

Understanding Clinical Trials



Introduction

Welcome to the Understanding Clinical Trials booklet – a resource to help you to understand key concepts and terminology around clinical trials and their analysis.

This guide focuses on cancer specifically, but the concepts and terms explained within it can be applied to other disease areas.

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1. Introduction to the drug development process

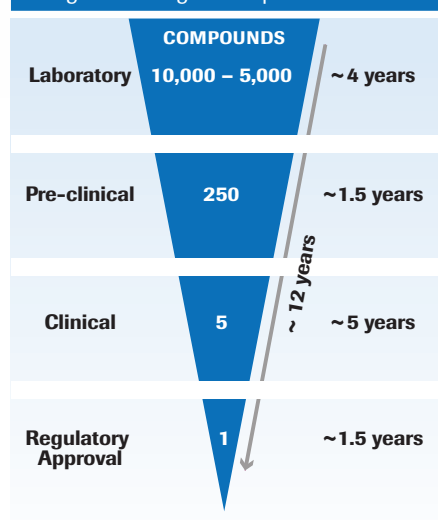
Of every 5,000 cancer molecules identified in the laboratory, about 250 will enter pre-clinical testing. Of this 250, fewer than 10 are tested in clinical trials and on average only one will be approved by regulatory authorities. The process of bringing a new treatment from the research stage (laboratory) to clinic is estimated to take between 10–13 years.¹

- New medicines originate in the laboratory where researchers identify, isolate and study thousands of molecules for their potential as future anticancer therapies.
- Once a candidate molecule (compound) has been identified in the laboratory, it is subjected to rigorous pre-clinical testing (in the laboratory and/or in animals) to assess its chemical, biological and toxicological properties (how harmful it is).
- These pre-clinical tests allow researchers a snapshot of whether a compound may have anticancer activity.
- If results of pre-clinical studies are positive, the compound may be entered into a clinical trial program: this involves several 'phases' of study, starting with small studies usually in healthy volunteers and progressing in steps through to evaluation of the drug in people with the disease. At each phase, only those compounds that meet strict criteria for safety and effectiveness (efficacy) advance to the next phase.
- When results of clinical trials indicate the compound being studied is safe and effective the company applies to *regulatory authorities* for marketing authorization (permission to sell,

and use the drug in daily medical practice). This usually occurs following a successful Phase III study, but may occur earlier in diseases where there are very few treatment options, sometimes described as a 'high medical need'.

- Finally, if the marketing authorization is granted, the new treatment is made available as prescribed by doctors. There are strict rules regarding the license given to the treatment – the pharmaceutical company may only promote the product for the treatment of patients with the diseases (indications) described in the license or label.
- The medicine's use continues to be carefully monitored in accordance with approved current medical practices.

Figure 1: Drug Development Process



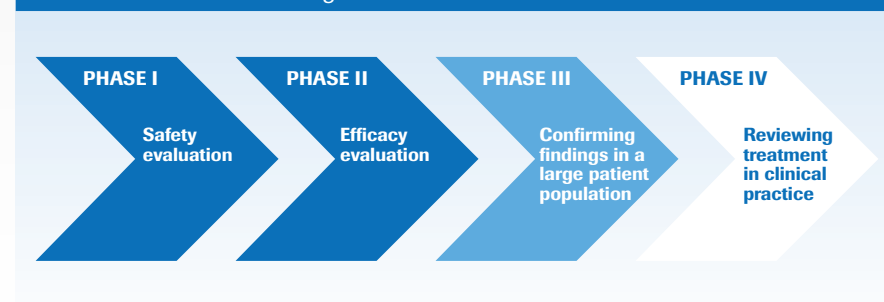
¹(Pharmaceutical Industries and Associations (EFPIA). A Highly Regulated Industry. Accessed November 2012. Available at: <http://62.102.106.100/Content/Default.aspx?PageID=361>)

2. Understanding clinical trials

Clinical trials explore how a treatment reacts in the human body and are designed to ensure a drug is tolerated and effective before it is licensed by regulatory authorities and made available for use by doctors. Studies vary in their primary goal or endpoint (i.e. the most important outcome of the trial), the number of patients involved, and the specifics of the study design. However, all clinical studies conform to a strict set of criteria to protect the patients involved and to ensure rigorous evaluation of the drug.

Clinical trials are categorized by phases:

Figure 2: Clinical Trial Phases



Trial Phase	Definition
I	The first investigation of a potential new drug in people, to determine how the drug reacts in the body, and how the body reacts to the drug – how it is absorbed, distributed and metabolized or altered / used by the body. Commonly conducted in a small number of healthy volunteers.
II	The first study to focus on the clinical effectiveness of the drug, and therefore performed in patients with the disease. At this stage the studies also determine any short-term side effects and safety risks associated with the investigational drug.
III	Studies carried out in large numbers of patients, comparing the investigational drug with the best existing treatment or standard of care in that particular disease. If positive results are obtained all data to date is compiled into a dossier and an application is made to regulatory authorities to request a license for clinical use.
IV	Also known as post-marketing studies, these are conducted after the drug is approved by regulatory authorities and may include thousands of patients. These trials are generally designed to evaluate the long-term safety and efficacy of a drug, and to test it in a "real world" setting of daily clinical practice.

3. Design of clinical trials

Clinical trials are designed with a number of parameters in order to generate meaningful results. These parameters include the patient population to be studied, treatment(s) to be investigated, endpoints and methods by which the trial will be conducted (e.g. randomized vs non-randomized).

■ Patient population

Patients must meet specific criteria if they are to be included in a trial. Common entry criteria include: having a certain type of cancer, having a particular treatment history, and being in a certain age group. Entry criteria help ensure that the people in the trial are as similar as possible to each other (in terms of basic profile, type and stage of disease), so that the results of any treatment effect can be associated as much as possible with the drug treatment being studied and not other factors.

■ Use of controls in a clinical trial

In controlled trials – most phase III and some phase II trials fall into this category – the agent or regimen being investigated is compared with a *control*. The control may be either a medically ineffectual treatment known as a placebo (if no effective therapies are available for the disease being studied) or a standard treatment – one in wide use and considered effective at the time the trial is designed. Although a placebo is sometimes used as a control in clinical trials, it is rarely used in cancer trials, where there may be ethical issues with this approach. It is important to note that because some clinical trials take months or even years to complete, the standard treatment may no longer be in wide use by the time results from the trial are reported.

■ Endpoints

The aim of a clinical trial is to measure key outcomes or *endpoints* and to test the clinical efficacy and tolerability of the treatment in a particular disease. The trial will usually specify a primary endpoint. This is the most important endpoint of the trial and, if met, means a positive result for the trial and the treatment.

The clinical trial protocol provides the design for the study conduct and sets out the endpoints of the study up-front. There is clear guidance on how and when to measure and evaluate the study endpoints.

The primary endpoint usually assesses the treatment efficacy (the ability of an intervention or drug to reproduce a desired effect). A trial may also define one or more secondary endpoints. These typically include secondary efficacy measures (additional evaluations designed to assess the clinical effectiveness of the drug in controlling disease) and safety endpoints (designed to measure tolerability and safety of treatment over the period of study).

■ Conducting the trial

The trial design is not complete when the trial population, treatment and endpoints have been identified and defined. In phase III and some phase II trials in cancer, the patient population may be *randomized* (randomly allocated to receive one or other of the alternative treatments being studied) and stratified (partitioned by a factor other than the treatment, often to ensure that equal numbers of participants with a characteristic thought to affect prognosis or response to the intervention will be allocated to each comparison group). The gold standard in clinical research is a scientifically rigorous, randomized, well controlled trial.²

²(Chin R, Lee BY. Principles and Practice of Clinical Trial Medicine. Amsterdam, The Netherlands: Academic Press; 2008:3-16.)

4. Understanding clinical trial endpoints

Key endpoints

Depending on the stage of the cancer, trials tend to look for changes in the following:

■ Overall survival (OS)

The percentage of patients alive at a defined period of time after diagnosis or, in treatment studies, the percentage of patients alive at a defined time after initiation of the treatment.

OS is often reported as a five-year survival rate, i.e. percentage of patients alive five years after diagnosis or treatment. The OS rates reported after diagnosis of different diseases can vary, since some cancers have a better outlook (survival rate) than others. The effect of a treatment on OS should be viewed relative to the background or expected OS for a given cancer.

Important points to note about OS as an endpoint:

- OS is seen as the 'Gold Standard' clinical endpoint for many health authorities because it is a measure of survival
- However, measuring OS can be problematic when evaluating earlier lines of therapy (the line of therapy is the sequence of therapies a patient undergoes e.g. *first-line* is the initial treatment used to target tumors and will be followed by a second-line treatment should the first line not be effective). This is because measurement of OS is often influenced by later lines of therapy making it difficult to determine the true effect first-line treatment may have on OS

■ Progression free survival (PFS)

The proportion of patients who continue to live with a disease that is not getting worse (i.e. not progressive disease (PD)).

For example, PFS-6 is the rate, or proportion of patients given a treatment that survive without their disease worsening at six months after treatment began.

Important points to note about PFS as an endpoint:

- Disease progression is often symptomatic and uncomfortable, so delaying disease progression is very meaningful for patients and is an important goal for physicians and nurses
- If a medication becomes ineffective, a patient can switch to another therapy (crossover) or take additional treatments. Unlike some other endpoints (e.g. OS), PFS is not affected by this crossover or subsequent lines of therapy (a later and usually different treatment to the previous one), as it is only applicable until disease worsens

■ Quality of life (QoL)

Clinical trials may assess the effect of treatment on a patient's well-being and ability to function in daily life. These are measured using quality of life tools (questionnaires and scales) which have been developed to assess specific aspects of quality of life recognized as affected by particular cancer diagnoses.

Some trials now include Patient Reported Outcomes (PROs) as one of the ways to measure QoL. These measures are particularly important for patients as they show the impact of the treatment on everyday life.

■ Response rate (RR)

Response rate measures tumor size, usually using a scan or X-ray. It gives an indication of whether the tumor is responding to a treatment – if the tumor size has shrunk, it is deemed that there has been a “response”. There are different ways of determining response rate and the internationally recognized RECIST (Response Evaluation Criteria In Solid Tumors) guidelines are often used in clinical trials .

• Complete response (CR)

Disappearance of all clinical evidence of disease. This typically means disappearance of tumors as measurable using medical imaging techniques (scanners/radiological tests) and/or by measurements of pathological specimens and samples (tissues, biopsies, blood etc).

• Partial response (PR)

At least 30% reduction in size of all measureable tumors.

• Stable disease (SD) or No change (NC)

Between a 30% reduction or < 25% increase in the size of all detectable tumors. The reason these ‘reductions’ or ‘increases’ are considered as ‘stable disease’ is because without treatment, it might be expected that many existing tumors would continue to grow or spread, not decrease in size or grow at a slower than expected rate.

• Progressive disease (PD)

Patients or proportion of patients with a $\geq$ 25% increase in size of tumors since previous measurement. Unlike a CR, PR or SD, PD suggests that the cancer is advancing, not reducing or stabilizing.

■ Objective response rate (ORR)

Percentage of patients whose cancer shrinks (Partial response – PR) and/or disappears (Complete response – CR) after treatment.

Important points to note about ORR as an endpoint:

- Objective Response rate is a physical measurement of tumor size, and is thought to be an indication of treatment effectiveness
- ORR can provide physicians with important information on how a patient is reacting to a treatment
- ORR can be particularly important in certain cancer types, especially those which cause disfiguring lesions e.g. basal cell carcinoma, where extensive surgery may be used to remove lesions

■ Disease control rate (DCR) or clinical benefit rate (CBR)

Percentage of patients whose cancer shrinks or remains stable over a certain time period. DCR is the sum of the complete, partial and stable disease rates.

■ Duration of response (DR)

Time from confirmation of a partial response (PR), complete response (CR) or stable disease (SD), until the disease has been shown to progress following treatment (progressive disease or PD).

Other common endpoints

■ Performance status (PS)

Measure of how well a patient with a cancer diagnosis can perform ordinary tasks in daily life before, during or after treatment. Specific numeric PS scales indicate levels of disability due to disease, and/or severity of symptoms. Two main scales are:

• The Eastern Cooperative Oncology Group (ECOG)

Rates a patient's performance status from zero to five, where zero is fully active and five is dead. A person is a three if they are capable of only limited self-care, or confined to bed or chair for more than 50% of waking hours.

• Karnofsky status

Rates the severity of cancer related symptoms and degree of disability on a scale from 100% (no symptoms) to 0% (dead). A 50% rating indicates that a patient requires considerable assistance and frequent medical care.

Treatments for cancer might be expected to impact on PS scores – both positively if disease burden is reduced or negatively if treatments have side effects that affect the patient's ability to perform ordinary tasks.

■ Time to progression (TTP)

TTP is the time from randomization until tumor progression, not including death. This is different from PFS which is the time from randomization until tumor progression or death.

■ Relative survival rate

Ratio of a cancer patient's chance of surviving a given time interval compared with that of an average person without cancer of the same age and sex.

■ Disease/recurrence free survival (DFS)

Length of time after treatment that a patient survives with no sign of disease.

■ Distant disease/recurrence free survival (DDFS)

Length of time after treatment that a patient survives with no sign of disease in a different part of the body to the site the disease was originally treated (i.e. time without the emergence of new metastases – the spread of a disease from one organ or part of the body to another non-adjacent organ or part.)

■ Invasive disease free survival (IDFS)

The time a patient lives (or survives) without return of invasive disease after *adjuvant treatment* (a treatment given in addition to the main form of treatment e.g. chemotherapy given in addition to surgery, that aims to delay or prevent recurring disease by destroying possible remaining cancer cells).

■ Minimum residual disease (MRD)

The presence of residual malignant cells that remain in the patient during or after treatment. It is a major cause of relapse in cancers like leukemia.

■ Event free survival (EFS)

Duration from the start of treatment to a pre-defined ‘event’, which may include specific complications of the disease or treatment.

■ Pathologic complete response (pCR)

The absence of any residual invasive cancer after treatment.

Pharmacokinetic (PK) endpoints

PK is the study of what happens to a drug when it enters the body. In particular, the concentration of the drug in the blood over a time period. Pharmacokinetic endpoints are primarily used when a trial is comparing the same molecule, and is seeking to identify the dosage at which the primary medical condition for which the drug is targeted is most effective.

Plotted curves (see fig. 3) indicate the concentration of two different formulations of a drug with respect to time.

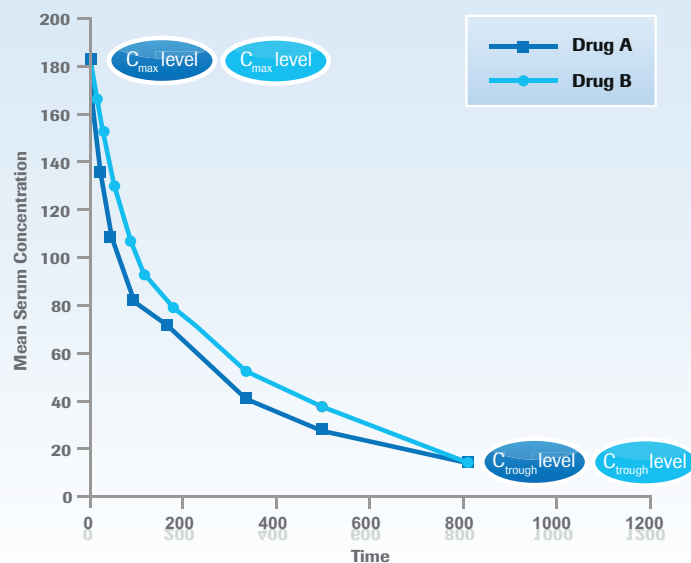
- $C_{\max}$ is the maximum concentration of the drug in the blood serum during a given dosing interval.

- C_{trough} is the minimum serum drug concentration during a given dosing interval. In terms of dosing, when a drug reaches its C_{trough} level this indicates when the next dose of the drug is needed – therefore the time from drug administration to C_{trough} correlates to the dosing frequency of a given drug.

Bridging study endpoints

Bridging studies test whether there is a difference in the pharmacokinetics of a drug with different subgroups of patients or methods of drug delivery. A bridging study could, for example, be used to compare populations who have very different Body Mass Indices (BMIs), to determine whether the dosing should be adjusted by weight.

Figure 3: Pharmacokinetic curve



The curves shown are hypothetical and do not represent actual data

Adverse events (AEs)

When a treatment is described as safe it does not mean there are no potential risks associated with its use, only that the benefits to the patient of taking the treatment are deemed to outweigh the potential risks. An AE is any unfavorable, unintended symptom, sign (for example an abnormal laboratory finding) or disease associated with the use of treatment. AEs can be graded based on their severity:

Table 1: Grades of AEs

Grade 1	Asymptomatic (no) or mild symptoms; for this grade of AE, treatment is not indicated.
Grade 2	Moderate; for this grade of AE minimal, local or noninvasive intervention may be indicated, for example, this might involve treating the symptom (e.g. nausea and vomiting caused by a cancer treatment managed/prevented by giving the patient drugs to stop sickness, rather than stopping the anticancer drug).
Grade 3	Severe but not immediately life-threatening; for such AEs hospitalization and investigation/management are often indicated.
Grade 4	Usually life-threatening consequences; for these AEs urgent intervention is indicated.
Grade 5	Death related to AE.

5. Understanding key statistical concepts

The average number of patients in the control arm and in the treatment arm of the study who reach a given endpoint can only tell so much about the effect of a treatment. What matters is to determine if the difference between the treatment arms is statistically significant (a difference which reflects a pattern rather than just chance) and thus could offer a genuine benefit to patients.

Statistical analyses measure and assess the data from the study to attempt to provide confident measures of the effectiveness of treatments, the probability that differences between treatments demonstrate relevant changes in the risk of certain events (signs, symptoms or factors of a disease) and give a mathematically accurate measure of the effectiveness and benefits of treatments.

Correct interpretation of clinical trial results is dependent on appropriate and accurate statistical analyses and understanding what they mean both numerically and for patients.

Describing differences using statistics

■ Statistically significant

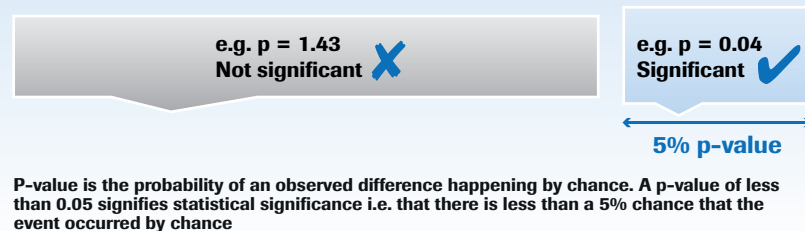
A mathematical measure of difference between groups; a difference in a value (e.g. number of people achieving a CR) seen in one treatment group compared with another is considered statistically significant if it is greater than that which might be expected to happen by chance alone.

■ Probability (p) values

A p-value is the likelihood of obtaining a statistical result by chance, assuming there is no difference between the treatments being investigated. The lower the p-value the less likely the result happened by chance, and the more likely the result can be attributed to the drug being tested.

The p-value which is considered to be significant can vary, but is usually set at 0.05. A p-value of 0.05 means that there is only a 5% likelihood that the result happened by chance – and therefore that the result is due to a true difference between the treatment effects and not chance alone.

Figure 4: p-Value and Statistical Significance



■ Averages – median and mean

Improvements in measures such as disease free or overall survival are often measured by the median.

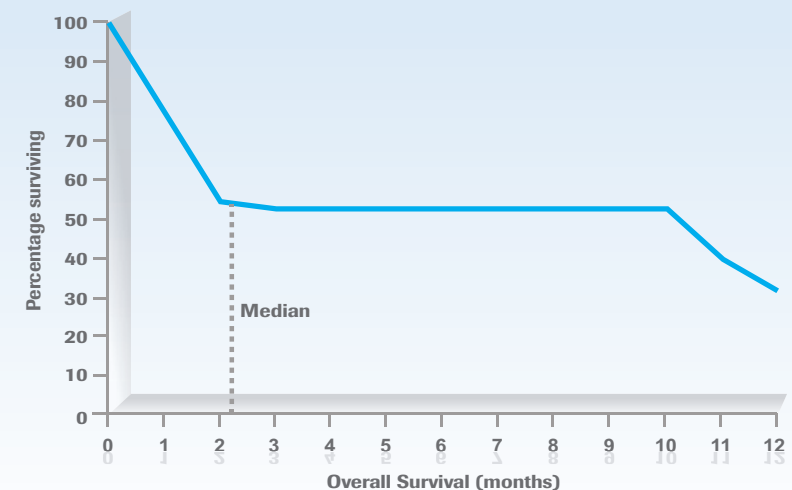
Median is the middle value in a set of numbers when they are all placed in order from smallest to largest, e.g. **the median of 5,7,9,10,13,18,23 is 10**. In a clinical trial, the median is reached when 50% of patients have experienced an event (such as death or recurrence). The median figure for an endpoint is normally noted with a small 'm' e.g. mPFS (median progression free-survival). It's important to remember that taking a median value for survival may not always provide the most accurate picture of the effects of a treatment. For example, if 51% of patients gain only two months or less survival

benefit from a treatment while 49% gain 10 months or more, the median survival would, in fact, be calculated as less than two months – which is not a true reflection of the benefit. Similarly, if a trial had, for example, 800 patients, the median would be reached once 400 reached the endpoint (e.g. experienced a particular event). But the other 400 may potentially do much better, and the median value would not reflect this.

Another form of average – **the mean** – is often used outside medicine but is rarely used for clinical trials because of the wide variation in the way patients' disease behaves.

Mean is the average calculated by adding a set of numbers (for example, a set of results) and dividing by the number of values. e.g. **the mean of 5,7,9,10,13,18,23 is 12.1**.

Figure 5: Median Value



The curve here is hypothetical and does not represent actual data

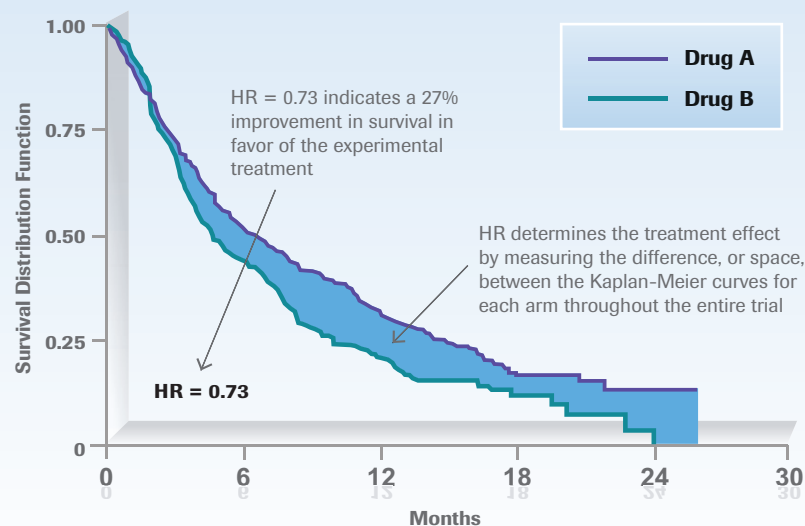
Hazard ratio (HR)

The hazard ratio is the relative risk of the event (e.g. disease progression) happening in one trial arm compared with the other, over the entire time period of the trial.

- A HR of 1 means there is no difference between the groups, a HR of 2 means that there is double the risk and a HR of 0.5 tells that there is half the risk.
- In the example below, a HR for OS of 0.73 indicates there is a 27% reduction in the risk of progression or death in the arm treated with drug A compared with drug B. It is calculated as follows $-1 - 0.73 \text{ (the HR)} \times 100 = 27\% \text{ risk reduction}$.

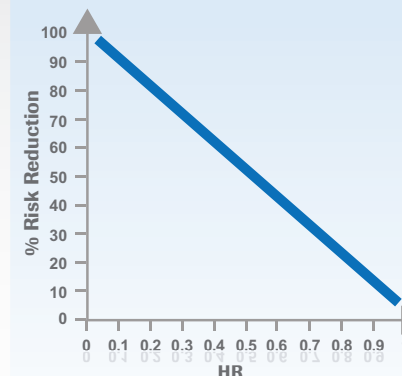
Importantly, and unlike median values, the hazard ratio takes into account the difference in events over the *entire period of the trial*, not at a specific point within it or at the end of the trial, so is a better predictor of the treatment's actual effect on the whole patient population. This methodology has the advantage of using all available information, including patients who don't complete the trial for any reason. A HR is thus most useful when the risk for the endpoint event being described is not constant with respect to time.

Figure 6: Hazard Ratio (HR)



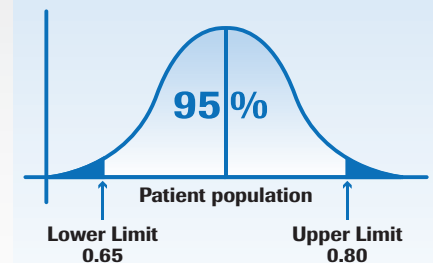
The Hazard Ratio shown here is hypothetical and does not represent actual data

Figure 7: Hazard Ratios & Risk Reduction



The Hazard Ratio shown here is hypothetical and does not represent actual data

Figure 8: Confidence Intervals (CI)



The Confidence Intervals shown here are hypothetical and do not represent actual data

Confidence intervals (CI)

The CI percentage indicates the certainty that a result will fall into a range of results noted by specified lower and upper 'confidence limits' e.g. A HR result with a 95% CI of 0.65 (lower) - 0.80 (upper) means that there is a 95% certainty that under the same study conditions the HR result for the same population will fall between 0.65 and 0.80. How narrow or wide this range is can provide valuable information regarding the precision of the results. A narrow CI implies high precision and a wide CI implies poor precision.

CIs are used as an indication of how a study result would be reflected in the general patient population outside of the investigation.

Absolute risk reduction (ARR) and relative risk reduction (RRR)

ARR is the absolute difference between the number of events (e.g. percentage of patients who have progressed) that occurred in the treatment group and the number of those events in the *control* group. For example, in a study where 10% of patients treated with drug A progressed vs. 15% of patients treated with drug B there is a 5% ARR in disease progression with drug A compared with drug B: **ARR = 15% - 10% = 5%.**

The RRR looks at that same difference between groups of patients given different treatments, but expresses the change in risk as a proportion, rather than an absolute difference. Using the example above the RRR of progression is reduced by 33% with Drug A compared with Drug B: **RRR = (15-10)/15 = 5/15 = 33.3%.**

■ Number needed to treat (NNT)

The NNT is a statistic that tells the actual number of patients who would need to be treated with a given therapy (or combination of therapies) for one patient to get a particular endpoint benefit. The NNT is calculated from clinical study data and is considered a useful measure for deciding if a treatment benefits a large number or just a small number of patients given a drug. The lower the NNT the more effective the treatment.

■ Odds ratio (OR)

A measure of treatment effectiveness, OR is the odds of an event happening in the treatment group expressed as a proportion of the odds of an event happening in the control group. The closer the OR is to one, the smaller the difference in effect between the treatment intervention and the control intervention. If the OR is greater (or less) than one, then the effects of the treatment are more (or less) than those of the control treatment.

6. Common ways of presenting clinical trial results

Importance of assessing changes over time

Statistical methods allow all the data from a study to be analyzed and examined over time to discover if there are statistically significant differences between treatments that simple median measures (a measurement taken at a particular point within the trial) cannot illustrate. With the right statistical tool, an accurate measure of the effect of a treatment can be made that takes into account the varying start times and lengths of time patients have been on treatments.

■ Kaplan-Meier (KM) curve

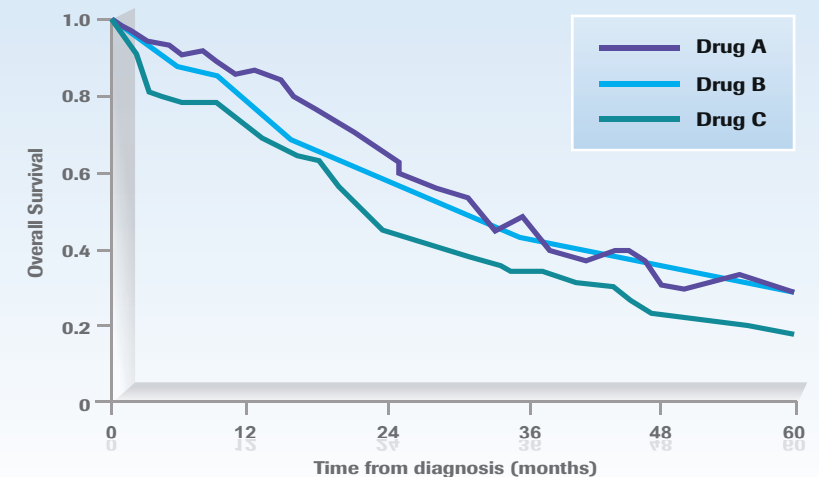
KM curves represent the proportion of the study population still surviving (or free of disease or some other specified outcome or endpoint) at successive times.

This is the most commonly used method for representing overall survival or efficacy. In the

case of KM curves in treatment studies showing overall survival, the curves provide a plot for a certain time period. They compare patients receiving the investigative drug to those in the [control](#) arm, showing the percentage of patients who are still alive at a certain time. It calculates this percentage according to how long a patient has been receiving a treatment, rather than when they entered the study.

The larger the separation of the curves the greater difference between the treatment groups in the endpoint being analyzed. If the treatment arms represented in the KM curve follow a similar path, it suggests that there is only a small amount of difference between the arms of the study in the endpoint being measured. If the arms were to meet, that would mean at that particular time point there was no difference between the two arms of the study in the endpoint being measured.

Figure 9: Kaplan-Meier (KM) curve



KM curve shown here is hypothetical and does not represent actual data

■ Forest plot (FP)

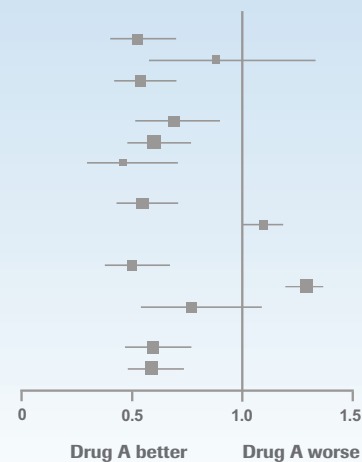
Where there are a number of studies that have looked at a treatment, or subgroups of patients within one study that may respond differently to treatment, a forest plot (FP) is a way to show and compare different groups of data.

The FP is a useful way of seeing at a glance whether the benefit or effect of one type of treatment is uniform across studies or across different subgroups of patients. A data set e.g. subgroup or study is usually shown as a square. The size of the squares is proportional to the size or weight (importance) of that data set, and the horizontal lines either side of each box represent the confidence intervals.

The plot shows visually whether a treatment does or does not provide a positive outcome in a particular group of patients relative to another treatment, using two columns and a dividing vertical line which represents the treatment having no effect. Typically, data that fall on the left of the vertical line shows that the intervention treatment is more effective than the comparator, while data that falls on the right side of the no effect (vertical) line suggests that in that subgroup or study the *comparator* is more effective than the intervention.

In the example below (see fig.9), PFS hazard ratios for different patient subgroups in one study are illustrated. Treatment A is more effective than treatment B in patient subgroups that fall to the left of the vertical line. However the subgroups that are on the right of the vertical line mean that in those patient subgroups treatment B is more effective than treatment A.

Figure 10: Forest Plot

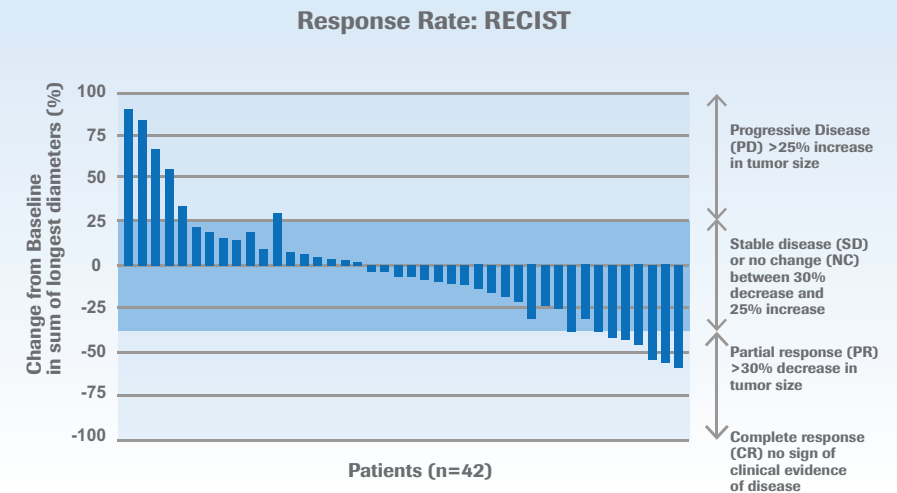


FP shown here is hypothetical and does not represent actual data

■ Waterfall plots

This type of graph reflects each patient individually e.g. looking at response rate status of each patient's tumor(s), whether it be progression, stability or improvement. In cancer studies waterfall plots are often used to illustrate ORR data.

Figure 11: Waterfall Plots



Waterfall plot shown here is hypothetical and does not represent actual data

7. Key questions to ask when evaluating the importance of a clinical trial

What **phase** is the study?

The phase of the study indicates how far along the development path a drug or treatment is. For example, a Phase III study in a large group of patients would only be conducted following encouraging results from earlier investigations, and would usually be used to support license applications.

What is the **primary endpoint**?

The primary endpoint is the most important endpoint of the trial and usually measures treatment efficacy. Understanding the relevance of the endpoint to a cancer type and what it means for patients is important to understanding the significance of any study.

What is the **comparator or control arm** of the study?

Understanding the significance of the comparator arm of the study will help in interpreting the importance of the study. For example, a study comparing an investigative treatment to the standard-of-care, would be more important than comparing the investigative treatment to a therapy not approved in the disease setting or a placebo.

How many **patients** are taking part in the study?

Typically, the more patients taking part in a study, the more significant the results. As the results are gained from a larger number of patients, the impact of certain, unusual, patient responses on overall statistics are reduced and thus the results offer a more accurate reflection of how the treatment will affect the general patient population outside of the investigation.

Is the **p-value** statistically significant?

The p-value helps to demonstrate the likelihood of study results being due to chance, rather than a difference between the treatments being tested. A p-value of less than 0.05 is significant and shows that there was a less than 5% likelihood that the result happened by chance.

8. Glossary of clinical trial terminology

The glossary includes common terms found in cancer clinical trial publications, including clinical papers in journals, congress reports of new data and press releases announcing trial findings.

Understanding these terms, particularly those referring to the trial design, can help with interpreting the clinical trial results and their relevance to people with cancer.

Adjuvant

A treatment given in addition to the main form of treatment (e.g. chemotherapy given in addition to surgery) that aims to delay or prevent recurring disease by destroying possible remaining cancer cells.

Biological marker

A characteristic, such as the presence of a specific protein, by which a disease or biological state can be recognized.

Blind and double-blind

In a blind clinical trial, the patient is not told whether they are receiving the active drug or another treatment/placebo. When neither the patient nor the investigators know to which group they have been assigned the study is double-blind. The blinding of trials is performed to try to avoid bias.

Comparator/control group

The 'arm' (or patient group) of a randomized trial in which patients are given the control treatment (i.e. placebo or the current accepted standard-of-care treatment). Responses of patients in the treatment arm (the group of patients given the new drug/drug under study) will be compared with the responses seen in the control group in order to measure treatment efficacy.

Endpoints/outcomes

Endpoints, set and defined in advance of the clinical trial, describe and define the goal(s) of the study. Examples of endpoints (which vary depending on the type and phase of trial) include overall survival, toxicity, tumor response, patient survival or quality of life.

First-line/second-line

The 'line' of treatment describes the order in which it is tried as a therapy for cancer. A first-line treatment is the initial treatment used to target tumors. Second-line treatment is given when first-line therapy doesn't work or stops working.

Institutional Review Board (IRB)

The panel responsible for reviewing clinical trials to ensure they meet ethical standards and that the patients taking part in them are properly protected.

Open-label

A descriptive term for a clinical study in which both health care providers and patients are aware of what treatment has been assigned, i.e. the study is not blinded.

Pivotal study

The clinical study forming the basis of the application to the regulatory authorities for approval of the drug. Usually a phase III, randomized, double-blind controlled trial of good size.

Placebo-controlled

A descriptive term for a clinical study in which one group of patients receives an inactive substance, or placebo, while the drug being evaluated is given to another group: designed to compare efficacy of the drug with 'no' treatment. Placebo-controlled trials are rarely used for cancer treatments, where a new treatment is more likely to be compared with the existing standard-of-care treatment.

Randomised

A descriptive term for a clinical study in which patients are randomly assigned to one of two or more treatment arms of the study.

Real-world setting

Studies performed in a 'real-world' setting gather data on cancer, and the effect of different cancer treatments, from groups (cohorts) of patients that are visiting and being treated by their own doctor or hospital (as compared with clinical trials where patients are specifically recruited to take part in a study with a highly prescribed set of rules).

Regulatory authorities

Regulatory authorities review and evaluate clinical study data and are responsible for ensuring new medications are safe and effective for their intended use before they are approved for use by patients. If a submission is successful the regulatory authorities will grant marketing authorization (permission to sell the drug). Examples of regulatory authorities include The Food and Drug Administration (FDA) in the U.S. and the European Medicines Agency (EMA) in Europe.

Stratification

Stratification is a way of grouping subsets of patients and is used in randomised trials when factors that can influence the intervention's

success are known. For example, participants whose cancer has spread from the original tumor site can be separated, or stratified, from those whose cancer has not spread, since it might be expected that these patients have more advanced and less advanced disease respectively and could respond differently to treatment interventions.

References

- BMJ Clinical Evidence – glossary. Accessed November 2012. Available at: <http://clinicalevidence.bmj.com/ceweb/resources/glossary.jsp>
- Harris M, Taylor G. Medical Statistics Made Easy Scion Publishing 2006 Ltd ISBN: 9781904842552
- Greenhalgh T. How to read a paper: Getting your bearings (deciding what the paper is about). BMJ 1997;315:243–6
- European Federation of Pharmaceutical Industries and Associations (EFPIA). A Highly Regulated Industry. Accessed November 2012. Available at: <http://62.102.106.100/Content/Default.asp?PageID=361>
- Response Evaluation Criteria In Solid Tumors (RECIST). RECIST. Accessed November 2012. Available at: <http://www.recist.com/index.html>
- The Eastern Cooperative Oncology Group (ECOG). Introduction to ECOG. Accessed November 2012. Available at: <http://www.ecog.org/general/intro.html>

F. Hoffmann-La Roche Ltd
GPS Public Affairs
4070, Basel, Switzerland

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