Drug Development and Clinical Trials

Translational Medicine

Chapter 4 – Medicine for MRCP

Oxford University Press

Background

Throughout history, medical discoveries have changed society and the way we live our lives. Patients suffering from currently incurable conditions hope that one day medical advances will enable them to have a healthy, symptom free, life. Beyond each individual patient's needs, new therapies can benefit the whole society by reducing the cost of healthcare and the negative impact of reduced productivity.

The pharmaceutical companies share the same goal of developing new medicines that can prevent diseases, improve patients' health, and save lives. When used appropriately, medicines can halt or slow disease progression, limit complications, improve quality of life, prevent hospitalizations and invasive therapies, and avert debilitating diseases.

Citizens in an ageing population are at greater risk of cognitive impairment, frailty and social exclusion, with considerable negative consequences for their quality of life and the sustainability of health and care systems. Any negative consequences of changing environment and demographics in the modern era could be reduced by earlier detection of risks associated with ageing, combined with the understanding of complex factors contributing to health preservation and the delivery of timely and targeted treatments.

Molecular biology

Progress made in molecular biology research enables a better understanding of disease pathogenesis and facilitates the discovery of new effective therapies targeting disease-specific abnormalities. Modern molecular biology started with the discovery of the double helix structure of DNA and its significance for information transfer in living material.

The following molecular biology technologies are used for more rapid generation of information and more efficient identification of therapeutic targets:

- **polymerase chain reaction (PCR)** - a molecular biology technology enabling the amplification of a single copy or a few copies of a fragment of DNA and generation of thousands to millions of copies of a particular DNA sequence
- **difference analysis** - a method which analyses the different gene expression patterns between different cells
- **transgenic/gene knockout technology** - a method which disrupts an existing gene's expression before birth or in an early embryo to induce a stable gene expression in an organism
- **gene therapy** - a method which enables gene delivery to cells and tissues for therapeutic purposes

Understanding of pathophysiology

There is a need to address the current knowledge gaps in understanding causes and mechanisms of disease in order to support innovation in the development of evidence-based treatments. In this context, a better understanding of the mechanisms that are common to several diseases, in particular of those leading to co-morbidities, constitutes an important challenge.

The understanding of pathophysiology has important therapeutic implications when designing new therapies:

- effective treatments often require combination therapy to correct multiple pathophysiological defects and/or the development of tachyphylaxis/resistance
- treatments should be based upon correction of established pathogenic abnormalities
- therapies should aim to prevent or alleviate symptoms and disabilities with objective improvement in quality of life
- therapy must be initiated early in the natural history of disease to prevent irreversible organ failure
- benefits must outweigh any unwanted acute, chronic or delayed unwanted effects

Pharmacogenomics

Pharmacogenomics uses information about a person's genetic makeup, or genome, to choose the drugs and drug doses that are likely to work best for that particular person. Much research is currently directed into understanding how genomic information can be used to develop more personalised and cost-effective strategies for using drugs to improve human health.

There are numerous examples of the use of pharmacogenomics in current practice, such as:

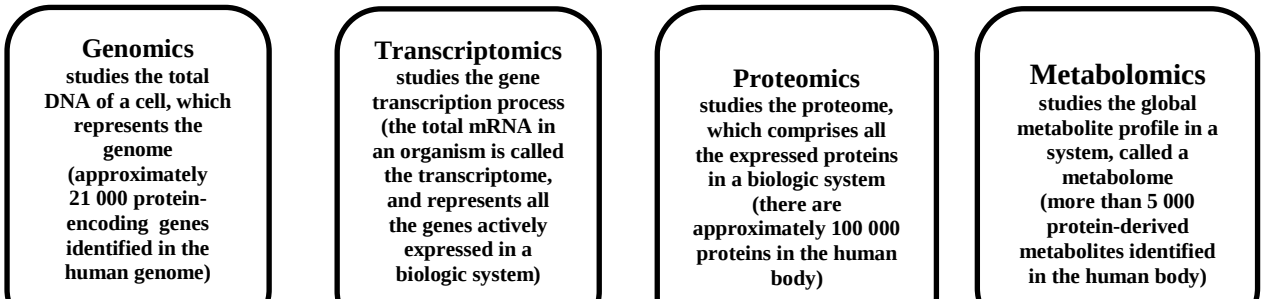
- selection of patients with breast cancer based on their particular genetic profile as it is recognised that patients with overproduction of a protein called HER2 (human epidermal growth factor 2) are responsive to trastuzumab
- genetic testing before starting treatment with mercaptopurine in patients with acute lymphoblastic leukemia and inflammatory bowel disease to exclude those with a genetic variant affecting the enzyme thiopurine S-methyltransferase that results in altered metabolism of the drug and can lead to severe myelosuppression
- identification of genetic variations that influence the response of depressed people to citalopram, which belongs to a widely used class of antidepressant drugs called selective serotonin re-uptake inhibitors (SSRIs)
- using a patient's CYP2C9 (an important cytochrome P450 enzyme with a major role in the oxidation of both xenobiotic and endogenous compounds) and VKORC1 (Vitamin K epoxide reductase complex subunit 1) genotype to determine the initial warfarin dose

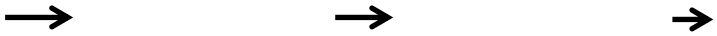
Genome research can help decide the way in which both existing drugs are used and new drugs are developed. Instead of developing drugs with broad action against a disease, researchers are now using genomic information to identify targets and design drugs aimed at subgroups of patients with specific genetic profiles. In addition, researchers are using pharmacogenomic tools to search for drugs that target specific molecular and cellular pathways involved in disease.

Other "omics" (transcriptomics, proteomics, metabolomics), epigenetics and informatics

'Omic' technologies are aimed at the universal detection of genes (genomics), mRNA (transcriptomics), proteins (proteomics) and metabolites (metabolomics) in a specific biological sample, providing a comprehensive way of analysing complex systems (Figure 1). A major challenge of the modern era is to apply usefully the information generated by 'omics' for the development of personalised and stratified approaches in health promotion, disease prevention and treatment. The integration of these technologies is called 'systems biology'.

Figure 1: The interaction of 'omics' sciences enables the study of a disease as an "integrated system" by identifying pathological abnormalities associated with different molecular and cellular processes.





Transcriptomics is the study of mRNA within a cell or organism, and reflects the genes that are actively expressed at a given moment in time (the transcriptome). The transcriptome is measured by gene expression microarrays, which identify the packaged mRNA (mRNA with the introns spliced out) as a summary of gene activity.

Proteomics defines the study of protein biochemistry on a genome-wide scale, including information on protein concentration, variation and modification, along with interacting partners and networks, in order to understand cellular processes. The complex understanding of the molecular basis associated with disease onset and progression has the potential to facilitate the discovery of effective treatments based on the identification of biomarkers.

There are a few general principles governing the synthesis and function of proteins in a living cell, which are studied by transcriptomics and proteomics:

- **One gene can encode more than one protein**
  - There are about 21,000 protein-encoding genes identified in human genome studies and the total number of proteins in human cells is estimated to be between 250,000 and one million.
- **Proteins are dynamic**
  - Proteins undergo continuous changes, such as cell membrane binding, coupling with other proteins to form complexes, or undergoing synthesis and degradation.
- **Proteins are co- and post-translationally modified**
  - This results in considerable variability between the types of proteins measured under different environmental conditions, or even within the same person at different ages or states of health.
- **Proteins have a wide range of concentrations in the body**
  - This makes identification of low abundance proteins in a complex biological matrix such as blood difficult.

Metabolomics is defined as the study of global metabolite profile in a biologic system (cell, tissue or organism) under a given set of conditions. The metabolome comprises the final downstream product of gene transcription, being at the same time the closest to the phenotype of the biological system studied, therefore having major implications in the study of disease pathogenesis and drug development.

Epigenetics is the study of dynamic alterations in the cellular transcription potential of a cell, generating cellular and physiological trait variations that are not caused by changes in the DNA sequence. Unlike genetics, which describes changes to the DNA sequence (the genotype), epigenetics studies the changes in gene expression or cellular phenotype caused by environmental stimuli. Examples of mechanisms that produce such changes are DNA methylation, histone modification and RNA-associated silencing, each of which alters how genes are expressed without altering the underlying DNA sequence.

Epigenetic changes may last through cell divisions for the duration of the cell's life, and may also last for multiple generations even though they do not involve changes in the underlying DNA sequence of the organism. While epigenetic changes are required for normal development and health, they can also be responsible for some disease states. Disrupting any of the systems that contribute to epigenetic alterations can cause abnormal activation or silencing of genes. Such disruptions have been associated with cancer, syndromes involving chromosomal instabilities, and mental retardation.

Informatics is defined as the science of computer information systems. This includes the study of the structure, algorithms, behaviour and interactions of natural and artificial systems which store, process, access and communicate information. The process of drug discovery involves the processing of a large amount of information, which is generated by innovative technologies. The role of informatics is to generate information from the large amount of data collected through clinical research and to generate knowledge through the processing of this information.

Health informatics, particularly with advances in technology, also has the potential to facilitate patient-centred care by enabling patients to share critical information with their physician, family, friends and other patients, and exert a greater control over their own care. Clinicians may also use information systems, such as electronic medical records, to coordinate care and share information with other clinicians, contributing in this way to the dissemination of medical knowledge. It is essential that any use of such data complies with the Data Protection Act (1998).

Process of developing a new medicine

The practical goal of biomedical research is to develop new medicines, which ultimately will lead to public health improvement. Translational research programmes aim at creating a link between basic science and clinical benefit, emphasizing the need to redefine the interface between pre-clinical and clinical research for identifying ways of translating basic biomedical discoveries into practical applications. Translational medicine ultimately aims to discover diagnostic and therapeutic solutions for the benefit of public health. Translational medicine (also named “discovery medicine” or “experimental medicine”) brings together pharmaceutical research and clinical pharmacology, when applied to drug discovery. The process of developing a new medicine comprises a primary translation from target discovery to clinical evaluation, followed by a secondary translation from market authorisation to real-life patient care, both with potential major impact on the optimal utilisation of research resources and patient care provision.

The main purposes of translational medicine are:

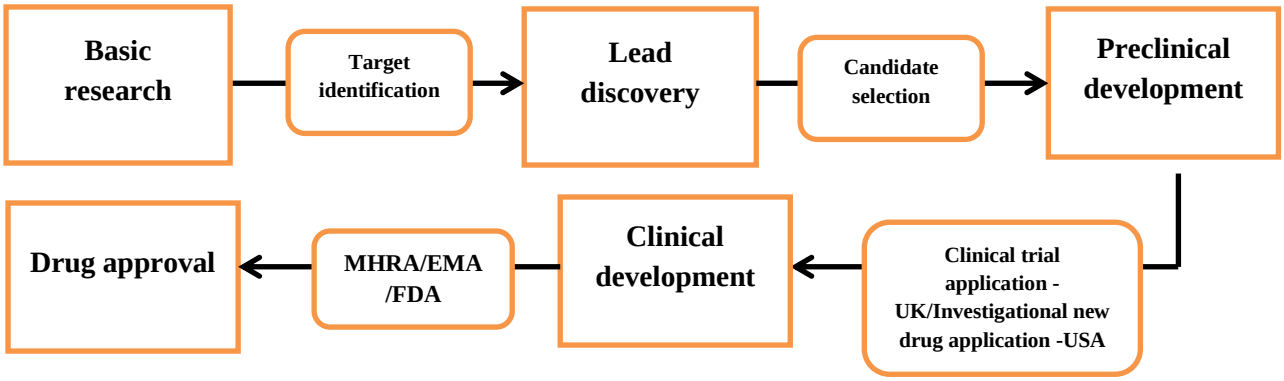
- To investigate and validate therapeutic targets in humans
- To investigate and validate biomarkers (characteristics that are objectively measured and evaluated as indicators of normal biological processes, pathogenic processes, or pharmacologic responses to therapeutic intervention)
- To evaluate the safety and efficacy of identified targets in humans using biomarkers
- To use the intact living human as the ultimate screening test system for the proposed therapeutic targets

Target identification/screening

The large and vast datasets generated through ‘omics’ technology revealed aspects of biological function that were not available to the traditional methods of biomedical research, easing the process of identification of potential targets. This approach was named ‘discovery-based research’ as large portions of genomes or proteomes may be examined for the purpose of identifying biomarkers with diagnostic and prognostic utility.

The process of drug discovery is usually triggered by an unmet clinical need and initiated by preliminary research, often performed in academia, generating hypotheses linked to the inhibition or activation of a protein or pathway, which can result in therapeutic benefit. Following the hypothesis generation and multiple testing, a potentially suitable target is selected, which will require further validation prior to being developed into the lead discovery phase if the selection justifies a drug discovery effort. During this process of lead discovery, the research is directed at identifying a drug-like small molecule or biological therapeutic, usually defined as a ‘development candidate’, which will hopefully progress into preclinical and further into clinical development, if successful in being proven safe and effective for a particular clinical application (Figure 2).

Figure 2: The phases of drug development



Target identification and validation are the most important steps in developing new medicines. A target is a generic term, which can refer to a broad range of biological entities, such as proteins, genes and RNA. A suitable target needs to be accessible to the drug molecule. Upon binding, a biological effect should be produced, both *in vitro* and *in vivo*. The reasons for failing to develop a drug from a suitable target include inadequate desired therapeutic effect and poor safety. Good target identification and validation is supported by suitable research data proving a functional link between target and disease, which usually proves that the modulation of the specific target is associated with mechanism-based effects.

Small molecules & biologics

Traditionally, drugs were small, chemically manufactured, active-substance molecules that were easily absorbed into the blood stream that exerted their effect by reaching virtually any desired destination within the body; often being able to penetrate cell membranes due to their small molecular weight and lipophilicity. Current advances in biotechnology have enabled the discovery of new therapeutic drugs, called biologics, which include protein-based drugs (monoclonal antibodies, therapeutic protein hormones, cytokines and growth factors), vaccines and cell or gene therapies. In comparison to small molecules, most biologics are large protein-based molecules, which can be optimised versions of human proteins obtained by genetic engineering. Over 200 monoclonal antibodies are now either licensed or are in clinical trials. Monoclonal antibodies bind to designated cell receptors or molecules, which are associated with the disease process. Antibody-drug conjugates act as carrier molecules for toxic substances enabling their delivery to their exact site of action, which improves efficacy and minimises toxicity. Therapeutic vaccines act by stimulating the immune system to target specific antigens associated with the disease. Cytokines are used for enhancing the immune response to cancer or for anti-inflammatory properties in chronic inflammatory conditions.

Advanced therapies

Unlike small molecules and biologics, advanced therapies are not made from chemicals or proteins but are classified into 4 groups, according to their mechanism of action:

- **Gene-therapy medicines:**
  - use recombinant genes created in the laboratory by combining DNA from different sources
  - scope of treating a variety of diseases, including genetic disorders, cancer or chronic diseases (e.g. Glybera ® has been approved to treat lipoprotein lipase deficiency, a genetic disorder that causes pancreatitis but the cost per treatment may be $1 million)
- **Somatic-cell therapy medicines:**

    - contain cells or tissues which are manipulated genetically to change biological characteristics so that they can be used for a different function than the original cells or tissues
    - can be used to cure, diagnose or prevent diseases (e.g. living, autologous, melanoma-derived lymphocytes (CD3+) for treatment of metastatic melanoma in patients pre-conditioned with chemotherapy and undergoing concomitant interleukin-2 therapy)
- **Tissue-engineered medicines:**
    - contain cells or tissues that have been modified to enhance their ability to repair or regenerate human tissue (e.g. allogenic cord blood cells modulated with 16,16 dimethyl prostaglandin E2 intended for the treatment of patients undergoing haematopoietic stem cell transplantation)
- **Combined advanced-therapy medicines:**
    - contain one or more medical devices, which are an integral part of the medicine (e.g. cells embedded in a biodegradable matrix)

Preclinical & clinical phases of drug development

Once a lead small molecule drug candidate is confirmed, which may be based on preliminary chemistry, pharmacology, toxicology, basic pharmacokinetics, bio-availability and in vivo model studies, and following detailed pre-clinical characterisation including stability testing, purity analysis and assay development, the new medicine is subjected to the formalised pre-clinical phases of drug development required before an investigational medicinal product can be administered to humans. These are highly regulated, and in most countries follow ICH (International Conference on Harmonisation) guidelines, which facilitate both the preclinical and clinical development of new medicines:

1. 14-28 day repeat dose toxicity studies in two species
2. Pharmacokinetics and toxicokinetics
3. Genotoxicity (to assess the likelihood of a drug to be mutagenic or carcinogenic)
4. Drug metabolism
5. Immunotoxicity
6. Reproductive toxicity
7. Juvenile toxicity
8. Carcinogenicity

The timing of some of the studies (5-8) in relation to first administration to human may vary depending on the nature of the molecule and the target population. Longer duration studies in animals primarily to determine toxicity associated with chronic dosing are usually conducted after the initial human studies.

The preclinical development of biologics, although following similar basic principles, is adapted to take into account that toxicity is more likely to be related to exaggerated pharmacology and “downstream” effects rather than “off target” effects (as a result of modulation of other targets related or unrelated biologically), that interspecies variation is much more likely and that the target may not be expressed in any species other than humans. The insertion of part or all of a human gene or gene sequence to create “humanised” mouse models can assist the *in vivo* assessment of biologics.

Following the regulatory approval of the investigational new drug/clinical trial application, the new medicine enters the phases of clinical development. Based on the clinical research objectives, the clinical studies are grouped into 3 phases before application for a product license to market the medicine. All protocols involving clinical trials of investigational medicinal products (CTIMPs) require regulatory and Research Ethics’ Committee approval in the UK.

Phase I clinical trials (Human Pharmacology):

Phase I clinical trials evaluate the tolerability, pharmacokinetics and, when possible, the pharmacodynamics of the investigational medicinal product (IMP). Phase I studies are commonly run in healthy volunteers. The trials are usually double-blind and placebo controlled. They include the administration of initial single ascending doses and short-term repeated-doses, in order to determine a practical dose range for Phase II studies and identify some potential side effects of the new medicine.

Increasingly, pharmacodynamic biomarkers, and in some indications, patients are included in Phase I to provide evidence of "proof of mechanism" or "proof of concept"; however these studies are not expected to produce direct therapeutic benefit to the participants.

Phase II clinical trials (Therapeutic Exploratory):

Phase II clinical trials are usually small-scale exploratory trials, including approximately 100 – 300 patients (but numbers can vary considerably), aiming to evaluate the drug's preliminary efficacy and safety profile in the target population. Additional clinical pharmacology studies in patients may be included in this category. Usually in a phase II trial, a new treatment is compared with another treatment already in use (considered standard of care), or with placebo (if ethical) in a randomised, and if possible, double blind design. If the results of phase II trials show that a new treatment may be as effective as existing treatments, or better, it then moves into phase III. One important objective of Phase II is to determine the appropriate dose or doses to be investigated in the "confirmatory" Phase III studies which involve larger numbers of patients, longer duration and increased expense.

Phase III clinical trials (Therapeutic Confirmatory):

Phase III clinical trials look at the safety and efficacy of a medication in larger patient populations (often hundreds or even thousands of patients) at many sites in different countries. These trials usually compare the new treatment with the standard treatment and help determine the overall benefit: risk of the new treatment. Most phase III trials are double blind and randomised.

Phase IV clinical trials:

Phase IV trials are undertaken after a drug has been shown to be effective with an acceptable safety profile and has been granted a license for use as a treatment for a certain indication(s). They may include different formulations, doses, durations of treatment and drug interactions. Their scope is to provide additional information about the tolerability and safety of the drug in wider, more varied populations, as well as the long-term risks and benefits.

Regulatory & ethics requirements

The process of developing new drugs is highly regulated to ensure the protection of public health. Pre-clinical studies of new treatments that are submitted to the regulatory authorities have to be conducted to the high standards of Good Laboratory Practice. The key principle of toxicology is to identify the potential side-effects of a given compound and assess the likelihood of humans to experience such hazards under the given circumstances of a clinical trial or therapeutic use. The following steps are usually taken to assess the potential risk of an investigational drug in the pre-clinical phase of development:

- Identification of principal side-effects in two animal species (one rodent, one non-rodent)
- Mechanistic and quantitative evaluation of the risk of such adverse events to occur in humans
- Assessment of uncertainty factors
- Balanced assessment of the risk against the expected therapeutic benefit.
- Removing the compound from the clinical development programme or redefining its conditions of use as necessary

Regulatory toxicity testing, employed to ensure an independent evaluation of medicinal products, includes 3 different phases according to the stages of drug development:

1. **Pre-clinical testing:** in vitro and in vivo studies - to screen for potential side-effects before the new medicine is tested for the first time in humans.
2. **Testing during phases 1 and 2 of drug development:** collection of toxicity data and information about effects on fertility and embryo-foetal development following medium and long term administration of the new treatment in animal models prior to clinical trials.
3. **Testing during phase 3 of drug development:** carcinogenicity and reproductive toxicity (peri- and postnatal development) studies to enable the registration of the drug intended for human use.

The pre-clinical animal and in vitro studies aim at identifying, predicting and quantifying risks for healthy volunteers and patients. The toxicology requirements needed for new drug approval are regulated by different agencies, as detailed below, in '**Regulatory and ethical approval**'.

Post-marketing pharmacovigilance

The need

Medicines and medical devices become available to the general population once they are approved for use, leaving the protected scientific environment of clinical trials. In the majority of cases, new drugs will only have been tested for a short period of time on small and carefully selected populations before being licensed for a specific medical indication. Once released, it is crucial that new treatments and medical devices are monitored for their effectiveness and safety under real-life conditions. Continuous and rigorous monitoring is essential long after release, since it is recognised that many drug interactions and side-effects became apparent many years later.

The post-marketing surveillance gives the possibility to study:

- low frequency reactions (not always identified in clinical trials)
- high risk population groups (usually not included in clinical trials)
- long-term effects
- drug-drug/food interactions
- increased severity or frequency of known adverse events (previously reported by clinical trials)

Pharmacovigilance is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or other problems related to the use of drugs. Pharmacovigilance programmes are designed to:

- improve patient care and safety in relation to the use of medicines, and other medical and non-medical interventions
- improve public health and safety in relation to the use of medicines
- contribute to the assessment of benefit, harm, effectiveness and risk of medicines (encouraging their safe, rational and effective use)
- promote education and clinical training in pharmacovigilance

Safety monitoring of medicines in common use should be an integral part of clinical practice and has a huge impact on the quality of health care. In the European Union the holder of an authorisation for a medicinal product (usually a pharmaceutical company) must have an appointed qualified person for pharmacovigilance (QPPV) who not only ensures a robust system for pharmacovigilance is established and maintained but also must provide reports as requested by Health Authorities and act as a single contact point for Health Authorities on a 24 hour basis. However responsibility for pharmacovigilance should not be restricted solely to health professionals, but should be redefined to address the changing patterns in drug use in modern society, where non-prescription medicines are widely available. The key partners in monitoring the safety of medicines are the following:

- Government and industry
- Hospitals and academia
- Medical and pharmaceutical associations
- Poisons and medicines centres information
- Health professionals
- Patients
- Consumers
- The media

- World Health Organization (WHO)

Indeed, the WHO has a Programme for International Drug Monitoring. National governments are responsible for the provision of good quality, safe and effective medicines and their appropriate use. The role of the national medicine regulatory agency is to ensure a multidisciplinary collaboration between the aforementioned partners responsible for education on rational use of medicines and pharmacotherapy monitoring. However, expert-only satisfaction with the level of safety of a given medicine or medical device is not sufficient; public perception of the risk associated with its use is equally important. Health-care providers, the pharmaceutical industry and governments have a duty to build public trust and accurately and effectively communicate available data regarding the level of safety associated with the use of medicines.

Adverse event reporting

Adverse effects to drugs are usually reported in the context of clinical trials or during the post-marketing surveillance period, following the licensing and release on to the market of a medicine or medical product. An adverse event (AE) is defined as "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment". In clinical trials, a clear distinction is made between adverse events and serious adverse events (SAE). By definition, any event which causes death, permanent damage, birth defects or requires hospitalisation is considered an SAE. It is crucial that unexpected health problems caused by an investigational new drug used in a clinical trial are identified as soon as possible. Mechanisms are in place to ensure adverse events are reported and participant risk is minimised during a clinical trial:

1. Each site investigator is required by law to notify the study sponsor if one of the study participants at their site has an SAE.

   If the reported SAE is considered unexpected (i.e. not previously associated with the investigational new drug or reported in the investigator brochure) and has a possible causal association with the investigational drug, it is reported as a SUSAR (suspected unexpected serious adverse reaction). Once aware of the event, the sponsor must notify the SUSAR to the Medicines and Healthcare products Regulatory Agency (MHRA) and all other investigators involved in the clinical trial:

   - as soon as possible and within seven days in the event of a SUSAR which is fatal or life threatening
   - within 15 days if neither fatal nor life-threatening.

   Reports of related and unexpected serious adverse events should be submitted to the Research Ethics' Committee (REC) within 15 days of the chief investigator becoming aware of the event. Reports of related and unexpected SAEs in double-blind trials should be unblinded.
2. In order to ensure that investigators uphold their obligations of care for study participants (and notify their institutional review board of unanticipated side-effects), they should be continuously informed about the developing risk profile of the investigated drug.
3. Annual Development Update Safety Reports (DSURs) which concisely describe all new safety information must be submitted to the MHRA and the REC.

Furthermore, the results of clinical trials (including reported AEs) are often included in the labeling of the medication to provide information both for patients and the prescribing physicians. The AEs, especially when previously unknown, should also be analysed and their significance should be communicated effectively to an audience that has the knowledge to interpret the information, ensuring that the right decision about the further use of the medicine is taken.

Virtually anyone can report drug related AEs to appropriate regulatory bodies using different reporting schemes, as detailed below. There are a few factors affecting the voluntary reporting of AEs outside the clinical trials environment:

- Media attention
- Litigation (class action lawsuits)
- Nature of the adverse event (the more severe ones are usually reported)
- Type of drug product and indication
- Length of time on market
- Extent and quality of manufacturer's surveillance system
- Prescription or "over the counter" product status
- Reporting regulations

Yellow card & other systems

The Yellow Card Scheme is a UK initiative run by the MHRA and the Commission on Human Medicines (CHM) aiming to gather information on AEs to medicines. This includes all licensed medicines, from medicines prescribed by physicians to medicines bought over the counter. The scheme also includes vaccines, blood factors and immunoglobulins, herbal medicines and homeopathic remedies, unlicensed medicines found in cosmetic treatments, and all medical devices available on the UK market. The scheme gives health care professionals including physicians, pharmacists and nurses, as well as patients, the possibility to report side-effects associated with the use of these products.

The Yellow Card Scheme is pivotal in monitoring the safety of all healthcare products in the UK, and ensuring the proper regulation of their use. The scheme collects information on suspected problems or incidents involving:

1. side effects (also known as adverse drug reactions or ADRs)
2. medical device adverse incidents
3. defective medicines (those that are not of an acceptable quality)
4. counterfeit or fake medicines or medical devices

It is important for people to report problems experienced with medicines or medical devices in order to determine previously unidentified issues. The MHRA will review the product if necessary, and take action to minimise risk and maximise benefit to the patients. The MHRA will also investigate counterfeit or fake medicines or devices, and take appropriate action to protect public health. The Yellow Card scheme plays a central role in public health protection in the UK.

The Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) in the USA is the equivalent of the Yellow Card Scheme in the UK. This is a computerised database including spontaneous reports of side-effects to medicines. There are 2 major sources of reporting:

1. Voluntary reports of patients, consumers and health professionals via the FDA MedWatch website - 5% of FAERS database
2. Manufacturer reports via the FDA (regulatory requirement) - 95% of FAERS database

Irrespective of the reporting systems used, the advantages of reporting systems include that they:

1. include all marketed medical products
2. include broad patient populations: elderly, children, pregnant women, populations with co-morbidities
3. capture events with a rare background rate
4. are useful for AEs that occur shortly after exposure
5. detect events not seen in clinical trials ("safety signals")
6. identify trends, possible risk factors, populations at risk and other clinically significant emerging safety concerns

The process of reporting AEs, irrespective of the system used, is central to expand the knowledge regarding the safety of medicines and medical products, and to ensure that the risk associated with their use is appropriately anticipated and managed.

Clinical trials

Clinical trials are a key research activity and aim to provide advances in medical knowledge to improve the quality of health care. This is achieved by comparing the value and effectiveness of various intervention(s) against a control in human beings. Typical interventions include, but are not restricted to, drugs, cells and other biological products, surgical and radiological procedures, devices, psychological interventions, changes in the process of care and preventative care.

Randomised Controlled Clinical Trials (RCTs) are considered “the gold standard” against which all other clinical research activities are measured. As physicians, we aim to base our decisions and actions on the best possible evidence to improve patient outcomes and minimise the risk of harm. Without such evidence, there is a risk that people could be given treatments that have no benefit, waste health system resources, and might even be harmful.

The ability to appraise critically medical information for validity and utility, whilst incorporating the growing body of evidence into one’s clinical practice has been termed “evidence-based medicine”. Clinical trials, if properly designed and conducted, provide the best available data for healthcare decision making.

Design

A good clinical trial design is one that is feasible, ethical and able to answer a research question with relevant clinical, public health and/or other scientific value. An ideal clinical trial is one that is prospective, randomised, controlled and double blinded. RCTs are comparative studies with an intervention group and a control group; the assignment of the subject to a group is determined by the process of randomisation (see below). In some clinical trials, deviation from this standard is unavoidable; however major potential drawbacks can be prevented by adhering to the fundamental rules of design, conduct and analysis (as imposed by appropriately reviewed and approved clinical trial protocols). Poor study design might expose participants to the risk of intervention or withholding of a beneficial intervention and/or might also affect the quality of data generated by the study.

Control

Control is a research strategy with two groups of subjects (samples): an experimental group of patients receiving the study intervention, and a second group of control patients receiving a placebo (a substance with no pharmacological effect). Often a new intervention is added to usual care or standard care, and compared against that care plus placebo. The clinical trial should not cause any harm by preventing the placebo group to be treated, if suitable therapies are available.

Blinding

Blinding refers to the concealment of group allocation from one or more individuals involved in a clinical trial. The optimal strategy to minimize the likelihood of a subject involved in a clinical trial receiving preferential treatment or influence the way he/she is assessed is to blind as many individuals as possible in a trial. If neither the patient nor the researcher knows who is receiving the study intervention or placebo, the process is called double-blinding. If participants are not blinded, knowledge of group assignment may affect their behaviour during the trial, and their responses to subjective outcome measures. Blinded clinicians, however, are much less likely to transfer influence to the participants or to provide differential treatment to the active and placebo groups. Since bias may also be introduced during the statistical analysis of the trial through the selective use and reporting of statistical tests, data managers and statisticians should also be blinded. It is not unusual to have a non-blinded clinician on a safety monitoring committee to ensure that if the risk:benefit ratio is clearly in favour of one treatment over another even before the trial is completed as planned, the study can be halted.

Inclusion/exclusion criteria

Inclusion criteria are defined as attributes of subjects that are essential for selection to participate in a clinical trial. Inclusion criteria are meant to reduce the influence of specific confounding variables and

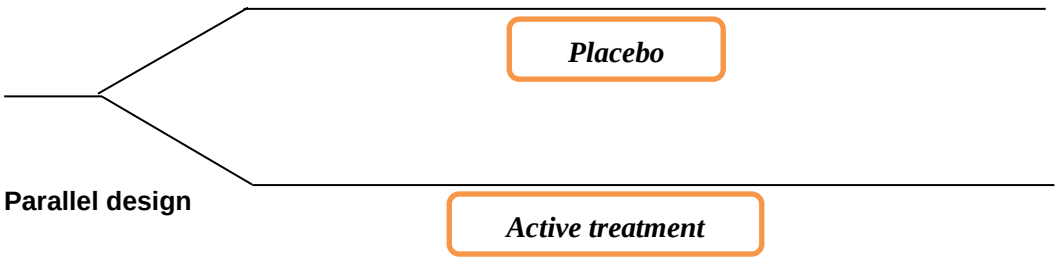
ensure a homogenous study population. Exclusion criteria are a set of predefined definitions used to identify subjects who will not be included, or who will have to withdraw from a research study after being included. Together with inclusion criteria, exclusion criteria represent the eligibility criteria that assess the suitability of potential participants to take part in a research study. Similar to inclusion criteria, exclusion criteria are established according to the scientific objective of the study, and have important implications for the scientific rigour and ethical principles of a study. Commonly used exclusion criteria seek to exclude subjects unable to comply with follow-up visits, those who are not able to provide biological specimens and data, and those whose safety and ethical protection cannot be assured if involved in the study.

Randomisation

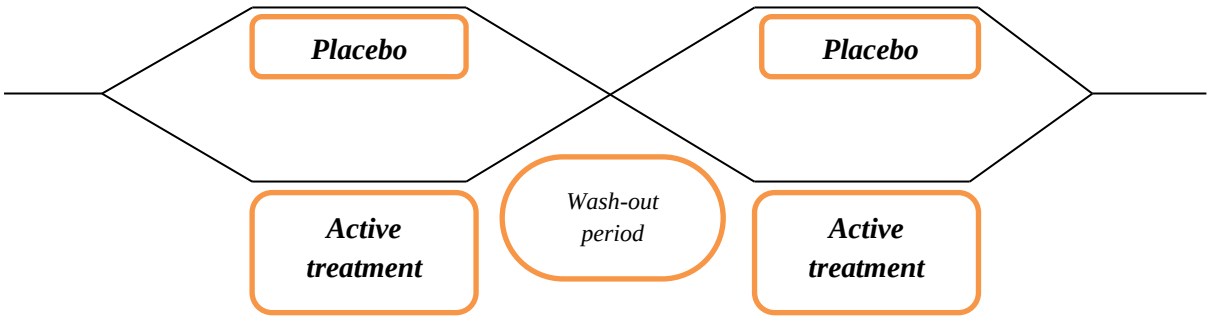
Randomisation is a process ensuring the baseline characteristics of participants are equally likely to be assigned to either the treatment/intervention group or the control/placebo group in a clinical trial, according to a random mechanism (i.e. a process analogous to the flipping of a coin). Random allocation is the most ethical approach because it is unreasonable to expect that an individual investigator has no preference in allocating a certain treatment to an individual.

Parallel and cross-over trial design

A parallel designed clinical trial compares the results of a treatment on two separate groups of patients. A cross-over design allows each participant to serve as his own control, as every participant will receive either intervention or control in the first period of the study and the alternative in the succeeding period.



Parallel design



Cross-over design

Figure 3: Parallel and cross-over trial design

The above diagrams are in reverse order to the text and Title of Figure 3. Could *Parallel design* be placed above the *Cross-over design* in Figure 3?

The duration of a parallel-group trial may be shorter because only one treatment period is involved; however this may be offset by the much larger number of patients needed to be recruited and the time involved in so doing. Parallel-group trials almost always require a multicentre design to enable appropriate recruitment, with the inevitable logistic problems involved in coordinating research activities in several centres and/or countries.

The cross-over design requires a much smaller number of patients for a similar statistical power because patients act as their own controls; a particular advantage when the type or severity of a medical condition varies widely in the patients recruited. As a result, the financial cost of the trial is smaller, and fewer patients are exposed to the study intervention. On the other hand, there is a theoretical risk that the beneficial effects given in the first treatment period might carry over into the second treatment period, and thereby confound the detection of treatment effects. In addition the time of an individual's participation in a crossover study is longer. This is not practical in some indications.

Table 1: General rules for the design and conduct of clinical trials

1. Clinical trial design should contain a control group, against which the intervention group is compared.
2. Randomisation is the preferred way of assigning participants to control and intervention groups.
3. Ideally, investigators would have no interests other than the well-being of the study participants and all the participants in the study should be blinded to the study interventions, assessments and data allocation.
4. Proper, voluntary informed consent must be sought before involving any potential participant in a clinical trial.

Regulatory and ethical approval

In addition to ethical approval, clinical trials of investigational medicinal products (CTIMPs) conducted in the UK require clinical trial authorisation (CTA) from the MHRA. Researchers wishing to conduct research within the NHS should seek NHS management permission (also known as R&D [research and development] approval). Clinical trials using medical devices also require MHRA approval, except where devices are to be used within their intended purpose, or where the device has been manufactured for 'in house' use. NHS permission is also required if the medical device is tested within the NHS. Non-CTIMPs (studies involving no investigational medicinal products) require only NHS permission and ethical approval.

International multicentre clinical trials provide a greater number of potential participants and access to broader populations, offering advantages for generalisation of the results. All clinical trials performed in the European Union (EU) must be conducted in accordance with the Clinical Trials Regulation EU No 536/2014. This enables a uniform application of the legislation in Europe, ensuring that the rules for conducting clinical trials are identical throughout the EU, and the application procedure for gaining approval is streamlined. It also aims to increase levels of legal certainty, safety and transparency of EU research projects.

Ethical review and approval is needed to ensure that clinical trials protect the health, safety and dignity of the people taking part in research. In order to ensure that all research activities involving humans are covered by the same regulations, the medical community generated the first set of ethical rules in 1964, when the Declaration of Helsinki was endorsed by the World Medical Association. Compliance with ethical standards included in this Declaration is needed to provide public assurance that the rights, safety and well-being of trial participants are protected, and that the data generated by clinical trials are credible. The Declaration defines the ethical principles of research in humans, without being a legally binding document in international law since it cannot overrule local legislations and laws. Its purpose is to provide guidance regarding human research, which must comply with the code of Good Clinical Practice (GCP). GCP is defined as "an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve human participants". The main objective of the GCP code of regulations is to offer an operational guideline for the conduct of clinical trials, which also details the responsibilities surrounding clinical trials. GCP has had a significant impact on the

globalisation of industry-sponsored clinical research, since clinical trial data collected in concordance with GCP regulation can be used for drug indication approval across the world.

The ethical approval of clinical research involving humans is granted by the Institutional Review Board/Independent Ethics Committees as set out in the GCP guideline for international use. The UK Central Office for Research Ethics Committees (COREC) is the main source for information on ethical issues related to clinical trials, and its guidelines are in concordance with the GCP guidelines and the Declaration of Helsinki.

RECs review and subsequently approve or reject research protocols submitted by investigators/researchers. There are different types of RECs; some review protocols for animal studies, some for human studies in social sciences (such as psychology and education), and others for clinical trials in patients or healthy volunteers. Many countries require and legally enforce approval by a REC before clinical trials can be initiated for testing new drugs or vaccines, medical devices, diagnostics and medical procedures. The following principles should be kept in mind when completing an application form for REC review:

- RECs include lay members; therefore it is essential to use non-technical language
- All the abbreviations used in the application should be explained
- The information included should be sufficient to enable a thorough ethics review (e.g. final version of the study protocol, patient information sheet and consent form, clinical trial advertising materials, letter to the GP, scientific review of the research proposal, sponsor letter etc.)

Questions

1. Which of the following statements is not correct?

A. Genomics defines the study of the genome

B. One gene usually encodes one protein

C. Epigenetics is the study of transcriptional variations that are not caused by changes in the DNA

D. Proteomics includes information about interactions of proteins in cellular processes

E. Transcriptomics reflects only the genes actively expressed at a given moment in time

Correct answer: B

The information carried by our genome in the form of DNA goes through various processes before it can translate into proteins; therefore, depending on the segments which are removed, several mRNAs can result from the same pre-mRNA sequence and different proteins are generated from the same DNA sequence. It is estimated that 70% of our genes code for at least 4 proteins each.

2. Which of the following is an advanced therapy?

A. Monoclonal antibodies

B. Small molecules

C. Gene therapy

D. Therapeutic vaccines

E. Cytokines

Correct answer: C

Gene therapy uses recombinant genes created in the laboratory by combining DNA from different sources, which are inserted into the body, for the scope of treating a variety of diseases. Small molecules are chemical compounds used for therapeutic purposes, and antibodies, cytokines and vaccines are all protein-based drugs.

3. Who is responsible for reporting drug side-effects?

A. Pharmaceutical companies

B. Patients

C. Investigators/ doctors

D. Media

E. All the above

Correct answer: E

All the above are responsible to protect the safety associated with the use of medicines by ensuring the timely reporting of side-effects.

4. A successful UK investigator of a new medicinal product plans a study to prove the efficacy of his newly discovered drug in patients with severe multiple sclerosis. A suitable study design is obligatory to include:

A. Long follow-up period

B. Cross-over design

C. Parallel design

D. Randomisation

E. Multi-national participants

Correct answer: D

The selection of a specific RCT design depends on the research question and population characteristics. There are no preset rules for the duration of study follow-up, number of sites or participants in RCTs.

5. Which of the following is not always required for a clinical trial ethical approval?

A. Evidence that the investigational product was tested and it is safe for use in humans

B. A complete clinical trial protocol

C. Consent form

D. Clinical trial advertising material

E. Patient information letter

Correct answer: A

In some cases (phase I clinical trials), the information regarding the safety of the investigational product in humans is not available but will be generated by the clinical trial seeking ethical approval.

6. For a typical IgG monoclonal antibody such as adalimumab, in comparison to a small molecule drug such as ibuprofen, which of the following is not correct:

A. Oral bioavailability is poor

B. Drug distribution is target-mediated

C. The pharmacokinetics are more likely to be non-linear

D. Elimination is predominantly renal

E. The elimination half-life is long

Correct answer: D

Degradation in and poor absorption through the gastrointestinal tract prevents oral bioavailability of monoclonal antibodies**.** IgG is too large to be filtered at the glomerulus**.** Monoclonal antibodies often demonstrate target-mediated distribution and elimination. Target-mediated elimination is capacity limited (saturable) because of finite expression of the target.

7. Before the first dose of a novel small molecule investigational medicinal product may be given to humans in a Phase I clinical study in the UK, which of the following is not required for Research Ethics' Committee review:

A. Summary of protocol in lay language

B. Results from 6 month toxicology study

C. Investigator CVs

D. Subject information and consent documents

E. Evidence of insurance and indemnity

Correct answer: B

Good Laboratory Practice standards dictate that toxicology studies of at least two weeks' dosing are required in two species, one non-rodent**.**

Reference

Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther. 2001; 69: 89-95