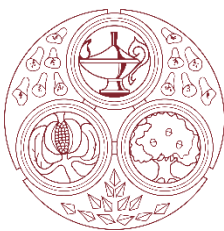


Candidate Guide and Syllabus

Diploma in Experimental Therapeutics



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1 Introduction

The principal investigator (PI) responsible for exploratory (Phase I/II) studies of investigational medicinal products (IMPs) requires particular specialist skills. These include the ability to interpret and critique non-clinical data relating to an IMP, optimise study design to obtain high quality data while minimising risk to study subjects, select dosage, apply and interpret pharmacokinetics and use appropriate biomarkers to assess pharmacodynamic responses.

In 2008, the Faculty of Pharmaceutical Medicine (FPM) established the 'Diploma in Human Pharmacology' (DHP), a 2-year competency-based training programme and qualification for doctors intending to serve as principal investigators (PIs) for human pharmacology studies of IMPs. The Diploma is now 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 Phase 1 studies.

FPM has now established a similar programme for physicians conducting Phase I/II studies within their particular specialty. The Diploma in Experimental Therapeutics (DET) comprises supervised workplace training with production of a portfolio of completed work that provides evidence of appropriate clinical and investigator skills. In addition, trainees are required to attend courses on applied principles of pharmacology and exploratory development of IMPs including 'First-in-Human' studies at an advanced level and to pass an FPM examination. This document describes the objectives, eligibility criteria, curriculum and syllabus of the DET.

2 Objectives

The overall purpose of the DET programme is to enable trainees to attain and demonstrate competence to serve as a PI for exploratory clinical studies of IMPs within their area of specialisation. Such studies will typically involve patients, 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.

FPM has no authority to make the DET a prerequisite for serving as a PI and the qualification cannot be considered as formal evidence of 'fitness to practise'. However, it is hoped that high calibre doctors working in experimental and translational medicine within the health service and other public or private clinical research facilities will attain the DET to provide them with particular specialist skills and competencies of direct relevance to the conduct of their clinical research.

3 Curriculum

The curriculum comprises the following:

1. a period of approximately 18 months' supervised training in the workplace with evidence of attainment of defined Learning Objectives provided by a portfolio and quality assured assessments;
2. 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 at King's College London (KCL), completion of the course assignments to a satisfactory standard and a pass in each of the KCL MCQ post-course tests;
4. a pass in an FPM Multiple Choice Question (MCQ) examination.

In addition, those who have successfully completed the DET curriculum will be required to have gained a Certificate of Completion of Training (CCT) in their specialty before the Diploma can be awarded.

Each of the elements of the curriculum is briefly described in the following paragraphs.

3.1 Supervised training in the workplace

Supervision of a trainee will be performed by a supervisor who will usually be a senior consultant in a related specialty with extensive experience of Phase I/II studies. Assessments of trainee competence will be performed by the supervisor and verified by an FPM Senior Specialty Adviser (SSA) or DET Director acting in the role of an external examiner / moderator.

3.1.1 Training record

The trainee is required to maintain a training record, 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 required to produce a portfolio of clinical research work completed over approximately 18 months. This period may be reduced to a minimum of 12 months by retrospective recognition of clinical research conducted prior to enrolment in the DET programme. However, an account of such previous research must be included in the portfolio in the required format and to the same standard as that required for work conducted during the period of DET registration. The portfolio should be reviewed and validated by the Educational Supervisor at least three times each year. At the end of the training period, the portfolio must be submitted to FPM for assessment.

The portfolio should provide a comprehensive overview of clinical research work performed by the trainee, starting with a list of clinical studies in which they have been involved (tasks) followed by a detailed account of their activities within each task.

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

- the title of the study (anonymised for confidentiality reasons if necessary);
- a brief summary of the protocol;
- specific roles and responsibilities of the trainee.
- reflective comments on design and conduct of the study.

Entries under relevant activities will typically include:

- a summary of written contributions of the trainee to the protocol, report etc,
- assessment of the preclinical package;
- risk assessment and discussion of safety issues;

- main information gleaned and what was learned from published literature;
- submission and presentation to the Research Ethics Committee;
- results of subject screening including reasons for rejection;
- adverse events encountered and their management

For each study, the emphasis should be on the contribution of the trainee and personal reflection e.g. what the trainee learned, discussion of how aspects of the study could have been improved. While the minimum number of times a particular procedure should have been performed by the trainee is not specified, the portfolio should provide a reasonable overview of experience gained e.g. number of patients screened by the trainee for each study, duration of each study, amount of time spent / sessions per week working on a study.

3.1.3 Learning Objectives

The trainee is required to achieve the following Learning Objectives:

1. Evaluate preclinical information relating to small molecule and/or 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. Contribute to study design and reporting of studies which involve administration of IMPs in exploratory (early) clinical development over a range of doses to assess dose-concentration-response and benefit:risk using pharmacokinetics and both desired and undesired pharmacodynamic effects.
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.
8. Supervise staff involved in the study e.g. other doctors, nurses, project coordinators, technicians etc, 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

In addition to the clinical care of study participants (healthy volunteers or patients), it is considered essential that trainees maintain a high level of 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.

3.3 Courses and private study

Trainees will be required to complete two courses at KCL:

1. Exploratory Drug Development - 40 contact hours (5 consecutive days) (Appendix 2);
2. Drug Development Pharmacology – 40 contact hours (5 consecutive 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 course 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, if necessary, will be moderated by FPM. The content, material and delivery of the courses will be quality assured by FPM.

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 or complete e-learning programmes on specific aspects of the syllabus e.g. statistics.

3.4 Examination

The DET examination is prepared and conducted by a subcommittee of the FPM Board of Examiners. It comprises an MCQ paper in 'True/False' format with 100 stem questions, each with 5 completions. Candidates are required to indicate which are true and which false; any number may be true or false.

The exam is intended primarily to test factual knowledge relating to any part of the syllabus. Trainees may sit the exam after completion of both courses but before submission of their portfolio 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. Cytotoxic and targeted therapies for cancer. 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, inverse 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. Risk mitigation strategies to include use choice of study population, size of cohorts, use of sentinel subjects, appropriate intervals between dosing of subjects, selection of route and rate of drug administration, interim reviews of data, choice of site, location within site, staffing and allocation of responsibilities. [1]
[SEP]

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 reproductive 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, 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.

18. Vaccines. Historical background. Study designs including assessment of safety, tolerability, immunogenicity and optimisation of dosage. Use of adjuvants. Specific issues relating to challenge studies. DNA vaccines. Oncolytic virus vaccines.

Safety

19. 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.
20. 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.
21. 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

22. 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

23. Regulatory Requirements and Procedures for Phase I/II studies
24. Ethics Review. Principles of ethics review; ethical issues in non-therapeutic clinical research; guidelines for ethics committee composition and practice; principles of informed consent.
25. Indemnity and Negligence. Principles; types of indemnity; legal responsibilities; negligence, definition and avoidance.
26. 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.

27. 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

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

5 Eligibility

5.1 Clinical Experience

Candidates eligible to enter the DET 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. FPM considers that adequate clinical experience involving acute care of patients is essential for principal investigators.

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 will be expected to have attained or be working towards a CCT within their specialty.

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

5.2 Experience in Experimental Therapeutics

Ideally, applicants will have gained some experience of conducting exploratory drug development 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 a hospital or other organisation capable of providing supervision of qualified doctors working as clinical trial investigators 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 suitability of the site as a training environment will be made at a visit by the DET Director from FPM.

Doctors who have worked for some years in a suitable training environment and have already gained hands-on experience in the conduct of exploratory clinical trials in an academic or commercial organisation may wish to gain retrospective recognition of some time previously worked under supervision as an investigator. Trainees wishing to gain such retrospective recognition will be required to include such work in their portfolio. The portfolio must provide evidence of appropriate experience and will be assessed by FPM (see section on Portfolio above). The maximum permitted period of retrospective recognition of workplace training will be six (6) 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 DET programme is currently approximately £5,800. The fee payable to FPM, which covers administration of the programme and the examinations, is £2,500. 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.

*as at 2019

APPENDIX 1: Learning Objectives

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

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

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
<p>Understands the advantages and disadvantages of different routes of drug administration with respect to safety.</p> <p>Has a broad knowledge of adverse drug reactions and in particular those relevant to short term administration of drugs.</p> <p>Is familiar with a variety of study designs with their implications for safety.</p> <p>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.</p> <p>Understands the measures which should be taken to minimise risk before and during the conduct of a study.</p>	<p>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.</p> <p>2.2 Can monitor safety parameters with a high degree of competence.</p> <p>2.3 Can construct and adjust dose regimens optimally.</p> <p>2.4 Can apply pharmacokinetic and ADME data to minimise risk.</p> <p>2.5 Can apply knowledge of the immune system to the potential risks of biological agents acting on the immune system.</p> <p>2.6 Capable of making appropriate decisions about discontinuation of subjects and studies on safety grounds</p> <p>2.7 Capable of judging the appropriate level of staffing for a study and organising the staff in a manner which optimises the care of study subjects.</p>	<p>Recognises the distinction between ‘minimising’ and ‘minimal’ risk and its relevance to selection of study populations.</p> <p>Recognises the importance of meticulous monitoring of safety parameters.</p> <p>Takes responsibility for repeated observation and follow-up of adverse events</p> <p>Respects patient/ subject autonomy.</p>

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

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

4. Contribute to study design and reporting of studies which involve administration of IMPs in exploratory (early) clinical development over a range of doses to assess dose-concentration-response and benefit:risk using pharmacokinetics and both desired and undesired pharmacodynamic effects.

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

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

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

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

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

Knowledge	Skills	Attitudes/Behaviour
<p>Has up-to-date working knowledge of relevant basic science, clinical pharmacology and later phase clinical trials and therapeutics within the specialty.</p>	<p>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.β</p> <p>7.2 Can draw conclusions from a range of publications about the quality of evidence for certain claims and conclusions.</p> <p>7.3 Can contribute to writing papers and reporting findings by oral and poster presentations at meetings.</p>	<p>Respects ethical principles underlying peer review.</p> <p>Uses electronic databases (eg Pubmed, Embase, Toxbase, Cochrane).</p> <p>Evaluates expert reviews (e.g. NICE).</p> <p>Uses library resources and reads scientific publications as an integral part of work and continuing professional development.</p>

8. Supervise staff involved in the study e.g. other doctors, nurses, project coordinators, technicians etc, negotiate with sponsors and communicate satisfactorily with all personnel in the workplace.

Knowledge	Skills	Attitudes/Behaviour
	<p>8.1 Effectively supervises staff e.g. doctors, nurses, technical, administrative on project related matters, maintaining cordial relations whilst getting the job done.</p> <p>8.2 Negotiates 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.</p> <p>8.3 Communicates appropriately and effectively and maintains good working relationships with colleagues.</p>	<p>Treats colleagues with respect and consideration.</p> <p>Keeps colleagues and sponsors fully informed as appropriate.</p> <p>Uses all forms of communication effectively and appropriately.</p> <p>Is open minded and prepared to change a view in light of discussion.</p>

APPENDIX 2: Outline of Exploratory Drug development Course

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.