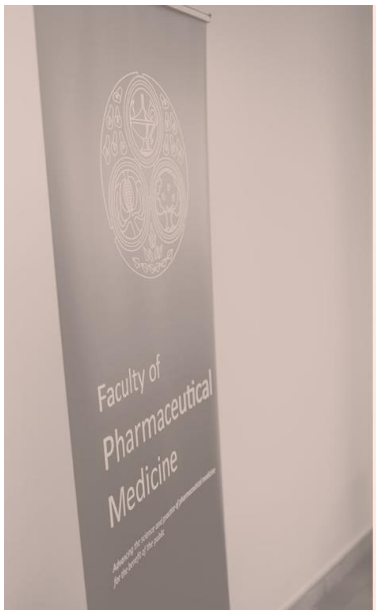
Candidate Guide and Syllabus

Diploma in Human Pharmacology



Faculty of
Pharmaceutical
Medicine

19 Angel Gate, 326a City Road
London, EC1V 2PT
+44(0) 20 3696 9040

Registered Charity No 1130573
Company No 6870644

Contents

1 Summary

In 2008, the Faculty of Pharmaceutical Medicine of the Royal Colleges of Physicians of the UK (FPM) established a 2-year training programme and qualification called the 'Diploma in Human Pharmacology' (DHP). The DHP is intended for medical doctors training to take on the responsibilities of a principal investigator (PI) for human pharmacology studies of investigational medicinal products (IMPs). It comprises supervised, structured workplace training with production of a portfolio of completed work and evidence of appropriate clinical and investigator skills. In addition, trainees are required to attend three courses. These cover exploratory development of IMPs including First-in-Human (FIH) studies, principles of pharmacology at an advanced level and management of adverse events in Phase I studies. At the end of the period of training, there is an examination comprising 3 written papers. This document describes the objectives, eligibility criteria, curriculum and syllabus of the DHP.

2 Objectives

The purpose of the DHP programme is to enable trainees to attain and demonstrate competence to serve as a PI for human pharmacology studies of IMPs, in particular those involving the first administration to humans. Such studies include those conducted in healthy and patient volunteers, in which the primary end-points are tolerability, pharmacokinetics and evidence of drug effects on biomarkers of efficacy and safety. The training in practical aspects of working as a PI is underpinned by a knowledge of the scientific basis of drug action.

The FPM has no authority to make the DHP a prerequisite for serving as a PI and the qualification cannot be considered as formal evidence of 'fitness to practise'. It also does not imply that an individual is sufficiently experienced or has all the appropriate skills to serve as a Medical Director. However, the Diploma is recognised by the Medicines and Healthcare products Regulatory Agency (MHRA) as the most appropriate qualification for PIs in the pharmaceutical industry and is taken into account in the accreditation of Study Units performing FIH studies. It is hoped that doctors working in clinical pharmacology in academia will also wish to study for the DHP to gain the particular skills and competencies of direct relevance to the conduct of their research in humans.

3 Curriculum

The curriculum comprises the following:

1. a minimum period of two years supervised structured training in the workplace with evidence of attainment of defined Learning Objectives provided by a portfolio and quality assured assessments;
2. acquisition and maintenance of up-to-date clinical skills including satisfactory completion of an Advanced Life Support or equivalent course;
3. attendance at two five-day DHP training courses with completion of assignments involving private study to a satisfactory standard and any other courses deemed necessary depending on the individual trainee's needs;
4. attendance at a one-day DHP training course on prevention and management of adverse reactions in Phase I studies;
5. a written examination at the end of the period of training.

Diplomates will be required to have completed all elements of the curriculum to a satisfactory standard. Each of these elements is briefly described in the following paragraphs.

3.1 Supervised training in the workplace

Supervision of trainees will be performed by clinical pharmacologists with extensive experience of Phase I studies. These Educational Supervisors will be trained and accredited by the FPM, having fulfilled defined eligibility criteria. Assessments of trainee competence will be performed by the Supervisor and verified by a Senior Specialty Adviser (SSA) or the DHP Director of the FPM acting in the role of an external examiner / moderator.

3.1.1 Training Log

The trainee is required to maintain a training log, with documented evidence of attainment of specified curriculum learning objectives, defined in terms of knowledge, skills, attitudes and behaviours.

3.1.2 Portfolio

The trainee is also required to produce a portfolio of work completed in the workplace over a minimum of two years. This portfolio should be reviewed and validated by the Educational Supervisor at least three times each year and by the SSA / DHP Director at least once annually. At the end of the training period, the portfolio may also be reviewed by the DHP Advisory Panel. The portfolio should provide a comprehensive overview of work performed by the trainee. This will include a list of clinical studies in which they have been involved (tasks) and a summary written by the trainee of their activities within each task.

Entries to be included for each task should include the following:

- the front cover of the protocol (anonymised for confidentiality reasons);
- a brief summary of the protocol;
- specific role and responsibilities.

Entries under the relevant activity heading will typically include:

- written contributions of the trainee to protocols, reports etc, assessment of preclinical packages, particularly for FIH studies;
- risk assessments and discussion of safety issues;
- main information gleaned and what was learned from a literature review;
- submissions and presentations to Research Ethics Committee;
- results of volunteer screening including reasons for rejection;
- adverse events encountered and their management.

The emphasis should be on the contribution of the trainee and not a list of procedures performed by others. In addition, the trainee should provide a commentary / personal reflection of the project e.g. what the trainee learned, discussion of whether aspects of the project could have been improved.

While the minimum number of times a particular procedure should have been performed by the trainee is not specified, numbers should be included to provide a reasonable overview of

experience e.g. number of volunteers screened by the trainee for each study, number of volunteers participating in each study.

3.1.3 Learning Objectives

The trainee is required to achieve the following Learning Objectives:

1. Evaluate preclinical information (pharmacology, ADME, toxicology, quality) relating to small molecule and biological IMPs, identifying the need for additional information, liaising with sponsors and seeking expert opinion when appropriate.
2. Apply in practice the principle of minimal risk with respect to assessment of new molecules, trial design and procedures, staffing and facilities.
3. Apply ethical principles, regulation and law relevant to human experimentation.
4. Design, recruit, conduct, report and interpret results of studies in healthy / patient volunteers involving:
   a. first administration of single and repeat doses of IMPs;
   b. PK e.g. bioavailability, interactions, organ impairment;
   c. administration of radiopharmaceuticals e.g. mass-balance, imaging;
   d. PD and other biomarkers to assess dose-concentration-response and benefit:risk;
   e. therapeutic interventions.

5. Conduct clinical trials in accordance with Good Clinical Practice and Good Pharmaceutical Medical Practice with formulated product produced in compliance with Good Manufacturing Practice.
6. Manage medical emergencies and anticipate, detect, manage and report adverse events and adverse drug reactions.
7. Evaluate critically published scientific literature, including basic and clinical pharmacology, Phase I-IV clinical trials and meta-analysis.
8. Supervise staff, negotiate with sponsors and communicate satisfactorily with all personnel in the workplace.

Each of these Learning Objectives is defined in terms of knowledge, skills, attitudes and behaviours listed in Appendix 1. The evidence of achievement will be provided primarily by the portfolio.

3.2 Clinical skills

It is considered essential that trainees acquire and maintain a high level of clinical skills to manage resuscitation and other medical emergencies including treatment of arrhythmias, anaphylaxis and other allergic reactions. Diplomates will be required to have a recent certificate of satisfactory completion of training in Advanced Life Support or equivalent.

In addition to management of emergencies, it is considered important that investigators should be able to exercise sound clinical judgement. Therefore, trainees will be encouraged to have attachments / periods of secondment to a hospital in which they will be involved in acute medicine.

3.3 Courses and private study

Trainees will be required to complete three DHP courses:

1. Exploratory Drug Development - 40 contact hours (five days) (Appendix 2);

2. Drug Development Pharmacology – 40 contact hours (five days) (Appendix 3).

These courses will involve:

- preparatory reading using recommended texts, guidelines, directives and other documents from regulatory and scientific sources;
- active participation in case studies and workshops as well as tutorial-style lectures;
- completion of assignments as private study and submission for assessment within a specified time.

Trainees will be expected to supplement their learning on the formal courses with private study. Completion of course assignments will involve literature searches as well as reference to recommended texts, guidelines, directives and other documents from regulatory and scientific sources.

Assignments will be assessed and must be of a satisfactory standard, which will be moderated by the FPM. The content, material and delivery of the courses will be quality assured by the FPM.

3. Medical care of participants in Phase I studies – 8 contact hours (1 day or 2 half days) (Appendix 4)
    - This will comprise lectures on medical care of study subjects

The individual needs of trainees will be assessed at the time of enrolment and during their training. It is possible that trainees will be required to attend additional courses on specific aspects of the syllabus e.g. statistics.

3.4 Examination

The Diploma examination is prepared and conducted by a subcommittee of the FPM Board of Examiners. It comprises three written papers. The Paper on Day 1 is intended to test factual knowledge relating to any part of the syllabus. Papers on Day 2 are intended to test knowledge relating to clinical safety / medical care of subjects participating in Phase I/II studies including the ability to interpret safety data and manage adverse reactions.

The papers are as follows:

Day 1

1. Multiple Choice Question paper in 'True/False' format. Each stem question has five completions. Candidates are required to indicate which are true and which false; any number may be true or false.

Day 2

2. Multiple Choice Question paper in 'Best of Five' format. Each stem question has five completions. Candidates are required to select the single best completion.
3. A Short Answer Question paper in which candidates are required to write answers in the form of short notes / bullet points or prose as specified in the questions, which may describe scenarios or contain data or text for interpretation.

Paper 1 is intended primarily to test factual knowledge relating to any part of the syllabus but excluding topics of a strictly clinical nature. Paper 2 is intended to test knowledge relating to clinical safety / medical care of subjects participating in Phase I/II studies including the ability to interpret safety data and manage adverse reactions. Candidates are expected to have a working knowledge of the mechanism of action, therapeutic benefit and adverse effects of common drugs. Paper 3 is also clinically focussed and is intended to test the ability of the candidate to apply their knowledge to ethical and safety aspects and the role of the investigator Diplomates are required to pass all three parts of the examination. Diploma trainees may sit Paper 1 before completion of their 2-year programme e.g. after 1 year and, if successful, will be entitled to gain the Certificate in Human Pharmacology. Please refer to FPM Examination Regulations and Appeal Procedures for further details.

4 Syllabus

Science

1. Clinical Pharmacology and Therapeutics. Major therapeutic small molecule drug classes and their mechanisms of action. Monoclonal antibodies and other biologicals. Vaccines. Gene therapies. Factors affecting therapeutic outcome.
2. The molecular basis of drug action. Receptor pharmacology, signal transduction, second messengers, enzymes, regulatory proteins, transcription factors, cellular sites of drug action, ion channels. Agonists, partial agonists, antagonists, dose-concentration-response.
3. Integration of information. Sources and critical review of scientific literature; evaluation of benefit / risk based on preclinical / early clinical data.

Guidelines

4. Guidelines for human pharmacology studies. Content of guidelines concerning the conduct of non-patient and patient volunteer studies including the elderly and women (e.g ABPI Guidelines for Phase I clinical trials, Guideline on strategies to identify and mitigate risks for First in Human clinical trials with Investigational Medicinal Products, EMEA/CHMP/SWP/294648/2007)

Study Design

5. Principles of Study Design. Advantages and disadvantages of different types of study design; specific study designs for first administrations of single and multiple doses (including methods for selection of starting dose, dose increments, maximum doses, stopping rules, details of study conduct including interim reviews); drug interactions; bioequivalence and bioavailability; demographic factors; organ failure.

Study Facilities and Conduct

6. Facilities, Equipment and Personnel. Standards for clinical facilities; guidelines, resuscitation equipment; qualifications and experience of physicians, nursing staff and non-clinical scientific staff; key issues in the organisation and administration of research units for the conduct of studies in healthy non-patient volunteers.

7. Selection of Non-Patient Volunteers. Identification of the healthy volunteer; screening for significant conditions; laboratory testing; cardiorespiratory assessment; allergy risks;

psychiatric assessment; screening for metabolic phenotype; detection of asymptomatic conditions; avoidance of multiple study participation; recruitment of volunteers; hazards of drugs of abuse; the issues surrounding studies in women of child bearing potential.

8. Studies in Patient Volunteers. Facilities; types of study, issues specific to patient studies; selection of patient volunteers; avoidance of multiple study participation.

9. Clinical Conduct of Studies. Responsibilities of the PI, other investigators, nursing staff and non-clinical scientific staff; potential `hazards' of participation for volunteers; follow-up of volunteers; non-drug influences on study outcome, monitoring of safety including cardiorespiratory, laboratory, drug specific measurements.

10. Routes of Administration. The safety, scientific and technical issues relevant to different routes of administration including oral, parenteral, topical, inhaled and modified release.

PK, PD, Data Analysis, Presentation and Interpretation

11. Pharmacokinetics. Principles of PK and ADME, importance of pharmacogenetics, objectives of and issues to be considered in the design of PK studies, presentation and interpretation of data, principles and performance of different bioanalytical techniques.

12. Pharmacodynamics. Principles underlying use of biomarkers, PD measurements, surrogates for clinical endpoints, objectives of and issues to be considered in the design of PD studies, commonly used biomarkers and surrogates for desired and undesired effects in different therapeutic areas, application of imaging techniques in the assessment of drug action.

13. Proof of Concept. Definitions of Proof of Concept (PoC), Benefit / Risk Balance, Use of PK/PD.

14. Principles of Medical Statistics. Hypothesis testing and hypothesis generation; within- and between-subject variation; power calculations; data summarising and display.

Pharmaceuticals with Particular Requirements

15. Biopharmaceuticals. The specific issues relating to early development of biopharmaceuticals, biopharmaceutical manufacture and formulations, particular issues relating to agonists, extrapolation of animal data to man, cross reactivity, toxicological evaluation, early clinical evaluation, determination of starting dose and duration of effect.

16. Radioactive molecules. Radiation protection in biological research. The specific legal requirements, facilities and radiation protection measures relating to administration of radiopharmaceuticals for mass balance, imaging and other studies including requirements of the Administration of Radioactive Chemicals Advisory Committee.

17. Gene therapies. The specific issues relating to the introduction of genetic material into human somatic cells for therapeutic, prophylactic or diagnostic purposes e.g. genetically

modified viral vectors, naked DNA injection and anti-sense techniques. Familiarity with Gene Therapy Advisory Committee guidelines.

Safety

18. Animal Safety Assessments for Initial Studies in Man. Design, conduct and interpretation of general and reproductive toxicology studies, genotoxicity and safety pharmacology, the use of preclinical pharmacological and pharmacokinetic assessments; principles of human risk assessment from animal toxicology studies; importance of toxicokinetics; inter-species scaling; differences between man and animals.

19. Adverse Events. Methodology for collection, mechanisms, types of adverse events, drug allergy, the extent of variation in normality; principles of event attribution; actions required and influence of adverse events on drug development.

20. Management of Medical Emergencies. Pre-trial interviews and screening procedures; up-to-date resuscitation procedures and guidelines; diagnosis and management of anaphylaxis and other severe allergic phenomena, cardiac arrhythmias, respiratory emergencies, syncope, convulsions and other neurotoxicity, dermatological adverse events; clinical pharmacology of drugs used in emergencies.

Quality

21. Quality of raw material and drug product. Identity of material, nature and quantity of impurities, stability, storage, certificates of analysis, role of the Qualified Person.

Regulatory, Ethical and Legal

22. Regulatory Requirements and Procedures for Phase I/II studies

23. Ethics Review. Principles of ethics review; ethical issues in non-therapeutic clinical research; guidelines for ethics committee composition and practice; principles of informed consent.

24. Indemnity and Negligence. Principles; types of indemnity; legal responsibilities; negligence, definition and avoidance.

25. Good Clinical Practice. Principles to ensure the validity of the data collected and the conclusions drawn; record keeping in clinical research; essential documents, responsibilities of the investigator, sponsor, monitor, regulatory authority, auditor; regulatory audit; fraud in clinical research.

26. Documentation. Summary of Data and Guidance for the Investigator section of Investigator's Brochure, protocols, clinical study reports, Clinical Trials Authorisation applications, Investigational Medicinal Product Dossiers.

Communication

27. Interpersonal Relationships. Effective negotiation with stakeholders, management of study personnel; team skills.

5 Eligibility

5.1 Clinical Experience

Candidates eligible to enter the DHP programme must be fully registered as a medical practitioner in their country of employment and have attained Level 1 competencies or equivalent in clinical training. This will generally require considerable experience in acute care of patients. The FPM considers that adequate clinical experience involving acute care of patients is essential for principal investigators. However, it is recognised that occasionally, doctors wishing to study for the Diploma, including some who may already have been working in Phase I / human pharmacology for some time, may not have completed the required period of clinical training.

UK doctors who qualified before 2005 will normally require a minimum of three years' clinical training post-qualification. In exceptional circumstances, and at the discretion of an eligibility panel, those with less than three years clinical training post qualification may be admitted to the programme.

UK doctors who qualified after 2005 (under the Modernising Medical Careers programme) will require a minimum of four years' clinical training post-qualification. Doctors who have between three- and four-years clinical training post-qualification may, at the discretion of a panel, be admitted to the programme on the condition that they undertake a clinical attachment during the programme, the details of which will be specified by the panel. Applicants with less than three years' clinical training post qualification will not be admitted to the programme.

Doctors who have graduated and worked outside the UK will be required to demonstrate equivalent qualifications and experience.

5.2 Experience in Human Pharmacology

Ideally, applicants will have gained some experience of conducting human pharmacology studies and will have a basic knowledge of the subject before enrolling in the programme, but this is not a requirement for eligibility.

Candidates should normally be working within an organisation and at a site capable of providing supervision of human pharmacology workplace training in which all learning objectives can be met. In exceptional cases, it may be acceptable for trainees to be seconded to another site for part of their training if this is not available in the normal workplace. A formal assessment of the site will be made at a visit by the DHP Director from the FPM.

Doctors who have worked for some years in a suitable training environment and have already gained hands-on experience in the conduct of human pharmacology studies in an academic or commercial organisation may wish to gain retrospective recognition of time previously worked under supervision as an investigator. Trainees wishing to gain such retrospective recognition will be required to present a portfolio of work undertaken in the period being considered. The portfolio must provide evidence of appropriate experience and will be assessed by the FPM DHP Advisory Panel (see section on Portfolio above). The maximum permitted period of

retrospective recognition of workplace training will be twelve (12) months, leaving a minimum of a further twelve (12) months of prospective workplace training for the Diploma.

6 Equal Opportunities

The Faculty of Pharmaceutical Medicine is committed to promoting equal opportunity and eliminating discrimination in all areas of its activity. Equal opportunities monitoring will be undertaken, and information obtained may be analysed to assess compliance with the policy. Information will be held confidentially and used for monitoring purposes only. Any reports will be anonymised to ensure that individuals cannot be identified.

7 Fees

The total cost of the DHP programme is currently approximately £5,800. The fee payable to the FPM, which covers administration of the programme, the 1-day course and the examinations, is £2,500. This may be paid in two annual instalments with the first half payable at enrolment. The fees for the two compulsory 5-day courses total £3,300 (£1,650 per course*) are payable directly to King's College London. Trainees must enrol with King's College to register for the courses. The fees do not include travel or accommodation expenses. Candidates who wish to enrol for Pharmaceutical Medicine Specialty Training (PMST) at the same time as the DHP may be eligible for a reduction in fees.

*as at 2019

APPENDIX 1: Learning Objectives

1. Evaluate preclinical information (pharmacology, ADME, toxicology, quality) relating to small molecule and biological IMPs, identifying the need for additional information, liaising with sponsors and seeking expert opinion when appropriate.

Knowledge	Skills	Attitudes/Behaviours
Theories of drug-receptor interactions and the related concepts of agonists, antagonists, partial agonists, structure activity relationships, affinity, efficacy, potency, specificity, selectivity. In vitro and in vivo tests of pharmacodynamics (PD). Pre-clinical evaluation of drug safety including secondary pharmacology, acute, subacute and chronic studies of toxicity, toxicokinetics, genotoxicity, reproductive toxicity. Absorption, distribution, metabolism and elimination of drugs. Pharmacokinetics (PK) in animal species. In vitro and in vivo tests of metabolism. Dose-concentration-response relationships and PK/PD interrelations. Particular points for consideration relating to new biological entities.	1.1 Can identify where data of critical importance for assessment of efficacy, dose-selection and safety are lacking. 1.2 Can use pre-clinical data for calculation of safe starting doses and maximal exposure in humans. 1.3 Can apply pre-clinical information to optimise the design of studies in humans 1.4 Can search relevant scientific literature and apply knowledge gained to the design of a study. 1.5 Can grasp the particular issues relating to the early evaluation of biological products in humans.	Recognises the primacy of subject safety and minimal risk. Appreciates the needs of sponsors and establishes and maintains satisfactory relationships with them. Appreciates the importance of communicating research data orally and in written form and is diligent in writing and rehearsal. Successfully negotiates with sponsors to obtain additional data of critical importance and modify study design when appropriate. Recognises when it is appropriate to seek expert opinion and responds appropriately to such consultative input.

2. Apply in practice the principle of minimal risk with respect to assessment of new molecules, trial design and procedures, staffing and facilities;

Knowledge	Skills	Attitudes/Behaviours
Understands the advantages and disadvantages of different routes of drug administration with respect to safety. Has a broad knowledge of adverse drug reactions and in particular those relevant to short term administration of drugs. Is familiar with a variety of study designs with their implications for safety. Is familiar with the particular safety issues raised by administration of biologicals in general. Has a working knowledge of immunological mechanisms by which novel biological agents can pose a risk to humans. Understands the measures which should be taken to minimise risk before and during the conduct of a study.	2.1 Can apply knowledge of potential risks of novel molecules in humans to optimisation of study design, inclusion of appropriate tests and safety parameters, selection of the most appropriate study population and minimising risk during the conduct of a study in humans. 2.2 Can monitor safety parameters with a high degree of competence. 2.3 Can construct and adjust dose regimens optimally. . 2.4 Can apply pharmaco-kinetic and ADME data to minimise risk. 2.5 Can apply knowledge of the immune system to the potential risks of biological agents acting on the immune system. 2.6 Can make appropriate decisions about discontinuation of subjects and studies on safety grounds 2.7 Can judge the appropriate level of staffing for a study and organising the staff in a manner which optimises the care of study subjects.	Recognises the distinction between 'minimising' and 'minimal' risk and its relevance to selection of study populations. Recognises the importance of meticulous monitoring of safety parameters. Takes responsibility for repeated observation and follow-up of adverse events Respects patient/ subject autonomy.

3. Apply ethical principles, regulation and law relevant to human experimentation.

Knowledge	Skills	Attitudes/Behaviour
Ethical principles underpinning ethics of research on human subjects including duties, rights and utilitarianism. The basis for decision making when ethical principles may appear to conflict with one another. The required constitution/ membership of research ethics committees (RECs). The appropriate terms of reference of RECs. Local arrangements for ethical review and regulatory applications. Declaration of Helsinki and ICH guidelines and relevant EC Directives. The legal framework in which RECs operate in Europe and the UK. Local legislation governing the conduct of clinical trials in patients and healthy volunteers.	3.1 Can prepare and submit REC applications 3.2 Can prepare information for trial subjects using appropriate language for lay people. 3.3 Can complete and submit Clinical Trial Applications and Amendments as appropriate, communicating effectively with the Competent Authority and REC 3.4 Can make effective presentations to a REC, can justify a research proposal in terms that are understood by the lay members of a REC, can handle questions appropriately and instil an ambiance of trust and professionalism.	Respects confidentiality of information. Demonstrates that ethical principles are always considered paramount when confronting dilemmas in the practice of clinical experimentation.

4. Design, recruit, conduct, report and interpret results of studies in healthy / patient volunteers involving:
   a) first administration of single and repeat doses of IMPs;
   b) PK e.g. bioavailability, interactions, organ impairment;
   c) administration of radiopharmaceuticals e.g. mass-balance, imaging;
   d) PD and other biomarkers to assess dose-concentration-response and benefit:risk;
   e) therapeutic interventions.

Knowledge	Skills	Attitudes/Behaviour
The role of Clinical Pharmacology in drug development. The advantages and disadvantages of different trial designs including various crossover and parallel groups, sequential and adaptive designs. The principles of controlled experiments, randomisation, use of placebo, blinding. The specific considerations relating to planning, design and conduct of FIH studies with single and multiple escalating doses of IMPs. Principles of statistical aspects of study design and analysis of data. PK associated with different routes of administration, ADME, interpretation of drug concentration data, features of bioanalytical methods Factors affecting PK of drugs including demography, disease and drug interactions. Principles, validation and familiarity with use of biomarkers as surrogates for clinical endpoints. Examples of use of imaging for PoC.	4.1 Can select a trial design appropriate to the research question and study population. 4.2 Can recruit research subjects, obtaining valid informed consent and screening volunteers (healthy and patients) in accordance with inclusion / exclusion criteria. 4.3 Can perform clinical procedures related to the routine conduct of studies. 4.4 Can measure end points reliably and record data accurately. 4.5 Can use biomarkers of efficacy/safety, analyse and interpret the data obtained in exploratory clinical studies. 4.6 Can use pharmaco-kinetic data to design appropriate dosage regimens. 4.7 Can keep records to the standard required by GCP.	Maintains absolute honesty, ensuring the integrity of data collected. Maintains meticulous attention to detail. Contributes to the professional manner in which a study is conducted and maintains a professional relationship with study subjects. Recognises the primacy of safety of the subject. Maintains a satisfactory professional relationship with study sponsors, working colleagues and subordinates and their employees (CROs etc).

Concepts of Exploratory Development, Learn-Confirm drug development, proof of concept and proof of principle. Principles of radiation safety and special considerations in design and conduct of studies with radiopharmaceuticals. Principles of gene therapy. Specific considerations in relation to evaluation of vaccines.	4.8 Can understand the principles of statistical analyses of data, interpret results and prepare reports suitable for inclusion in a final clinical study report.	

5. Conduct clinical trials in accordance with Good Clinical Practice and Good Pharmaceutical Medical Practice with formulated product produced in compliance with Good Manufacturing Practice.

Knowledge	Skills	Attitudes/Behaviour
The EC Clinical Trials Directive. The EC GCP Directive ICH GCP ABPI guidelines on Phase I studies Local standard operating procedures. The principles of GMP for drug substance and finished product The principles of Good Pharmaceutical Medical Practice	5.1 Can apply GCP to situations that may be encountered in practice of Human Pharmacology. 5.2 Practical application of local SOPs. 5.3 Can assess and confirms IMPs have been produced according to GMP and that local pharmaceutical services comply. 5.4 Can manage study subjects according to the principles of Good Medical Practice. 5.5 Can oversee site inspections and audits	Demonstrates a willingness to comply with the requirements of GCP in daily practice of human pharmacology. Responds positively to deficiencies found by auditors and inspectors. Demonstrates a positive attitude to the implementation of GXPs.

6. Manage medical emergencies and anticipate, detect, manage and report adverse events and adverse drug reactions.

Knowledge	Skills	Attitudes/Behaviour
The terms tolerability, safety, adverse events, adverse reactions. The mechanisms whereby drugs cause adverse reactions and classification of ADRs. Important (common and/or severe) adverse effects of a wide range of drugs. Important adverse effects associated with drug interactions. Common clinical presentations of ADRs. Appropriate management of suspected ADRs including use of antidotes. The regulatory requirements for expedited reporting of serious ADRs and SUSARs to regulatory authorities.	6.1 Can manage common and serious adverse events including hypotension, anaphylaxis and other allergic reactions, arrhythmias, broncho-spasm, central effects, cytokine release, disturbance of liver and renal function and haematology 6.2 Keeps up to date and competent in advanced level resuscitation skills. 6.3 Can report suspected ADRs appropriately.	Manages communication of information with respect to Adverse Events to colleagues, sponsors, RECs, study subjects and regulatory authorities in an appropriate and professional manner. Is prepared to share information and admits own mistakes which may have contributed to adverse events. Consults with colleagues over judgements such as risk/benefit of rechallenge.

7. Evaluate published scientific literature critically, including basic and clinical pharmacology, Phase I-IV clinical trials and meta-analysis;

Knowledge	Skills	Attitudes/Behaviour
Has up-to-date working knowledge of basic and clinical pharmacology and therapeutics in several therapeutic areas.	7.1 Can analyse critically published papers with respect to rationale, objectives, experimental design, methods of analysis, potential sources of bias, confounding factors, conflict of interest, appropriateness of discussion, validity of conclusions. 7.2 Can draw conclusions from a range of publications about the quality of evidence for certain claims and conclusions. 7.3 Can contribute to writing papers and reporting findings by oral and poster presentations at meetings.	Respects ethical principles underlying peer review. Uses electronic databases (eg Medline, Embase, Toxbase, Cochrane). Evaluates expert reviews (e.g. NICE). Uses library resources and reads scientific publications as an integral part of work and continuing professional development.

8. Supervise staff, negotiate with sponsors and communicate satisfactorily with all personnel in the workplace;

Knowledge	Skills	Attitudes/Behaviour
	8.1 Can effectively supervises staff e.g. doctors, nurses, technical, administrative on project related matters, maintaining cordial relations whilst getting the job done. 8.2 Can successfully negotiate with sponsors in a professional manner, showing flexibility in approach but, when necessary, changing views of sponsors and pointing out when certain a course of action might not be advisable or acceptable. 8.3 Can communicate appropriately and effectively and maintains good working relationships with colleagues.	Treats colleagues with respect and consideration. Keeps colleagues and sponsors fully informed as appropriate. Uses, telephone, email and other forms of communication effectively and appropriately. Is open minded and prepared to change a view in light of discussion.

APPENDIX 2: Outline of Exploratory Drug development Course

Duration: 5 days
Pre-reading
Day 1

- Assessment of Preclinical Data before FIH – small molecules, biologicals
- Selecting the starting dose for FIH with case study

Day 2

- Preclinical assessment of biologics
- Study designs for FIH – small molecules, biologicals,
- Ethics of Healthy Volunteer studies – consent, compensation, ethical dilemmas
- Pharmacokinetics I – Principles, PK parameters, FIH studies

Day 3

- Pharmacokinetics 2 – Formulations, bioavailability, bioequivalence, routes
- Pharmacokinetics 3 – Distribution, Blood Brain Barrier
- Pharmacokinetics 4 – Metabolism, renal elimination, pharmacogenetics
- Pharmacokinetics 5 – Demographics and Disease, Population PK, PK/PD
- Drug interactions

Day 4

- Study designs for early phase oncology
- PK of biologicals
- Biomarkers and surrogates
- Use of Imaging
- Case Study

Day 5

- Gene Therapies
- Vaccines for infectious diseases and cancer,
- Regulatory affairs and Accreditation
- When things go wrong
- Pharmacogenomics and other factors affecting PK and PD

NB: Self assessments will be performed each day

Assignments
There will be 2 written assignments to be submitted within 8 weeks of completing the 5-day course. The precise detail of the assignments may vary from year to year but essentially, they are about design of specific clinical pharmacology studies.

APPENDIX 3: Outline of Drug Development Pharmacology Course

Pre-reading

Day 1

Fundamentals

- Pharmacological terms: affinity, potency, efficacy, selectivity, specificity
- Dose - Response
- The therapeutic window
- Agonists, antagonists, partial agonists, inverse agents, paradoxical pharmacology
- Chirality – relevance to drug action
- Targets for drug action: receptors, ion channels, enzymes, nucleus, other targets

Day 2

Targets for drug action

- Cell signalling- relevance to drug action e.g. cyclic nucleotides, phosphorylation of G-proteins, transcription factors
- Techniques for assessing drug action: radioligand binding, high throughput screening, cell culture, isolated tissues, whole animal studies,
- structure activity relationships

Evaluation of preclinical data before 'First-in-Human'

- Informed decision making
- The investigator's brochure

Day 3

Pharmaceutics

- Bioavailability,
- Routes of administration,
- Dosage forms and formulations

Drugs and the nervous system

- Autonomic pharmacology – parasympathetic and sympathetic agonists, nicotinic antagonists, anticholinesterases
- Pharmacology of drugs used for degenerative CNS disorders, in particular Parkinson's disease, Epilepsy, psychiatric disorders in particular depression, schizophrenia
- Use of animal models for discovery of CNS drugs and identification of side effects

Day 4

Drugs and the cardiovascular system

- Physiology of the vasculature
- Ischaemic heart disease
- Heart failure: ACE inhibitors and related drugs, diuretics, pre-load reduction, afterload reduction; inotropes
- Hypertension
- Hyperlipidaemia

Workshop on assessment of preclinical data and the Investigator's Brochure

Day 5

Immunopharmacology and biologics

- Inflammation - pathophysiology
- Rheumatoid arthritis
- Psoriasis
- Approaches to modifying the immune system: immunosuppressants, immunomodulators, immune stimulants with examples of mAbs for antiangiogenesis, EGFR, MHC molecules, vaccines, fusion proteins,

Drugs and the Respiratory System

- Asthma
- COPD
- Rhinitis
- Cough

Drugs and cancer

- Targets for new classes of cancer therapies

Assignments

There is one written assignment for this module comprising an essay on a particular aspect of clinical pharmacology requiring some in-depth scientific writing supported by references. A wide choice of subjects is available. The assignment must be submitted within 8 weeks of completing the 5-day course.

APPENDIX 4: Outline of Course on Medical Emergencies in HP studies

Duration: 1 day

- Serious Adverse Events in Phase I Studies
- Risk assessment, risk mitigation, use of antidotes
- Loss of consciousness: hypotension, syncope, convulsions
- Ocular problems
- Cutaneous drug reactions and photosensitivity
- Acute allergic reactions and anaphylaxis
- Acute ophthalmological adverse events
- Cytokine release syndrome
- Cardiac arrhythmias
- Drug-induced proarrhythmia
- Psychiatric adverse events