study showed which nucleosides cause fat loss on a cellular level.

8. SMART treatment interruptions and inflammation

El-Sadr W et al. 13th CROI, 2006. Abs LB106.

www.retroconference.org/2006/Abstracts/28085.HTM

The most important study from the last 5 years. SMART was able to show the risks from interrupting treatment because it was a large randomised study.

Linking risk to detectable viral load, it found that HIV treatment protects against heart, liver and kidney disease and led to a new trial called START looking at earlier treatment.

These are just a few examples from hundreds of key studies. Reading abstracts and following research is difficult but exciting.

All these studies changed expert opinion and clinical practice. Well-conducted research was essential for care to improve and change.

Notes

0808 800 6013

i-Base treatment information phoneline

mon > tues > wed > 12.00–4pm

i-Base can also answer your questions by email or online:

questions@i-Base.org.uk

www.i-base.info/questions

i-Base publications

All i-Base publications are available free. Treatment guides are written in everyday language. HTB is written in more technical medical language. Please send me: (please write

- Introduction to Combination Therapy ☐
- Changing Treatment: Guide to Second-line Therapy ☐
- Pregnancy and Women's Health ☐
- Guide to Avoiding & Managing Side Effects ☐
- Guide to HIV and Hepatitis C Coinfection ☐
- HIV Treatment Bulletin (HTB) ☐

Publications in other languages are available in pdf format at www.i-Base.info

Name: _____

Address: _____

_____ Postcode: _____

Tel: _____ Email: _____

Please post to: i-Base, HIV i-Base, 3rd Floor East Thrale House, 44-46 Southwark Street, London SE1 1UN or fax to: 020 7407 8489

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