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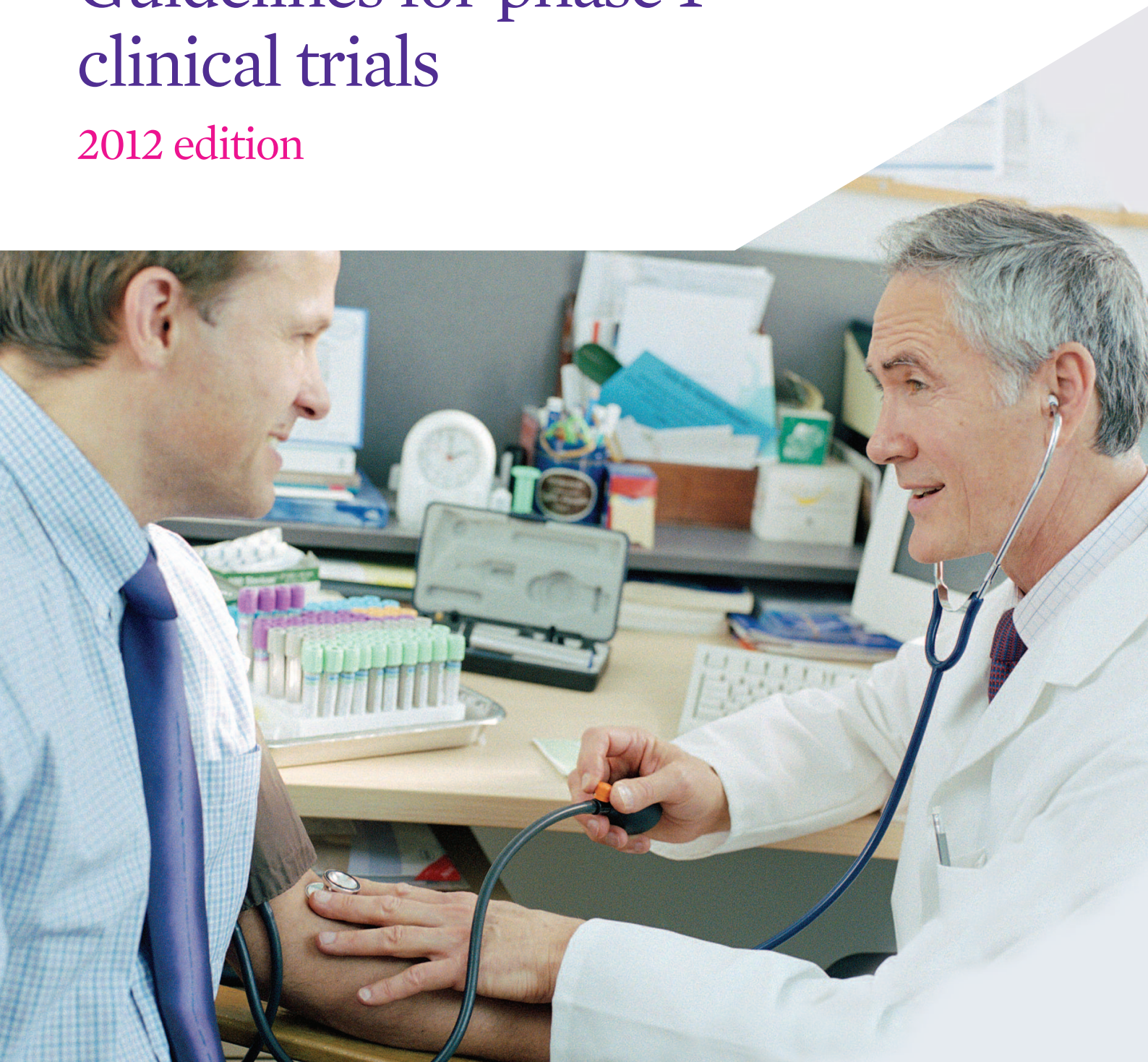
Bringing medicines to *life*

Guidelines for phase 1 clinical trials

2012 edition



Foreword

The development of new and better medicines is vital for the public health. A key step in medicines development is the transition from the laboratory to the human subject in a phase 1 clinical trial, when potential new medicines are given to humans for the first time. Phase 1 is the gateway between scientific research and clinical medicine.

The phase 1 trial falls within the realm of experimental science, and requires a range of skills and expertise of the highest standard. Confidence in the results depends upon the clarity and understanding of the questions asked, and upon the quality of the trial designed to answer them. However, the safety and well-being of the subjects – whether they be healthy individuals or patients – must always have priority.

The translation of advances in the biological sciences into health benefits, via the development of new medicines, is likely to occur at an increasing pace in the coming years. New medicines will be based on progressively refined biological and biochemical insights. There may be no prior experience in humans of many of the new types of medicine that advances in molecular pharmacology should yield. The challenges for phase 1 trials include: finding methods to assess the potency and effectiveness of these new medicines; sharing of safety information; calculation of the starting dose; design of dose-escalation protocols; and, in the interests of the well-being and safety of the subjects, ever-vigilant attention to risk reduction and risk management in the conduct of the trial.

This 2012 edition of the ABPI Guidelines for Phase 1 Clinical Trials is science based, and is a remarkably thorough and notably clear compilation of updated information and guidance on best practice. It covers all of the key points, and warrants close reading and frequent reference by those involved in the development, investigation and regulation of new medicines. As we enter an era of high expectation in the provision of much-needed innovative medicines, the ABPI is to be commended on the timely production of professional guidance that will underpin the safe and effective conduct of future phase 1 trials.

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Preface

The first edition of these ABPI guidelines was published in 1970.[1] They were revised in 1977[2] and 1988. The 1988 revision resulted in two sets of guidelines, one for procedures[3] and another for facilities.[4] In 1986, the Royal College of Physicians (RCP) published a report on research in healthy volunteers,[5] which has never been revised. But the 1988 revision of the ABPI guidelines took the RCP report into account.

These editions were written when many ABPI member companies had their own facilities and used their own staff as a source of healthy volunteers. Nowadays, contract research organisations (CROs) do most of the phase 1 trials in the UK,[6] and many sponsors are from countries outside the UK.

In 2007, the guidelines underwent a major revision. It took into account the many changes that had taken place in the two decades since the 1988 edition. Numerous sections were updated and expanded: premises, facilities equipment, staff emergency procedures and equipment, pharmacy and laboratory, records and archiving, justification for studying healthy subjects, recruitment and payment of subjects, frequency of volunteering, ethics committee, and compensation. New sections were added to reflect the significant changes to the regulations and the ways in which Phase 1 trials were being conducted.

The 2007 edition was extremely well received and became a useful guide not only to sponsors and investigators but also to ethics committees and trial volunteers, read by people well beyond the borders of the United Kingdom.

However, developments in the regulatory arena are moving at a fast pace and a considerable amount of what previously constituted guidance has now become a legal requirement. Moreover, an impressive range of guidance documents dealing with various aspects of conducting clinical trials has been published by Health Authorities and other stakeholder organisations around the world in recent years. Hence, many readers still feel the benefit from a comprehensive, largely jargon-free document that outlines the framework within which Phase 1 research is conducted and provides pointers for further, more in-depth reading. The ABPI therefore decided to release an updated version of the 2007 edition.

In addition to recent regulatory changes, the new edition contains the latest ABPI guidance on insurance and trial subject compensation. It also responds to the feedback received from many stakeholders, several of which had commented that the guidelines had become over-prescriptive in places, especially in the sections on premises and facilities. Thus, these sections have been scaled down.

The new edition is in line with the references cited below:

- Potential new medicines are called investigational medicinal products (IMPs).[7]
- Clinical trials of an IMP that do not benefit subjects – whether they be healthy subjects or patients – are called phase 1 or non-therapeutic trials.[7]
- The premises where trials are conducted are called phase 1 units, or simply units.
- People who take part in clinical trials are called subjects:[7] healthy subjects when they are truly healthy, and patients when they have the disease for which the IMP is being developed.
- The discipline that underpins phase 1 trials is called clinical or human pharmacology.[8, 9]

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1: Developing a new medicine

The pharmaceutical industry is the main sponsor of medicines research in the UK. Sponsors have to demonstrate the safety, quality and efficacy of a potential new medicine – called an investigational medicinal product (IMP) – through a series of rigorous trials in humans in order to obtain a licence, so that doctors can give the medicine to patients.

However, before an IMP can be given to humans, sponsors must first test it thoroughly in animals. The main aims of these pre-clinical studies are:

- to find out the effects of the IMP on body systems (pharmacodynamics)
- to study the blood levels of the IMP, and how it is absorbed, distributed, metabolised and eliminated after dosing (pharmacokinetics)
- to find out if a range of doses of the IMP, up to many times higher than those intended for use in humans, are toxic to animals[10] and if so, to identify the target organs and the margin of safety in terms of (a) the no-observed-adverse-effect dose level (NOAEL) relative to body weight and (b) IMP exposure – the concentration of IMP in the bloodstream over 24 hours (toxicokinetics),[11] and
- to make a formulation of the IMP, such as a capsule or injection, suitable for early studies in humans.

After the pre-clinical studies, there are four phases of trials in humans, which in practice often overlap. Phases 1 to 3 are done before a licence is granted and Phase 4 is done after authorisation to market the drug. The phases are different in terms of the number and types of subject studied, and the questions asked. The numbers in the table are indicative only and can vary.

Phase	Number and type of subject	Questions
1	50–200 **healthy subjects** (usually) or **patients** who are not expected to benefit from the IMP	• Is the IMP safe in humans? • What does the body do to the IMP? (*pharmacokinetics*) • What does the IMP do to the body? (*pharmacodynamics*) • Might the IMP work in patients?
2	100–400 **patients with the target disease**	• Is the IMP safe in patients? • Does the IMP seem to work in patients? (*efficacy*)
3	1000–5000 **patients with the target disease**	• Is the IMP really safe in patients? • Does the IMP really work in patients?
4	many thousands or millions **patients with the target disease**	• Just how safe is the new medicine? (*pharmacovigilance*) • Does the medicine work in the real world? (*real world data collected to demonstrate value*) • How does the new medicine compare with similar medicines?

Phases are also often subdivided. For instance, small-scale, exploratory efficacy studies in a limited number of patients may be referred to as 'Phase 2a'. In contrast, slightly larger trials that test the efficacy of a compound at different doses ('dose-range finding' studies) might be designated 'Phase 2b'.

Phases 1 to 3 can take up to 10 years for a successful IMP. However, many IMPs are withdrawn from development, mainly because:[12]

- they are not well-tolerated or safe enough in humans, or
- their pharmacokinetic or pharmacodynamic profile in humans is disappointing, or
- they do not work or do not work well enough in patients with the target disease.

In a 10-year review of IMPs[13], only 60% progressed from Phase 1 to 2, and a mere 11% became a marketed product. Phase 1 trials can identify IMPs with potential for success as well as excluding failures and thereby preventing unnecessary exposure of the IMP to many more subjects.

The past decade has seen the introduction of exploratory studies that are performed prior the traditional Phase 1 Single-Dose Escalation. These studies, which involve exposure of a limited number of subjects to a much-reduced dose (also referred to as a *micro-dose*) of a novel compound, are beyond the scope of these guidelines, which only cover conventional Phase 1 experimental studies. Guidance on this type of study can be obtained from the Food and Drug Administration (FDA) as well as the European Medicines Agency.[14, 15]

While the categorisation of human drug development trials into distinct phases implies chronology, in practice there can be considerable overlap. A range of Phase 1 studies is performed when the IMP is already in a more advanced stage of development.

A Phase 1 study is defined as a non-therapeutic, exploratory trial in human subjects who may be healthy or have a specific disease. In contrast to later phase studies, subjects can usually expect no therapeutic benefit from a Phase 1 trial.

The primary parameters tested in Phase 1 studies (which can involve single or multiple doses of the IMP) are:

- Safety and tolerability
- Pharmacokinetics
- Pharmacodynamics

There is a range of distinct Phase 1 studies, each of which is designed to address a particular question or set of questions:

First-in-Human trial

The first trial of an IMP in humans is usually a trial of single doses given in increasing amounts. The aims are to assess the tolerability, safety, pharmacokinetics and, if possible, the pharmacodynamic effects of the IMP, and to compare the results with those from the pre-clinical studies. Details about the conduct and design of these trials can be found in the ABPI's First *In Human Studies* guidelines.[16]

Subsequent trials

After the First-in-Human trial, the next one is usually a trial of multiple ascending doses. Examples of other Phase 1 trials are trials to assess:

- the effects of potential influences, such as food, gender, age and genetic differences, on the activity of the IMP
- the relationship between dose or concentration of the IMP and the response – for example, by measuring biomarkers[17] or using challenge agents (Section 18)
- the possible interaction of the IMP with marketed medicines
- the absorption, distribution, metabolism and elimination of a radiolabelled IMP
- the bioavailability or bioequivalence of the IMP,[18] and
- the effect of the IMP on the QT interval of the electrocardiogram (ECG).[19]

There is an increasing tendency for sponsors to combine the first single-dose and multiple-dose trials of an IMP, and even add a trial of the effect of food or age, so that the First-in-Human trial is merely the first of a 'bundle' of trials.

Some of these trials, such as the interaction trials and QT-interval trial, may be done during any stage of development of an IMP. While it is customary to refer to pharmacokinetic studies as 'Phase 1', it is not very helpful and might lead to confusions.

2: Regulations

In recent years, there have been many changes to the regulatory aspects of clinical trials. Most changes stem from the introduction of Good Clinical Practice (GCP), Good Manufacturing Practice (GMP) and the Clinical Trials Directive, which is based on GCP and GMP. The main documents are:

- International Conference on Harmonisation (ICH) Guideline for GCP[20]
- European Union (EU) Clinical Trials Directive 2001/20/EC[21]
- GMP for Medicinal Products. EudraLex Vol. 4[22, 23] and Annexes, especially Annexes 1,[24] 13[25] and 16[26]
- Directive 2003/94/EC on GMP for Medicinal Products and IMPs[27]
- Directive 2005/28/EC on GCP[28]
- Governance Arrangements for Research Ethics Committees (GAfREC)[29]
- Standard Operating Procedures (SOP) for Research Ethics Committees (REC)[30]
- European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), July 2007. Guideline on strategies to identify and mitigate risks for first in human trials with Investigational Medicinal Products (EMEA/CHMP/SWP/28367/07).[31]

The Clinical Trials Directive was implemented in the UK through the Clinical Trials Regulations[7] in May 2004 or Statutory Instrument (SI) 2004/1031. The SI has since been amended on an annual basis. Its aims are:

- to simplify and harmonise clinical trials across Europe
- to give better protection to subjects who take part in clinical trials, and
- to enforce by law the principles of GCP and GMP.

In addition to the Clinical Trials Directive, the European Commission has published a set of guidelines covering a range of clinical trial aspects (EudraLex, Vol. 10).[22] EudraLex is a 10-volume body of regulations and guidelines governing medicinal products in the European Union.
The scope of the Clinical Trials Directive is wide; it covers all commercial and academic clinical trials of IMP and marketed medicines, apart from trials of marketed medicines prescribed in the usual way. The types of IMP are:

- chemical entities
- biotechnology products
- cell therapy products
- gene therapy products
- plasma derived products
- other extractive products
- immunological products, such as vaccines, allergens and immune sera
- herbal products
- homeopathic products
- radiopharmaceutical products.

In addition, a placebo, or a marketed product used or assembled in a way different from the approved form, is an IMP when used as a comparator.

The impact of the Clinical Trials Directive on Phase 1 trials is as follows.

- Trials of IMPs in healthy subjects are now regulated. They were excluded from the Medicines Act 1968[32] because healthy subjects get no therapeutic benefit from an IMP. All non-therapeutic trials of IMPs – whether they involve healthy subjects or patients – are now called Phase 1 trials.[7]
- Sponsors must apply to and receive approval from the Medicines and Healthcare products Regulatory Agency (MHRA) for a Clinical Trial Authorisation (CTA), and for substantial protocol/CTA amendments.
- Investigators must apply to and receive approval from a REC (Section 13) for the protocol and substantial amendments; the type of REC depends on whether the trial is in healthy subjects (Type 1) or patients (Type 2 or 3). Previously, any REC could review a Phase 1 trial.
- The MHRA and REC must respond to applicants within 30 and 60 days, respectively. (They have longer for biological IMPs – Section 16.) Both must respond to protocol amendments within 35 days.
- Whoever imports, manufactures, assembles or repackages IMPs must have a Manufacturer's Authorisation [MIA (IMP)] from the MHRA and must follow GMP, just like manufacturers of marketed medicinal products.
- Sponsors from third countries – countries from outside the European Economic Area[33] (EEA), such as Japan and USA – must manufacture IMPs at least to EU standards. Also, they must have a legal representative in the EU.
- Sponsors must get a European Clinical Trials Database (EudraCT) number for all trials, and send safety information to the MHRA and REC.
- The MHRA must inspect sponsors, trial sites and other trial-related activities to check that the Clinical Trials Directive is being followed.

The First-in-Human trial of TGN1412[34] has also had a big impact on Phase 1 trials. All subjects who received it had severe adverse reactions. As a result, the UK Government set up the Expert Scientific Group (ESG) to consider the transition from pre-clinical to First-in-Human Phase 1 trials, and the design of these trials, with specific reference to:

- biological IMPs with a novel mechanism of action
- IMPs with highly species-specific activity
- IMPs that target the immune system.

The findings and recommendations of that group were published in a report in 2006 and have influenced regulatory guidance on Phase 1 trials (Section 4).

3: MHRA

CTA application

The sponsor of a clinical trial of an IMP must submit a CTA application to the MHRA. There is an algorithm for deciding if a trial requires a CTA.[22] The MHRA must respond to a valid application within 30 days (longer for certain biotechnology products – Section 12).[7] However, applications for Phase 1 Healthy Volunteer Studies are usually assessed and processed within 14 days or fewer.[6]

The MHRA reviews trials of higher-risk IMPs (see Section 4) differently from trials of other IMPs. They seek advice for First-in-Human trials of higher-risk IMPs from the Expert Advisory Group of the Commission on Human Medicines (CHM) before approval can be given. Sponsors can seek advice from the MHRA about whether their IMP is higher risk. First, they must submit a summary of the nature of the IMP, its target or mechanism of action, and the relevance of the animal model(s).

Protocol amendments

The MHRA reviews any substantial protocol amendments, and is allowed 35 days to do so. In reality, the agency reviews Phase 1 protocols in a much shorter time-frame, typically within 14 days. Some amendments for Phase 1 trials need to be reviewed quickly to keep the study running smoothly. However, the MHRA has no formal procedure for expedited review. Therefore, whoever writes the protocol should try to allow for unforeseen findings and thereby avoid protocol amendments.

Inspections

The MHRA can inspect any site involved in a clinical trial. The inspectors assess GCP and GMP compliance separately. Inspections are compulsory, system- or trial-specific, and may be announced or unannounced. Units should be prepared for an inspection at any time.

The inspector prepares for an inspection by reviewing the sponsor's CTA application and requesting and reviewing documents from the site, such as SOP, details of computer systems critical for GCP, charts of how the staff are organised, and contracts.

During the visit, the inspector starts by meeting key staff, and then interviews selected staff, inspects the facilities, and reviews relevant documents and records. The inspector gives verbal feedback to staff at the end of the visit.

After the visit, the inspector writes and circulates a report (urgent action may be required before this); requests and reviews the investigator's or site's responses to the findings (which are graded in the report); and makes conclusions and recommendations (this might include re-inspection or enforcement action).

In 2007 the MHRA introduced a scheme of voluntary accreditation. Under this scheme, units are inspected by the agency against sets of pre-defined standard or supplementary classification criteria. The latter is required for units performing trials across the entire Phase 1 range, including First-in-Human trials, with risk factors that would require a review by the *Clinical Trials Expert Advisory Group of the Commission on Human Medicines* (CTEAG – see above). While the scheme is still voluntary, it has found widespread acceptance and Phase 1 units are encouraged to apply for MHRA accreditation to demonstrate that they meet those criteria.

Detailed information about the scheme, including a Question & Answer document, can be found on the MHRA's website.[15]

Breaches of GCP or trial protocol

The sponsor or delegate must notify the MHRA within seven days of any serious breach of GCP or the protocol. A serious breach is one that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial, or
- the scientific value of the trial.

Sponsors and investigators should have a procedure in place to assess whether a deviation from the protocol or a failure to comply with the principles of GCP constitutes a serious breach. The sponsor has responsibility for assessing the impact of the breach on the scientific value of the trial. The MHRA offers guidance on identifying and notifying serious breaches, and the consequences.

4: Risk assessment

All IMPs

Subjects who volunteer for Phase 1 trials get no therapeutic benefit from the IMP, so the risk of harming the subjects must be minimal.[5] The risk must be fully assessed before each trial, especially during the transition from pre-clinical studies to the First-in-Human trial, when uncertainty about tolerability and safety of the IMP is usually at its highest. The sponsor must have the pre-clinical data reviewed by people who have the appropriate technical, scientific and clinical expertise. At least one reviewer should be independent of the project. Sponsors that do not have the expertise themselves must use external advisers instead. All aspects of the IMP – such as its class, novelty, species specificity, mode of action, potency, dose- and concentration-response relationship for efficacy and toxicity, and route of administration – must be taken into account. Risk must be assessed on a case-by-case basis, and there is no simple formula. The seriousness of possible adverse reactions and the probability of them happening must both be considered.[5]

Higher risk IMPs

The ESG Report[35] deemed some agents to have a 'higher potential for risk of harm to volunteers during the first human exposures'. The group provided examples of factors that should trigger particular caution:

- any agent that might cause severe disturbance of vital body systems
- agents with agonistic or stimulatory action
- novel agents or mechanisms of action for which there is no prior experience
- species-specificity making pre-clinical risk assessment difficult or impossible
- high potency, eg compared with a natural ligand
- multifunctional agents, eg bivalent antibodies
- cell-associated targets
- targets that bypass normal control mechanisms
- immune system targets, and
- targets in systems with potential for large biological amplification *in vivo*.

The term 'higher risk' means that the assessment of the IMP needs even greater care and expertise than is usual; it does not mean that the risk to the subjects can be more than minimal. The EMA *Guideline on strategies to identify and mitigate risks for first in human trials with Investigational Medicinal Products*[31] provides advice on risk factors to consider in FIH trials, particularly but not exclusively around:

- mode of action
- nature of the target
- relevance of animal models.

A copy of the risk factors listed in the guideline can also be found in the ABPI document *First in Human Studies: Points to Consider in Study Placement, Design and Conduct*.[16]

Other factors

The risk assessment must also take into account other factors, such as the procedures and any non-IMP (Section 17) used in the trial, and whether the trial should be done in healthy subjects or patients.

5: Risk management

Before every Phase 1 trial, as well as assessing risk and justifying that assessment, there must be a strategy for ensuring that any risk is minimal throughout the trial.

Should potential investigators be concerned about the level of risk of the IMP, the sponsor must give them access to people with responsibility for the relevant pre-clinical work. Also, the sponsor's physician should liaise with the investigator. If investigators still have concerns about pre-clinical data, they should consult an independent adviser.

Assessment and management of risks should be documented (eg through a risk management plan). The strategy for managing risk should consider all aspects of the trial.

Starting dose

Previous ABPI guidelines[2] suggested that the starting dose of an IMP should be a small fraction – not more than 10% – of the predicted therapeutic dose.

The FDA Guidance[36] method of calculating the safe starting dose in man follows a stepwise process:

- first, convert the NOAEL from the toxicology studies[10] to a human equivalent dose (HED) on the basis of body surface area
- then, select HED from the most appropriate species
- after that, apply a safety factor (≥10-fold) to give a Maximum Recommended Starting Dose (MRSD)
- finally, adjust the MRSD on the basis of the predicted pharmacological action of the IMP.

This method is simple and supported by a wealth of historical evidence. But the emphasis is on selecting a dose with minimal risk of toxicity, based on the NOAEL, rather than selecting one with minimal pharmacological activity in humans. Also, the focus is on the dose of the IMP rather than exposure.[11]

Following the recommendations of the ESG report,[35] the EMA *Guideline on strategies to identify and mitigate risks for first in human trials with Investigational Medicinal Products*[31] advises the use of a different approach to calculate a safe starting dose for high-risk agents, based on the minimal anticipated biological effect level (MABEL).[37] This approach uses all relevant information, taking into account: novelty; potency; mechanism of action; degree of species-specificity; dose-response data from human and animal cells *in vitro*; dose- and concentration-response data from animals *in vivo*; pharmacokinetic and pharmacodynamic modeling; calculated target occupancy versus concentration; and concentration of the target or target cells in humans *in vivo*.

If different methods give different estimates, the lowest value should be taken and a margin of safety built into the actual starting dose. If the pre-clinical data are likely to be a poor guide to responses in humans, the calculated starting dose should be reduced, and the dose increased in smaller increments lest the dose-response curve be steep. A detailed discussion of the MABEL can be found in a recent paper by Muller *et al*.[37]

Increasing the dose

In an ascending dose trial, the dose is often increased three- to five-fold at each increment at the lower doses and smaller increments around the expected therapeutic range. Increases in dose, and the amount, should be made only after carefully assessing all of the available data from previous doses. Serial measurements of the IMP in blood during the trial allow increases in dose to be guided by exposure to the IMP.[11] As a general rule, the 'dose/toxicity or dose/effect relation observed in non-clinical studies, depending on which is steeper, should guide the dose increment between the two dose levels. The steeper the increase in the dose/toxicity or dose/effect curves, the lower the dose increment that should be selected.'[38]

The investigators and the sponsor's physician, and the sponsor's expert in pharmacokinetics, if appropriate, should review all of the available data, including the pre-clinical data, before deciding to increase the dose. Sponsors without a physician experienced in First-in-Human studies should use an independent medical monitor. An intermediate dose should be given if there are any concerns about tolerability and safety of the IMP or exceeding the NOAEL, but only if the protocol (Section 7) allows. The basis of all decisions on increasing the dose must be documented.

Administration of doses

The number of subjects dosed on any one occasion, and the interval between dosing individual subjects and cohorts of subjects, will depend on the IMP, its route of administration, and the type of trial. For example, only one subject should be given an active IMP at the very first administration of a high-risk IMP. And if the route of administration is intravenous, the dose should be given by slow infusion, perhaps over several hours, rather than by rapid injection, unless there is a good reason for that method. The protocol should include details for the rate and duration of infusion. In contrast, if the IMP is of low risk and the route of administration is oral, cohorts of subjects can be dosed on the same occasion, and at short intervals, say every 5–10 minutes.

Facilities and staff

First-in-Human trials of an IMP are regarded as higher risk than later Phase 1 trials. However, the risk during transition from pre-clinical studies to the very First-in-Human trial may be no higher than it is during other transition trials, such as from single to multiple doses, from young to elderly subjects, and from administration of the IMP alone to giving it with established medicines during interaction trials. Sponsors must place their trials of an IMP – especially a First-in-Human trial and other transition trials – with Phase 1 units, including their own, whose staff, premises and facilities (Section 9) match the level of risk of the IMP. Furthermore, investigators must not take on trials of an IMP for which they do not have adequate experience or training (Section 10).

The investigator must assess the risk of harm, by reviewing the protocol, investigator's brochure, IMP dossier, CTA application (Section 12) and, as required by the Declaration of Helsinki,[39] any relevant medical and scientific literature. In addition, the investigator must weigh the foreseeable risks and inconveniences against the expected benefits for the individual subject, and for future subjects with the target disease. Finally, the investigator must explain and justify any risks in the information leaflet for trial subjects (Section 11) and in the REC application (Section 13).

Appendix 1 of the MHRA's accreditation scheme document lists a range of standards relating to facilities, staff and procedures that are expected to be met by clinical research units conducting Phase 1 studies in the UK. These standards serve as guidance even for units that opt not to apply for accreditation.

Procedures

Non-invasive trial procedures should be used whenever possible. If invasive procedures – such as an arterial cannula, a biopsy or an endoscopy – are used, they must be done or supervised by someone skilled in the procedure.

Subjects

The decision as to whether a Phase 1 trial should be conducted in healthy subjects or patients should be made on a case-by-case basis. Compared with patients, healthy subjects are easier to find, more robust, free of other medicines, more likely to respond uniformly, and better at completing long and complex trials. Typically, healthy subjects tolerate IMPs better than patients.[42] On the other hand, for some IMPs, obese subjects or subjects with high serum cholesterol may be more suitable than truly healthy subjects. Other IMPs – such as cancer therapy and most types of gene therapy (Section 12) – should be given only to patients with the target disease (Section 11). Pharmacokinetic and/or pharmacodynamic findings in healthy subjects might have limited predictive value compared to the situation in patients.

6: Safety record of Phase 1 trials

Reviews of the safety of Phase 1 trials show that they have a good safety record.[40 - 42] Overall, the incidence of serious adverse events related to the IMP was about 0.02%. However, some healthy subjects have died. A man died of cardiac arrest after taking an IMP in a trial in Ireland in 1984. When he was screened for the trial, he did not declare that he had recently been given a depot injection of an anti-psychotic medicine.[43] A woman died after receiving a high dose of lidocaine – a widely used local anaesthetic – to prevent discomfort from endoscopy in a trial in the USA in 1996.[44] She was discharged soon after the procedure and died at home. Another woman with mild asthma died of lung damage after inhaling hexamethonium in a trial in the USA in 2001.[45] Hexamethonium is an old medicine – given by injection to treat conditions other than asthma – and is now rarely, if ever, used. Lung toxicity of hexamethonium was first reported many years ago.[46]

These cases show that established medicines as well as IMPs have the potential to harm subjects in Phase 1 trials. Also, they highlight the need to:

- contact the subject's General Practitioner (GP) to check the medical history (Section 11)
- keep subjects overnight when necessary, and
- review all the relevant scientific and medical literature before starting a clinical trial.

At one time, almost all IMPs were new chemical entities (NCE). Now, many are biological in nature (Section 16). Many biological IMPs – such as proteins,[47] cytokines,[48] and monoclonal antibodies[49, 50] – have been tested safely in First-in-Human trials in healthy subjects or in patients. However, compared with NCE, there is a paucity of data about their overall safety. Some reasons why biological IMPs, especially monoclonal antibodies, should be seen as different from NCE are:

- Proteins can cause anaphylactic or infusion reactions.
- Even a single dose of a fully humanised protein can induce an immune response.[51]
- There is a report of a delayed hypersensitivity reaction[52] to re-challenge with a monoclonal antibody after a long period of non-exposure.

- Two monoclonal antibodies[53, 54] in clinical use have caused progressive multifocal leukoencephalopathy(PML), a rare and usually fatal infection of the brain and spinal cord due to reactivation of a virus (JC polyoma) which most people carry. However, PML has almost always occurred in patients with profound immune dysfunction.
- TGN1412 – a monoclonal antibody that differs from those in clinical use in that it activates rather than blocks an immune response – caused a 'cytokine storm' and organ failure in all six previously healthy subjects who received it in a First-in-Human trial.[34]

If the risk of giving a biological IMP to healthy subjects is more than minimal, patients with the target disease might be studied instead (Section 11). However, the substitution of patients for healthy volunteers must be carefully considered, especially if no potential benefit is expected to arise from participation in the study. Their condition might make patients more susceptible or less tolerant to unwanted effects from the investigational product. Also, the mass of tissue being targeted by the IMP may be much increased in patients compared with healthy subjects. A careful risk/ benefit analysis should be performed before deciding on the appropriate study population. Properly validated biomarkers[17] may help monitoring potential risks.

7: Protocol

A clinical trial must be scientifically sound and described in a clear, detailed protocol.[22] Compared with the protocol for an IMP at later phases of development, the protocol for a Phase 1 trial should emphasise:

- the pre-clinical information – such as pharmacology and toxicology – about the IMP
- the assessment of risk of harm from the IMP, trial procedures and any non-IMP (Section 18), the justification of that assessment, and how the risk will be kept minimal throughout the trial
- the methods of deciding: the first dose; the maximum dose; the increases in dose; the route of administration; the rate of administration of intravenous doses; the interval between dosing individual subjects; and the number of subjects to be dosed on any one occasion; the minimum set of data or subject numbers required for decision-making
- any assessment of dose- or concentration-response relations
- any pharmacy work needed to prepare doses of the IMP for administration (Sections 14 and 15)
- stopping or withdrawal criteria.

Many Phase 1 trials, especially the early ones, cannot be completed without protocol amendments. There are three types – substantial, urgent and minor. An amendment is substantial if it is likely to have a significant impact on:

- the safety or physical or mental integrity of the trial subjects
- the scientific value of the trial
- the conduct or management of the trial, or
- the quality or safety of any IMP used in the trial.

The sponsor decides whether an amendment is substantial, and whether a substantial amendment requires MHRA and/or REC approval. Guidance on what constitutes a substantial amendment can be found in CT1 Vol 10, as well as the SOP of the National Research Ethics Service (NRES). The investigator and sponsor may implement a substantial amendment without REC and MHRA approval, respectively, if the change is an urgent safety measure to protect the trial subjects. However, the investigator and sponsor must notify the REC and MHRA within three days afterwards – by telephone first and then by a written report.

In order to cope with unexpected findings, and to prevent the need for protocol amendments, an appropriate degree of flexibility should be built into the protocol. For example, there should be scope to modify dose increments and frequency of blood sampling as safety and pharmacokinetic data become available. Additionally, the investigators should be able to use their clinical judgment to allow inclusion of subjects with minor out-of-range results of safety tests of blood and urine, and minor variants of the ECG.

The need to increase efficiency in the drug development process has seen the introduction of more flexible protocol designs (so-called 'adaptive designs'), where progression within a given study (eg subsequent doses in an ascending dose study) is not dictated by the protocol but by the results of individual trial sections. In such a setting, the protocol would simply provide the framework (eg minimum and maximum doses to be administered) but leave the exact dose at any given step and the number of steps to be determined during the trial depending on interim results, thus being 'adaptive' to the findings during the trial.

8: Contracts

When entering into an agreement to conduct a trial, the sponsor must provide the investigator with copies of: the protocol, up-to-date investigator's brochure, IMP dossier, CTA application and approval letter, indemnity, and insurance (Section 22), all of which the investigator must review.

If the investigator agrees to do the trial, there must be a written, dated and signed trial-specific contract between the sponsor and the investigator, and between the investigator and any subcontractors, which sets out the obligations of the parties for trial-related tasks and for financial matters. Examples of subcontractors are a laboratory and a commercial archivist. The protocol may serve as the basis of a contract. In order to protect the trial subjects, contracts must be in place before the start of the trial.

The contract between the sponsor and the investigator should state that the investigator agrees to:

- start the trial only after it has been approved by the MHRA and REC
- start and complete the trial in realistic times
- undertake all the trial-related duties and functions allocated by the sponsor to the investigator
- carry out the trial according to the Clinical Trials Regulations and Amendments, GCP, GMP, all relevant regulatory requirements, and the protocol agreed to by the sponsor and approved by the MHRA and REC
- comply with procedures for recording or reporting data
- allow direct access, by the sponsor's monitors and auditors, and by the MHRA and REC, to the trial site, and to source documents, source data, and reports.

Also, the contract should include statements relating to:

- confidentiality, publication policy, payments, reasons for non-payment, stopping the trial, storing and destroying trial-related documents, any equipment provided by the sponsor, and ownership of trial materials, records and results, and
- the sponsor abiding by Section 22 of these ABPI guidelines about compensation for injury to trial subjects and indemnity for the investigator.

Units that manufacture or import IMPs must have a technical agreement with the sponsor (Section 15).

The sponsor may transfer any or all of their trial-related duties and functions to a CRO. The CRO must have sound finances, so that they can meet their contractual obligations. Thus, in these ABPI guidelines, what applies to the sponsor may also apply to a CRO. However, the sponsor retains overall responsibility for the trial.

9: Trial subjects

Recruitment

Potential trial subjects may be recruited:

- from a paper or electronic database of people who have indicated their willingness to take part in a trial
- by advertisements in a newspaper or magazine, or on a noticeboard in places such as a university or hospital, or on the radio or television, or on a website
- by word of mouth, or
- by referral from another doctor.

All study-specific advertisements must be approved by a Research Ethics Committee The Clinical Trials Directive guidance document on REC applications[22] and the ABPI Medical Commission Guideline[55] give advice about advertising for subjects for clinical trials. Advertisements should say that the trial involves research and that the advertisement has been approved by a REC, and should give a contact name and phone number and some of the selection criteria. In addition, advertisements may give the purpose of the trial, where it will take place and the name of the company or institution carrying it out. However advertisements must never over-stress payment, use REC or MHRA approval as an inducement, name and promote the product, or claim that it is safe.

In contrast to study-specific advertisements, general advertising and screening procedures do not need to be reviewed by an ethics committee. General screening constitutes non-invasive procedures that are undertaken to evaluate a subject's eligibility to join a trial unit's volunteer panel. Further guidance can be obtained from Section 4.55 of the Standard Operating Procedures For Research Ethics Committees (of the United Kingdom).[30]

Whatever the method of recruitment, subjects must be recruited of their own free will. They should not be made to feel obliged to take part in a trial, nor should they suffer in any way if they do not take part. Additionally, they should be recruited only if they:

- are capable of giving valid consent, and
- have been fully and properly informed so that they understand:
  - the nature and purpose of the trial
  - any risks, either known or suspected, and any inconvenience, discomfort or pain that they are likely to experience
  - that they can withdraw at any time and without giving a reason
  - that the investigator may withdraw them at any time if they do not follow the protocol or if their health is at risk.

All units must keep records of subjects who take part in their trials and avoid excessive use of any subject. The number of trials that a subject may take part in during any 12-month period will depend on:

- the types of IMP and their half-lives
- the routes of administration of the IMP

- the frequency and duration of exposure to the IMP
- the procedures involved, and
- the total volume of blood taken from the subject.

Subjects must not:

- take part in more than one trial at a time
- receive more than 10 milliSievert of radioactivity (Section 17) in any 12-month period.

In general, subjects should not receive an IMP systemically less than three months after the previous one. However, on occasions a shorter interval may be justified, especially when using well-characterised, marketed drugs with a short half-life and little risk of carryover effects.

Monitoring overexposure

Trial subjects must provide proof of identity before they take part in a trial and should be monitored and prevented from taking part in too many trials. The ways to ensure this are:

- counselling the subject
- including warnings in the information leaflet and consent form
- for units to keep a register of their clinical trials and subjects who have taken part in them – keeping photographic evidence of a subject's identity should be considered
- contacting the GP
- being vigilant when screening trial subjects, eg look for evidence, such as needle marks on the forearm and low blood counts, that the subject may have taken part in a trial recently, and
- using an internet-based central register called TOPS,[56, 57] which is run by a registered charity and used by most UK Phase 1 units.

REC applications must include information about procedures for checking simultaneous or recent involvement of potential subjects in other trials.[7]

Special populations

Women

A woman capable of having a child should take part in a trial of an IMP only if:

- the reproductive toxicology studies have been completed and the results raise no concern against participation in clinical trials[58] or there is a good reason why reproductive toxicology studies are not needed
- she is not pregnant, according to her menstrual history and a pregnancy test
- she will not be at risk of becoming pregnant during and for a specified interval after the trial
- she is warned about the potential risks to the developing child should she become pregnant, and
- she is tested for pregnancy during the trial, as appropriate.

Women using a hormonal contraceptive, such as 'the pill', should use an alternative method of contraception until the possibility of an interaction with the IMP has been excluded.

Children

IMPs should be tested in healthy children only if the circumstances are exceptional and the guidelines for trials in children are followed.[59, 38]

Elderly

Trials of IMPs in elderly subjects are justified if the product is intended for use in the elderly, and especially if its effects and metabolism might differ from those in younger subjects.

Vulnerable subjects

Investigators must be wary of recruiting vulnerable trial subjects, such as the unemployed, or employees of the company or students of the institution that is sponsoring or carrying out the trial. Employees and students are, or may feel, vulnerable to pressure from someone who can influence their careers. Should such subjects decide to take part in the trial, they must be dealt with like other subjects in the trial, and not be allowed to let their normal work interfere with the trial. The investigator should forewarn employees, in a written agreement, of the possible implications of having their personal data processed at work by their colleagues. Employees and students may need to get permission from their employer or institution beforehand. Some sponsors bar use of employees from trials of IMPs.

Patients

All non-therapeutic trials of IMPs – whether they involve healthy subjects or patients – are now called Phase 1 trials.[7] The following are examples of Phase1 trials involving patients.

- Subjects who are well but have a chronic, stable condition – such as asthma, hayfever, type 2 diabetes or hypertension – may be given single doses or short courses of an IMP from which they do not benefit therapeutically. Such trials, especially if they include a challenge agent (Section 18), can help decide whether or not to proceed to trials in larger numbers of patients, who may benefit therapeutically.
- The First-in-Human trial of a cytotoxic IMP to treat cancer is sometimes single-dose rising in design, to assess the pharmacokinetics of the IMP. Such trials have to be done in patients.
- Regulatory authorities usually want sponsors to do trials on the pharmacokinetics of an IMP in patients with varying degrees of impaired kidney or liver function, and if necessary to recommend adjustments to the dose in such patients. Such trials are difficult to do because of slow patient recruitment and ethical concerns. For those reasons, they are usually done late in the development of the IMP.

Payments

Many trials are demanding of the subject and involve long periods of residence, many visits to the trial site, urine collections, and multiple blood tests and other procedures that cause discomfort, as well as lifestyle restrictions. So it is right to pay subjects – healthy subjects and patients – who volunteer for Phase 1 trials more than just any expenses that they incur.[5] The amount should be related to the duration of residence on the unit, the number and length of visits, lifestyle restrictions, and the type and extent of the inconvenience and discomfort involved. As a guide, payments should be based on the minimum hourly wage[60] and should be increased for procedures requiring extra care on the part of the subject or involving more discomfort.[5] Payment must never be related to risk.

Subjects who withdraw or are withdrawn even for medical reasons should not always be paid the full amount. The investigator should decide the amount of payment depending on the circumstances. Payment may be reduced, if a subject does not follow the protocol, or may be increased, if the protocol is amended to allow further tests or visits.

If a trial is postponed or cancelled, subjects may be paid for setting aside time to do the trial. Reserve subjects, who 'stand by' in case someone drops out or are withdrawn from the trial before first dosing, should be paid.

The policy on paying trial subjects, and the amount, must be stated in the subject information leaflet and be approved by the REC.

Obtaining informed consent

The investigator or delegate must:

- obtain the consent of subjects only after the REC has approved in writing the information and consent form
- fully inform potential trial subjects before they agree to take part in the trial
- give the subjects oral and written information that is free of jargon and is easy to understand
- give the subjects enough time and opportunity to ask questions about the trial, answer their questions accurately and honestly, and ensure that they understand the answers
- ensure that neither the investigator nor other staff coerce subjects to take part or continue to take part in the trial
- give the subjects, in writing and after approval of the REC, any new information that might make them change their mind about taking part in the trial, and
- ensure that the subjects, and who informs them, sign and date a consent form, and are given a copy.

Details of the contents of the information and consent form are in Appendix 2. NRES has issued guidelines[61] for writing information and consent forms for clinical trials. The Plain English Campaign[62] gives advice about how to write medical documents for members of the public.

Screening

The investigator should judge trial subjects suitable on the basis of tests, such as:

- a medical history and examination
- medicines taken within a set period before the start of the trial
- a 12-lead ECG
- routine safety tests of blood and urine
- tests for drugs of abuse – such as alcohol, cannabinoids, cocaine, morphine, benzodiazepines, barbiturates and amphetamines
- tests for HIV, hepatitis B and hepatitis C
- pregnancy tests in women capable of having a child and at risk of becoming pregnant
- trial-specific tests, such as 24-hour ambulatory ECG, echocardiogram, lung function tests, kidney function tests and genetic tests
- for IMPs that affect the immune system: tests to exclude active or recent infections, such as tuberculosis and genito-urinary infection, and willingness not to travel to countries for which vaccinations are intended or that present a higher risk of infectious diseases during the period that the IMP may be active, and
- information from the General Practitioner.

Before subjects decide to have the tests for viruses and for drugs of abuse, the investigator must explain to them what will happen if one of the tests turns out to be positive.

Healthy subjects often have minor out-of-range results of safety tests of blood and urine, and minor variants of the ECG. For example, serum transaminases that are out-of-range,[63] red blood cells in the urine,[64] and nodal rhythm of the ECG[65] are common findings. Some monitors and auditors regard these as deviations from the protocol of a trial in healthy subjects. However, usually they have no clinical relevance and do not justify excluding subjects from a trial. A physician should decide their clinical relevance, and the protocol should allow for use of clinical judgement. If subjects are deemed unsuitable for a trial, they should be told why.

Investigators should ask potential trial subjects if they have taken part in a study in previous months. In addition, they should look for evidence, such as needle marks on the forearm and low blood counts, that the subject may have taken part in a trial recently.

Timing of recruitment and screening

Panel: Investigators can recruit and screen subjects at any time for a panel of subjects interested in taking part in a Phase 1 trial, providing the REC has given written approval of the 'screening' protocol and the subjects have given written consent.

Specific trial: Investigators can start to recruit subjects for a specific trial after the REC has given written approval. However, investigators must not screen subjects for a specific trial before obtaining written approval of both the REC and MHRA, and of course the subjects.

If the investigator has REC approval for panel recruitment and screening, and if the sponsor agrees, the investigator may transfer subjects and their data from a panel to a specific trial, but only after the REC and MHRA have both given written approval for the specific trial and the subject has given written consent for the specific trial. Before transferring subjects, investigators must not carry out procedures that are not covered by the protocol for panel recruitment and screening.

Identification

Subjects who are judged suitable at screening should be photographed to check their identity at subsequent visits to the unit. Subjects who are resident in the Phase 1 unit should be fitted with some form of identification, such as a wristband, with the subject's number and trial code. The subject's identity must be checked before carrying out procedures, such as taking blood samples, giving the trial IMP, or recording information in the case report form. The subject's number or barcode should be used on all samples and results.

Informing the subject's General Practitioner

The investigator should ask potential trial subjects for permission to contact their General Practitioner (GP). Subjects who do not have a GP or do not want their GP to be contacted should be excluded from the trial unless there is a good reason to the contrary.

The investigator should inform the GP that their patients have agreed to take part in a trial and should ask if their patients:

- have or have had any relevant illnesses
- are taking or have recently taken any medicines
- have taken part in another clinical trial recently.

The investigator should ask the GP to reply in writing and may offer them payment for responding. The investigator must be able to justify including in the trial a subject whose GP does not give any information. Whether or not the GP responds, the investigator is ultimately responsible for making sure that subjects are suitable for the trial before allowing them to take part in it.

Safety

The investigator must assess the health of trial subjects throughout the trial and should withdraw any subject whose health is at risk. The methods, which should be described in the protocol (Section 7), include:

- asking subjects about adverse events
- medical examinations
- measuring vital signs such as heart rate and blood pressure
- routine safety tests of blood and urine
- continuous monitoring of variables such as the ECG and pulse oximetry, and
- trial-specific tests, such as lung function tests.

Follow-up

The investigator must follow up:

- all subjects after their last dose of IMP, for a period depending on the IMP and the trial
- subjects with adverse events, including clinically-relevant abnormal laboratory results, until they have resolved or it is clear that they are resolving, and
- subjects who withdraw or are withdrawn from a trial, as if they had completed it, providing they agree.

10: Research Ethics Committee

General

Before starting a Phase 1 trial in healthy subjects or in patients, the investigator must obtain written approval of a Research Ethics Committee (REC) recognised by the United Kingdom Ethics Committee Authority (UKECA). Guidance on the process of applying for ethics approval, types of RECs, communications with RECs during a clinical trial, and protocol amendments can be found on the website of the *National Research Ethics Service*.

11: Pharmacy

Premises, facilities and equipment

All units should have a designated pharmacy area that is secure and accessible only to certain staff. The type of premises, facilities and equipment should reflect the types of trial that the investigator does for sponsors. For example, the investigator for a trial of an IMP that is packed and labelled ready for administration to individual subjects will need only basic facilities to store and dispense the IMP, and procedures to keep records of its receipt, use, disposal and retrieval. However, an investigator who assumes some or all of the sponsor's responsibilities for an IMP will need to have the right premises, facilities, equipment and procedures, such as:

- premises that are purpose-built or adapted for the purpose
- the right environment, such as directional air-flow that is controlled for particles, microbiological contamination and temperature, and is monitored appropriately
- a designated storage area, with a quarantine area, for the IMP
- the right equipment, such as a laminar flow cabinet to prepare sterile products
- procedures to comply with GMP[23] and the annexes, especially the current versions of annex 1,[24] annex 13,[25] and annex 16[26]
- a rigorous quality management system, and
- a Manufacturer's Authorisation [MIA (IMP)][7] to manufacture, assemble or import IMPs, including placebo and other comparators.

Storage

IMPs should be stored in designated areas under conditions and for times recommended by the sponsor. Storage areas should:

- have adequate space for different IMPs to be stored apart
- be temperature-controlled and, if appropriate, humidity-monitored, with alarm controls
- be protected from direct sunlight
- be mapped to identify and avoid using hot and cold spots, if appropriate
- be secure
- be accessible only to authorised staff
- have records for logging IMPs in and out.

The pharmacy should keep a stock of marketed medicines for managing common adverse events – such as headache and nausea – and for managing medical emergencies other than cardiopulmonary resuscitation (Section 20) – such as convulsions and low blood sugar. The sponsor should indicate whether an antidote to the IMP exists and ensure its supply. These medicines must be readily available to clinical staff.

Staff

The pharmacy staff must be suitably qualified and experienced, and sufficient in number for the type and amount of work that the pharmacy undertakes.

A registered pharmacist, ideally with manufacturing experience, should prepare or assemble the IMP. A pharmacist may delegate work to pharmacy technicians or assistants, but must supervise their work.

A physician or a pharmacist should have overall responsibility for IMPs and marketed medicines, including emergency medicines.

Holders of an MIA (IMP) must:

- allow the MHRA to inspect the premises at any reasonable time
- have access to a qualified person
- provide the qualified person with adequate facilities and staff.

Types of work

The work that the pharmacy might undertake, and for which GCP and GMP sets the standards, includes: importing; packaging and labelling; randomisation; manufacture; batch release; sampling and testing; blinding and emergency unblinding; retrieval; and disposal.

12: Investigational medicinal products

Manufacture

Whoever imports, manufactures, assembles or repackages IMPs must apply for and get a Manufacturer's Authorisation [MIA (IMP)][7] from the MHRA and must follow GMP. Many of the pharmacy tasks that Phase 1 units do for sponsors need an MIA (IMP). Some examples are:

- re-packing bulk capsules or tablets into unit-dose containers, and randomising and labelling them
- weighing bulk material directly into capsules
- preparing, under aseptic conditions, a formulation for parenteral use
- receiving labelled unit-dose containers from a third country.

During the early stages of development of an IMP, the manufacturing process may change as the sponsor learns more about the product. So the sponsor's early formulations of an IMP may be primitive and require finishing work by the Phase 1 unit before they are ready for administration to the trial subjects.

Documents

Pharmacies that manufacture or prepare IMPs must have written instructions and records for their manufacturing processes. It should be possible to trace the history of each batch and any changes introduced during IMP development.

Records
The pharmacy should keep records of manufacture, preparation, packaging, quality control, batch release, storage conditions, and shipping of an IMP.

Supplying the investigator
The sponsor should not supply the investigator with an IMP before:

- the CTA application is approved in writing
- the REC application is approved in writing
- the IMP has been certified by the sponsor
- the code-break is in place
- the technical agreement between sponsor and investigator is in place.

However, the sponsor may release the IMP to the qualified person (Section 19) of the Phase 1 unit, providing he or she quarantines it until the above conditions have been met.

Transport to the trial site
The sponsor should pack the IMP properly and ensure that storage requirements are met during transport to the investigator. If the IMP is transported cold or frozen, temperature loggers should be added to the container.

Accountability at the trial site
The investigator, pharmacist or other delegate should keep records of each stage of the handling and use of an IMP, such as:

- receiving it and assessing its condition on arrival, and notifying the findings to the sponsor
- dispensing or manufacturing it
- giving each subject the dose or doses specified by the protocol
- returning unused product to the sponsor or delegate, or destroying it, as instructed by the sponsor
- keeping an inventory
- reconciling all the IMP received from the sponsor.

These records should include the dates, quantities, batch numbers, expiry dates and the unique code numbers assigned to the IMP and to the trial subjects.

Recall
The unit must have a system for retrieving the IMP promptly at any time.

Retention of samples
Manufacturers or importers of the IMP must retain samples of each batch of bulk product, and of the packaging components used for each finished batch, for at least two years after the trial. Pharmacies may not be able to meet those requirements if they manufacture only small quantities or individual doses of an IMP, or if the finished product is unstable. In those circumstances, the MHRA may agree to other sampling conditions, which should be described in the protocol or the CTA application.

Randomisation
There should be written procedures as appropriate for generation, distribution, handling and retention of any randomisation code used for packaging an IMP.

Emergency unblinding
The investigator or delegate must have a written procedure for rapidly identifying a 'blinded' IMP in an emergency. The procedure must be secure, readily available at all times during the trial, and not allow breaks of the blinding to go undetected.

Quality management

Manufacturing and dispensing IMPs is more complex than manufacturing and dispensing marketed products due to:

- production processes that are often not validated
- the lack of fixed routines
- the increased risk of contamination, including cross-contamination
- the need for blinding and randomisation in most trials.

Therefore, units must have robust quality control and quality assurance procedures for manufacturing and dispensing IMPs. The people responsible for manufacturing and dispensing should be independent of those responsible for quality management.

13: Biotechnology products

General

Examples of biotechnology IMPs (also called biological IMPs) are: recombinant proteins, hormones, cytokines, monoclonal antibodies, genetically modified micro-organisms (GMM) and gene therapy. They are regulated differently from other IMPs, as follows.

- They need different pre-clinical studies to support clinical trials.[66]
- The Clinical Trials Directive allows the MHRA and REC an extra 30 days to review trials of gene therapy, somatic cell therapy or GMM. It allows another 90 days to consult others.
- Clinical trials of gene therapy need approval of the Gene Therapy Advisory Committee (GTAC)[67] in addition to the MHRA and REC.
- Clinical trials of live GMM must follow the Health and Safety Executive regulations controlling contained use of GMM.[68] Guidance on risk assessment and containment is available from www.hse.gov.uk.
- The MHRA handles trials of higher risk biological IMPs differently from trials of other IMPs (Section 12).

Proteins and monoclonal antibodies

Units must have the appropriate experience (Section 6), facilities (Section 9), and staff (Section 10) to do trials of these types of IMPs. The investigator must be capable of managing immune reactions, including anaphylactic reactions.[69] Proteins often have long half-lives, and are designed for infrequent dosing regimens in patients. Thus, depending on the molecule's characteristics, there should be enough follow-up of subjects – three months or even longer – to obtain a full pharmacokinetic profile and to allow reliable assessment of the immune response.

Gene therapy

Gene therapy is the deliberate introduction of genetic material into human somatic cells for therapeutic, prophylactic or diagnostic purposes. Examples include genetically modified viral vectors and naked DNA injection. GTAC has issued guidelines for applications for gene therapy trials,[67] and expects the investigator to have:

- a substantial multidisciplinary team of researchers
- suitable clinical and laboratory facilities
- on-site support, such as infection-control measures
- a proven track-record of high-grade clinical research.

Investigators who are unsure if an IMP is gene therapy, or if it is appropriate to give it to healthy subjects, should seek advice from GTAC. GTAC has approved certain non-therapeutic trials of gene therapy in healthy subjects.

Genetically modified micro-organisms

Some GMM, such as vaccines containing genetically modified viruses intended to raise a prophylactic immune response to the wild virus, can be given to healthy subjects. GTAC does not normally wish to review such trials.

14: Radioactive substances

General

Radioactive substances contain a radioactive isotope. Examples of radioactive substances that may be given to healthy subjects are:

- radiolabelled IMPs – usually with ^{14}C but also ^{3}H, ^{99m}TC and other isotopes – to assess their absorption, metabolism, elimination and gastrointestinal transit as well as the performance of individual product formulations
- imaging agents – such as receptor ligands labelled with ^{11}C or ^{18}F for PET (positron emission tomography) scans, and ligands labelled with ^{99m}Tc for SPECT (single photon emission computed tomography) scans – to produce images of organs such as the brain or heart
- biological products – such as red blood cells labelled with ^{51}Cr or proteins labelled with ^{131}I – to assess their life span
- radiolabelled products with which to assess the effect of an IMP on normal function, such as ^{51}Cr-EDTA to assess renal function, and ^{99m}Tc to assess cardiac function.

Administration of radioactive substances is governed by the Medicines (Administration of Radioactive Substances) Act (MARS)[70] and the Ionising Radiation (Medical Exposure) Regulations (IRMER).[71] Clinical trials of radioactive substances must follow the Ionising Radiations Regulations[72] and must be approved by the Administration of Radioactive Substances Advisory Committee (ARSAC) before they can start. ARSAC decides if the radiation exposure that the trial subjects are to receive is within acceptable limits. ARSAC guidelines[73] state that the radiation dose should be as low as reasonably practical in healthy subjects, and should not exceed 10 milliSievert annually.

A hospital department of nuclear medicine may have a licence to use a radionuclide, such as ^{99m}Tc, for routine diagnostic purposes in patients. However, a clinical trial involving ^{99m}Tc in healthy subjects still needs ARSAC approval.

Microdose trials

A single microdose of a radiolabelled IMP can be used to obtain early information about its pharmacokinetic or receptor-selectivity profile by means of PET imaging or AMS (accelerator mass spectrometry)[74] or other very sensitive analytical techniques. A microdose is defined as less than one hundredth of the predicted pharmacological dose but not exceeding 100 micrograms.[75, 76] Because the risk of harm from a microdose is much lower than a pharmacological dose, fewer or different pre-clinical studies are required to support a microdose trial. Also, a very low dose (less than 1 microSievert) of radiation does not need ARSAC approval.[73]

Premises, facilities and equipment

The premises must be located, constructed and maintained to suit the operations to be carried out in them, and must be registered by the Environmental Agency under the Radioactive Substances Act[77] to keep, use and dispose of radioactive materials. Sites that manufacture radiopharmaceutical products must comply with specific GMP guidelines[78] as well as standard GMP guidelines. When making an ARSAC application for a trial, investigators must provide evidence of the suitability of:

- the equipment to undertake the procedure involved
- the working areas and related equipment
- the staff to supervise, dose and nurse the trial subjects.

For example, a trial of a radiolabelled IMP to assess its absorption and metabolism needs only facilities to collect specimens of the subjects' blood, urine and faeces, a suitable counter to measure radiation, for safety purposes, and access to a laboratory scintillation counter to measure radioactivity in the specimens. In contrast, a trial involving an imaging agent, such as a ligand labelled with ^{11}C or ^{18}F for PET scans, needs much more sophisticated resources, including access to a cyclotron unit to make the ligand, and a PET scanner to measure binding to the receptor site.

Staff

The investigator must hold a certificate from ARSAC to administer or supervise the administration of radioactive substances. Applicants for certificates are normally of consultant status and supply information on their training and experience as well as on the services – such as departments of radiopharmacy and medical physics – that support them. Other staff should be suitably qualified and experienced. There must be a Radiation Protection Supervisor whose work must be supervised by the area Radiation Protection Adviser. Trials of radioactive substances usually need the collaboration of several groups of experienced researchers.

Trial subjects

When selecting healthy subjects for trials of radioactive substances,[73] the investigator should:

- study subjects over 50 years old, unless younger subjects can be justified
- study as few subjects as possible
- exclude women capable of having a child
- not expose subjects to more radiation than necessary
- exclude subjects exposed to radiation during their work
- exclude classified radiation workers
- exclude subjects who have received more than 10 milliSievert of radioactivity in the past 12 months.

15: Non-investigational medicinal products

Non-investigational medicinal products (non-IMPs) are often used during Phase 1 trials:

- to induce a physiological or pharmacological response to assess the activities of an IMP (in which case they are often called challenge agents), or
- as support or escape medication for preventative, diagnostic or therapeutic reasons.

Under these circumstances, they do not fall within the definition of an IMP[25] and investigators who prepare them do not need a Manufacturer's Authorisation for an IMP (MIA (IMP)). Nor does a trial of a non-IMP by itself require a CTA.

An algorithm defining what does and does not constitute a NIMP can be found on the MHRA's website.[79] The site also contains a file with mock examples of NIMPs. Further guidance on the requirements for and the use of NIMPs can be found in the European Union's *Guidance on Investigational Medicinal Products (IMPs) and Other Medicinal Products used in Clinical Trials, Volume 10, Chapter 5.*[22]

The ABPI maintains an online register for the purpose of sharing adverse event data associated with NIMPs in Phase 1 clinical trials (www.nimps.org/).

16: Qualified Person

Requirements

Units with a pharmacy that manufactures, assembles or imports IMPs, including placebo and other comparators, must have an MIA (IMP) on which a qualified person (QP) must be named. A QP is someone who meets the permanent provisions of Directive 2001/83/EC[80] or is someone who met the eligibility criteria during the transitional period[7] after implementation of the Clinical Trials Directive. People who achieved QP status during the transitional period should make sure that their job description accurately reflects the duties of a QP[80] and that they keep up to date with GMP.

Responsibilities

The QP must make sure that:

- each batch of IMP that is made within the EU meets the requirements of GMP and the CTA
- for an IMP made in a third country, each batch meets the requirements at least equivalent to those in the EU, and the CTA requirements
- for a comparator from a third country, if documents are not available to show that it was made in accordance with EU GMP, that it has had all the analyses, tests or checks necessary to confirm its quality in accordance with the CTA.

The scope of the work of the QP will depend on what the sponsor delegates to the unit. For example, a unit might receive, store and account only for an IMP made in the EU, and a QP need not be involved. On the other hand, a unit might import the IMP from a third country, obtain evidence that it was made according to GMP, store it, manufacture or assemble batches of it, release it, and account for it, and the services of a QP would be essential.

In an industrial setting, a single QP cannot usually be closely involved with every stage of manufacture, so the QP who certifies a finished product batch may have to rely on the advice and decisions of others. Before doing so, the QP must ensure that the advice is well founded. If another QP confirms compliance with GMP, he or she must do so in writing and state exactly what is being confirmed. The arrangements should be set out in the technical agreement.

Releasing IMP prepared by the pharmacy

It is the role of the QP to release batches of IMP. The manufacture and release of IMP for Phase 1 trials differs from that of marketed products. Marketed products are usually made in large batches during continuous sessions of work, and a QP releases each batch before it is marketed. Although a Phase 1 unit may prepare an IMP in one continuous session, it is more usual to prepare an IMP for small groups of subjects or just one subject at a time, and perhaps at unsocial hours. The time between preparing the IMP and giving it to the trial subjects may be a few hours or even minutes. It is not clear what constitutes a batch of an IMP. It is also not practical to have a QP available at all times. Therefore, units should devise a written procedure for releasing IMP and be prepared to justify it during inspection for an MIA (IMP). The QP may have to release some batches retrospectively. However, that should happen only on exception and stated in the CTA application.

When deciding whether to accept an IMP prepared in the pharmacy for use in a clinical trial, the QP should take into account, as appropriate:

- CTA application
- randomisation code
- protocol and amendments

- pharmacy instructions
- pharmacy SOP
- details of any deviations from procedures and action taken
- production records
- results of QC testing
- certificate of analysis
- certificate of compliance with GMP
- stability data
- inspection of finished product
- environmental monitoring records
- validation, calibration, servicing and maintenance records
- findings of any audits
- IMP accountability and storage records.

Manufacture of IMP

European Union or European Economic Area

If an IMP is manufactured in EU countries, an MIA (IMP) is required as part of the CTA application, to show that the IMP has been made to GMP standards. The same applies to an IMP made in the European Economic Area (EEA). The sponsor provides evidence of compliance with GMP, and a QP signs off each batch.

Third country: importing an IMP

If an IMP is manufactured in a third country (outside the EU or EEA), the QP named on the MIA (IMP) who authorises importation must certify that the IMP has been made to GMP standards. The QP must submit a declaration – available on www.mhra.gov.uk – as part of the CTA application.

The EU has negotiated a Mutual Recognition Agreement (MRA)[33] with some countries, and equivalent GMP standards apply to those countries. The latest news of MRA is available on the website.[33]

17: Resuscitation procedures, equipment, medicines and training

There must be procedures, equipment, medicines and trained staff to deal with any medical emergency that might arise during a trial, as follows.

General procedures

Trial subjects must:

- have a call button by their bed and in places such as toilets and showers, to call trial staff
- be given the information and consent form and an appointment card with the names and telephone numbers of the trial physicians, so that the subject (or another doctor who might see the subject) can call the 'on-call' physician or a trial physician at any time.

Trial staff must have access to:

- medical cover throughout the trial
- an 'on-call' doctor who they can contact by telephone at any time
- the sponsor's medical monitor or defined delegates whom they can contact by telephone at any time. A cascade of contactable personnel on the sponsor's side should be available to the investigator site – this can be added to the study protocol or be detailed in a separate document

- a procedure to report serious adverse events
- the randomisation code, should a subject have a severe adverse event
- an alarm system, to call for assistance in case of a medical emergency
- continuous monitoring of vital signs, such as ECG and pulse oximetry
- procedures for dealing with the most likely medical emergencies,[71] such as profound syncope, hypotension, anaphylaxis and cardiopulmonary arrest
- a procedure to transfer a trial subject to hospital (see below).

Resuscitation equipment and medicines

In each of the main clinical areas of the premises, there must be a resuscitation trolley with equipment and medicines that can be moved quickly to where they are needed in a medical emergency. Each trolley should have the same equipment and medicines, which must be checked at least weekly and after use, and records of the checks must be kept. The main items on each trolley should be:

- a defibrillator with an ECG monitor (both mains and battery operated)
- suction apparatus
- an oxygen cylinder and flowmeter
- oropharyngeal airways and face masks
- a self-inflating bag
- a laryngoscope and endotracheal tubes or laryngeal mask/alternative supraglottic airway device
- consumables such as intravenous cannulae and fluid infusion sets
- emergency medicines, including intravenous fluids
- a transcutaneous cardiac pacer (one should be enough for the whole premises).

The website (www.resus.org.uk/pages/eqipIHAR.htm) of the Resuscitation Council (UK) has a full list of recommended equipment and medicines.

Antidote

If there is an antidote to the IMP being tested, it must be readily available at all times. The same applies to NIMPs.

Resuscitation training

Physicians, nurses and other staff who help to care for trial subjects must all be trained and hold a valid certificate in basic (BLS), immediate (ILS), or advanced life support (ALS) procedures, as appropriate.[69] For example, all physicians must be trained and hold a valid certificate in ALS or ILS.

The medical director or another doctor with clinical expertise in resuscitation should set and maintain standards of training and assessment of the unit's staff, and ensure that competence is maintained by regular refresher training. Appropriately trained people, such as doctors and resuscitation training officers, should do the training and assessment.

Further guidance on training requirements for clinical staff and medical cover can be found in Appendix 1 of the MHRA's Phase 1 Accreditation Scheme Document.[15]

18: Confidentiality

Sponsors

Sponsors expect investigators to keep confidential any commercially-sensitive information, such as the protocol, investigator's brochure, IMP dossier, and CRF. Trial subjects who ask to see the protocol should be allowed to do so, but not be allowed to keep a copy.

A statement about confidentiality is normally included in the trial protocol or contract. So when trial-related documents are not in use, trial staff must store them in a secure place with access limited to authorised people – the trial staff, the sponsor's monitors and auditors, the REC, and the MHRA and other regulatory authorities. An investigator who undertakes trials for different sponsors should keep the trials apart while they are in progress on the unit. In addition, the monitors and auditors of different sponsors should have separate spaces in which to work during site visits.

Trial subjects

The investigator should give each trial subject a unique identifier to conceal the subject's identity when recording and reporting trial related data. However, the investigator must identify the subject when contacting the subject's GP.

If employees or students of the company or institution that is sponsoring or carrying out the trial wish to take part in it, the investigator should forewarn them of the possible implications of having their personal data processed at work by their colleagues.

Data Protection Act

The Data Protection Act81 covers the processing of personal data, whether written or electronic, of trial subjects. The investigator should comply by:

- entering on a national register details of all the classifications of data held, the subjects and the recipients
- obtaining the subjects' consent for their personal data to be processed
- using personal data only for the purposes set out in the protocol and the information and consent form
- making sure that personal data are relevant to the trial, accurate, not excessive and kept for no longer than necessary
- keeping paper and electronic documents in lockable offices, archives or storage cabinets, and allowing access only to authorised people
- making sure that personal data stored on computers are secure so that only authorised people can change or delete them
- telling subjects in the information and consent form that they may see information about themselves on request
- not transferring personal data outside the EU without adequate protection.

Human Tissue Act

Investigators must have informed consent from the trial subjects and approval from the REC to take any samples of tissue. Consent may be sought for long-term storage and future research as well as for use in the specific trial. Under the Human Tissue Act,[82] REC approval makes it lawful to store and use the samples for the specific trial only. Sponsors who continue to store samples after the trial has ended – either for their own research or to distribute to other researchers – are acting as a tissue bank, and must obtain a storage licence from the Human Tissue Authority.[82]

19: Compensation, indemnity and insurance

Compensation

For many years the ABPI has required that special provisions should apply to the provision of compensation to volunteers involved in healthy volunteer studies and patient studies that are sponsored by industry. However, different compensation provisions apply to healthy volunteer studies and to patient studies. In relation to the former, the applicable guidelines are the guidelines of 1988 (as amended in 1990) entitled 'Guidelines for Medical Experiments in Non-

Patient Human Volunteers' ("the 1988 Guidelines"). In relation to the latter, the guidelines are the 1991 guidelines entitled 'Clinical trials - compensation for medicine-induced injury' ("the 1991 Guidelines").

As is noted at Section 5 of these guidelines, the expression 'Phase 1 studies' may straddle both studies in healthy volunteers and studies in patients, depending primarily upon the characteristics of the medicine under research and whether it is only appropriate to administer it to patients with the target disease. In the circumstances the different guidelines will apply as follows:

- The 1988 Guidelines apply to studies in healthy volunteers, sometimes referred to as studies in non-patient volunteers, where the volunteers are not known to suffer from any significant illness relevant to the proposed study and where their mental state is such that a valid consent to participate can be given. The medicine under research is administered to identify and measure effects in man and the subject has no expectation of benefit. This definition does not exclude patients who are not in perfect health (eg if they have had a hip transplant). The 1988 Guidelines also apply to studies in persons who are 'patient volunteers' in the sense that they suffer from a chronic, but stable condition, but who do not suffer from the disease that is a target of the research programme and where the administration is simply to obtain additional, but potentially important, pharmacokinetic data about the medicine under research. As with healthy volunteers, the volunteer must possess a mental state such that a valid consent to participate can be given, but has no expectation of benefit from the administration of the medicine.
- The 1991 Guidelines apply whenever studies are carried out in patients with the disease which the medicine under research is intended to treat because the risks of administration due to the inherent toxicity or other qualities of the medicine are such that the chance of adverse events occurring cannot be viewed as minimal. These guidelines will, for instance, apply to medicines being developed to treat cancer and to gene therapy. Compensation payable under these guidelines can depend on a variety of factors including the provision of warnings about possible side-effects.

The nature of the compensation policy should be clear from the information and consent form, and subjects should be invited to seek explanation of any aspect of the undertaking that is not clear to them.

Subjects may make a claim directly to the sponsor or through the investigator. The sponsor should involve the investigator in any discussions with trial subjects about their right to compensation.

Indemnity

Before the start of a commercially sponsored Phase 1 trial, the sponsor must indemnify the investigator against any loss incurred by the investigator (including the cost of legal representation) as a result of claims arising from the trial, except to the extent that such claims arise from the negligence of the investigator for which the investigator remains responsible.

Insurance

In relation to the sponsor's obligation to comply with the above compensation policy, the sponsor must ensure that insurance or indemnity is in place to cover its liability and that of the investigator.

The Phase 1 unit must have insurance to cover claims for negligence, or must provide evidence of financial resources to meet any such claim. Also, physicians involved with the trial must have insurance – such as that offered by a medical defence organisation – that will respond to any

negligence claim. Nurses must hold professional indemnity insurance: for example, that which is provided by membership of the Royal College of Nursing.

The sponsor and investigator must be able to satisfy the REC and MHRA that subjects who take part in a Phase 1 trial are adequately protected against injury. In addition, the sponsor and investigator should do everything possible to ensure that a subject who is involved in a compensation claim is dealt with sympathetically and quickly.

Detailed guidance on insurance and compensation in the event of injury in Phase 1 clinical trials was developed by a cross-sector group convened by ABPI[83]. Published alongside the guidance in June 2012 is a template Statement of Insurance Cover developed by NRES, to give clinical trial sponsors a consistent document to provide to the ethics committee. The statement will be incorporated into the standard application for Phase 1 clinical trials within the Integrated Research Application System for health and social care research in the UK[84].

20: Pharmacovigilance

Although the sponsor has overall responsibility for monitoring the safety of its IMP, the investigator and sponsor should work together to help the sponsor meet their obligations. The investigator must:

- record all adverse events (AE), including abnormal laboratory results, as instructed in the protocol
- report to the sponsor, within the time frame identified in the protocol, all serious adverse events (SAE), except those identified as exempt in the protocol or investigator's brochure
- provide follow-up reports of SAEs, and any other information requested, within the time frame identified in the protocol.

The sponsor must:

- report to the MHRA:
  - suspected unexpected serious adverse reactions (SUSARs) that occur in the trial and are associated with any IMP used in the trial
  - SUSARs that are associated with any IMP used in the trial and that the sponsor learns about from other sources, for example, a SUSAR that occurs in another trial.
- report to the REC:
  - SUSARs that occur in the trial at a site in the UK and are associated with any IMP used in the trial[30]
  - SUSARs that are associated with use of any of the IMP in the UK (for example a SUSAR in another trial), if the IMP is not marketed in the EU.
- report to the investigator(s):
  - SUSARs, as they occur, without unblinding the investigator.

Where a trial is conducted in more than one site/country or different trial with the same IMP is undertaken elsewhere, the sponsor's reporting duties extend to all other involved investigators, ethics committees, and health authorities.

Sponsors must report fatal or life-threatening SUSARs to the MHRA and REC within seven days, and provide further information within another eight days, and report all other SUSARs within 15 days.

Sponsors may delegate their responsibilities to the investigator, providing the investigator is not unblinded in the process.

21: Pathology laboratory

General

All units should have access to a pathology laboratory for assays of blood, urine and other body fluids. Some units may have their own laboratory, whereas others may use a subcontractor.

The laboratory should have external accreditation, such as Good Laboratory Practice[85] (GLP), College of American Pathologists[86] (CAP), Clinical Pathology Accreditation[87] (CPA) or ISO 17025. It should be inspected regularly and participate in continual improvement schemes, such as NEQAS.[88]

Premises, facilities, equipment and procedures

The pathology laboratory should:

- be purpose-built or adapted for the purpose
- have automated equipment for routine haematology, biochemistry and serology tests
- have procedures for analyser calibration and quality control
- regularly maintain all the equipment, including point-of-care equipment
- have a procedure for transporting samples safely and quickly from clinical areas to the laboratory
- have written procedures for all assays, and validate the assays
- have a stock control procedure to make sure that reagents and consumables are used within their expiry dates
- keep records, including source documents and final reports
- have a procedure for authorising and releasing results
- have a procedure for 'flagging' and notifying medical staff of abnormal results
- have a laboratory information management system, and validate and backup the system
- provide protective clothing and safety equipment for staff
- have a central alarm system for all fridges and freezers
- have an internal audit programme.

Staff

The number and type of laboratory staff will depend on the workload, the complexity of the work, and the extent to which the equipment is automated and computerised.

Laboratories usually have a head of department, with a professional qualification such as FIBMS, who is responsible for the scientific and technical work, staff management and training, and administration.

There should be enough trained and competent staff to ensure a good service for specimen turnaround times, completion of acute work on the day of its receipt, and arrangements for urgent specimens. All staff must follow the laboratory's SOP and the Institute of Biomedical Science guidelines,[89] and receive GCP training.

22: Data management, statistics, report and publication

General

Sponsors may do their own data management and statistics on trial data or may subcontract it to a unit with the right facilities and staff. Whoever does it, the credibility of the numerical results of the trial depends on the quality and validity of the methods and software used.

Data management

Data management includes data entry, storage, verification, correction and retrieval. Data managers should:

- have computer systems that are:
  - validated, secure and allow only authorised access to the data, and
  - contain an internal audit trail, so that all changes to the data are documented and that entered data are not deleted
- back up each trial database
- test the database setup and verification checks for each trial with dummy data before any trial data are entered
- enter the data twice, or once with 100% check of data
- keep records of all queries and their resolution
- have a formal procedure for locking and unlocking the database.

Data released to Data Monitoring Committees/Data Safety Monitoring Boards for the purpose of making dose escalation decisions should undergo quality control and be kept in the Trial Master File.

Statistics

There should be a statistical analysis plan (SAP) for each trial.[90] The analysis plan could either be a stand-alone document or be integrated into the protocol. A statistician should:

- write and sign off on the analysis plans before the trial data is available and before any analysis has started
- describe in the protocol or SAP the hypotheses being tested and how conclusions will be drawn, the analyses that will be done, the procedures for dealing with missing data and avoiding bias, and the selection of subjects to be included in the analyses
- put sample tables and listings in the SAP, to show how data will be presented
- include any planned interim analyses in the SAP
- describe and justify in the trial report any deviations from the SAP
- ensure all steps of the data management, reporting and analysis process have fully validated procedures to avoid the potential for errors. These procedures would normally be included in a company's Standard Operating Procedures library.

The Report of the Royal Statistical Society[91] gives guidance about the statistical aspects of First-in-Human trials.

Report and publication policy

Whether the trial is completed or stopped prematurely, the sponsor should ensure that an end-of-trial report is prepared from the data and is given to the investigator, for comments and signature. The report should be based on the ICH Guideline for Clinical Study Reports[92] and has to be submitted to the MHRA within one year of the end of the trial.

The trial findings should be published,[35] as an electronic and/or paper document, within a reasonable time after the end of the trial. The sponsor and investigator should agree the publication policy in the protocol or contract, before the start of the trial. The sponsor must be allowed enough time to obtain any patent protection. Either party may prepare a manuscript for publication in a peer-reviewed journal. Each party should allow the other at least 30 days to comment before any results are submitted for publication. Authorship should reflect work done by both parties, in accordance with recognised principles of scientific collaboration.

Staff

The statistician, data managers and data entry staff should be suitably qualified and experienced. Data managers should be life science graduates or of similar status. Pharmacokinetic data should be interpreted by an expert in pharmacokinetics.

23: Essential documents, trial master file and archiving

Trial master file

The investigator must keep a trial master file[22] of essential documents that:

- allow MHRA inspectors to assess how the trial was done, and the quality of the data
- show whether the trial followed the relevant EU Directives, including the Clinical Trials Directive, GCP Directive, and GMP Directive.

Essential documents should be:

- generated and be on file before the trial starts
- added to the files during the trial, to show that any new information is documented as it becomes available
- in the file after the end of the trial.

Quality of documents

Essential and supporting documents:

- should be complete, legible, genuine, traceable to a specific trial, and readily available to the sponsor and MHRA upon request
- should not be altered without permission and creation of an audit trail, particularly if the documents are stored on electronic, magnetic, optical or similar media
- may be copied or transferred to other media for archiving, if the method has been validated to ensure that information will not be lost or altered and if the copies or transfers are certified for accuracy and completeness
- should be readily available in printed form, if stored on media that require processing.

Storage of documents

A specific person, an archivist, should store trial documents. The archivist should:

- have enough dedicated space that is suitable to store documents from all current trials on site and to store documents from all completed trials either on-site or off-site in a commercial archive
- have storage facilities that are secure and adequately protected from fire, flood, pests, extremes of temperature and humidity, and unauthorised access
- inform the sponsor about the arrangements for storing documents, and about any changes to the arrangements
- notify the sponsor if the investigator becomes unable to store trial documents, so that the sponsor can arrange for them to be stored elsewhere.

Duration of storage

Essential and supporting documents, including the trial subjects' records, must be archived until at least five years after the end of the trial. Access to documents must be restricted to the people with responsibility for archiving:

- until at least two years after the last approval of a marketing application in the EU and until there are no pending or intended marketing applications in the EU or
- until at least two years after stopping the development of the IMP or
- for a longer period, if required by the MHRA or the sponsor.

Disposal of documents

The investigator must not destroy any essential documents without the sponsor's permission. The reasons should be recorded and the records kept for five or more years. Sponsors should inform the Phase 1 unit when the retention period is over.

24: Project management and monitoring

Some sponsors allocate to every Phase 1 trial a project manager, to manage the administrative aspects of the trial, and a monitor, to carry out the traditional duties of a monitor.[20] Other sponsors may have one person do both jobs. The project manager and monitor should be life science graduates or of similar status. They should be trained in GCP, the relevant aspects of GMP and monitoring, as appropriate.

Phase 1 trials have special features, as follows. Nowadays, commercial CROs conduct most Phase 1 trials.[6] The trials start and usually end on schedule, especially if the trial subjects are healthy volunteers. Beds, staff and resources for the trial are booked, and subjects set aside time to take part. So any delay causes problems and many people are inconvenienced. In a Phase 1 trial, many data are collected from few subjects. Unforeseen findings often need protocol amendments to keep a trial running. A unit with an MIA (IMP) may have to manufacture, assemble or import the IMP.

Hence, Phase 1 trials need more input from the sponsor. For example, the project manager and/or monitor should:

- know the pre-clinical data and be able to deal with any concerns that the investigators might have about the risk assessment, by arranging for them to discuss their concerns with the sponsor's physician or pre-clinical staff
- assist the investigator in obtaining from the sponsor in good time any documents required to support applications to the REC or MHRA
- ensure that all the trial documents and the IMP are delivered in good time for the trial to start on schedule
- monitor the trial for GMP compliance – if the unit manufactures, assembles or imports the IMP – as well as for GCP compliance
- schedule monitoring visits for key days of the trial, such as when the IMP is first administered, the dose is increased and a non-IMP is administered
- get the sponsor to provide the investigator in good time with any pharmacokinetic data that are needed before the dose can be increased in a dose-rising trial, and
- participate in and document, if appropriate, any discussions between the sponsor and the investigator before the dose is increased, and ensure that the protocol is followed.

25: Quality management

Quality system

The sponsor is ultimately responsible for the quality and the integrity of the trial data. However, all units should have their own system, such as ISO 9001, for quality control and quality assurance, which the staff must follow. The scope of the system and the number and types of staff

who operate it will depend on the size of the unit and the sort of work carried out. All units should have written, authorised procedures and should:

- keep a current version of each procedure at each point of use
- remove obsolete versions from circulation, but keep copies for reference
- review the procedures regularly
- inform relevant staff of any changes to procedures or of any new ones, and train those staff, if necessary, and
- keep records that make it possible to trace which version of a procedure was current at any given time.

Quality control

Trial staff should check each stage of the trial to ensure that the regulations are being followed and that the data generated are correct.

Auditors

Auditors should:

- be life science graduates or of similar status
- be trained in auditing
- be independent of whatever they audit – if a unit does not have its own independent auditor, the sponsor or a subcontractor may conduct the audit
- regularly audit the quality system
- audit the validation of computerised systems
- regularly audit the facilities, and frequently-used subcontractors such as laboratories, against the relevant sections of these ABPI guidelines
- know the details of the unit's quality system and of Directives such as 2001/20/EC, the guidance documents, GCP, GMP, GAfREC and SOP of NRES, MHRA regulations, and other relevant documents
- check whatever tasks have been delegated to the investigator by the sponsor against those documents as well as the protocol, and
- devise and follow an audit plan based on the type and complexity of the trial, the number of subjects and any problems encountered.

Audits

A full clinical trial audit should include:

- the CTA and REC applications
- the trial documents – protocol, information and consent form, blank CRF, and the trial report
- the trial procedures
- the presence, completeness and accuracy of essential documents in the trial master file
- the case report forms and source documents
- the trial database and statistical analysis
- a written report of the audit findings for the investigator and other relevant staff, and
- an audit certificate for the trial master file.

Sponsor's auditors

The sponsor's auditors should audit the unit's facilities or systems or a specific trial, as necessary.

26: Health and safety

Units must have a health and safety at work policy,[93] and policies or procedures for the relevant parts of the legislation, including:

- safety in the workplace
- personal protective equipment
- equipment and electrical safety, and
- control of substances hazardous to health (COSHH).[94]

Units should follow the guidelines of the Advisory Committee for Dangerous Pathogens for containment level 2 as a minimum.[95] All staff at risk of contact with body fluids should be vaccinated against hepatitis B. In addition, there must be a policy to prevent and manage needlestick injuries.[96]

Units that prepare and serve food must follow the Food Safety Regulations.[97] Kitchens and areas where food is served must be kept clean and disinfected. Food must be prepared and stored hygienically, and served at the right temperature.

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Association of the British Pharmaceutical Industry (ABPI)
www.abpi.org.uk

Association for Human Pharmacology in the Pharmaceutical Industry (AHPPI)
www.ahppi.org.uk

UK BioIndustry Association (BIA)
www.bioindustry.org/home/

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www.cpa-uk.co.uk

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www.cap.org/apps/cap.portal

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www.legislation.hmso.gov.uk/acts.htm

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https://eudract.ema.europa.eu/

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www.nres.nhs.uk/

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www.resus.org.uk

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www.official-publications.co.uk

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www.tops.org.uk

Appendix 1: Qualifications relevant to Phase 1 trials

Diploma in Pharmaceutical Medicine

The primary qualification for pharmaceutical physicians is the Dip Pharm Med, awarded by the Faculty of Pharmaceutical Medicine of the Royal Colleges of Physicians. (**www.fpm.org.uk/trainingexams/exams/dippharmmed**). It can be obtained:

- by sitting an examination – the University of Wales runs a course geared to the examination (**www.cardiff.ac.uk/phrmy/degreeprogrammes/postgraduate/pharmaceuticalmedicine**); or

- as part of the MSc course in Pharmaceutical Medicine or Clinical Pharmacology (**www.surrey.ac.uk/fhms/study/Postgraduate/**) run by the University of Surrey.

Diploma in Human Pharmacology

Developed by the Faculty of Pharmaceutical Medicine (FPM), the Diploma and Certificate in Human Pharmacology (DHP and CHP) have been structured specifically to fit the needs of all with an interest in exploratory drug development.

Diploma Programme

The DHP is a two year programme of structured training for doctors to attain and demonstrate competence to serve as a Principal Investigator for exploratory studies of Investigational Medicinal Products (IMPs) in man. It is anticipated that the DHP will become the primary qualification for PIs.

Certificate Programme

The CHP is a 1-year part-time programme for doctors and scientists to attain and demonstrate a comprehensive knowledge of all aspects (design, monitoring, analysis, reporting, safety, ethics, regulation and law) of exploratory studies of IMPs in man.

These integrated training programmes address the requirements of Principal Investigators (PIs) and all scientists involved in Phase 1 studies, whether based in CROs, pharmaceutical companies, universities or regulatory authorities. Information on the DHP and CHP programmes and exams can be found at: www.fpm.org.uk. Details and dates of the accredited compulsory Diploma and Certificate courses provided by King's College London can be found at: www.pharm-med.kcl.ac.uk/fpm.html.

MSc

The modular MSc in Clinical Pharmacology run by the University of Surrey is tailored to physicians, nurses and life science graduates working in the pharmaceutical industry. Barts the London School of Medicine and Dentistry , part of the Queen Mary University of London, runs an MSc course in early drug development (**www.mds.qmul.ac.uk**).

The Universities of Aberdeen (**www.abdn.ac.uk**) and Glasgow (**www.gla.ac.uk**) run MSc courses in Clinical Pharmacology.

The European Centre of Pharmaceutical Medicine in Basel awards a Diploma in Pharmaceutical Medicine (**www.ecpm.ch**], as does the Claude Bernard University of Lyon (**www.univ-lyon1.fr**).

The Universities of Glamorgan (**www.glam.ac.uk/courses**) and Liverpool John Moores (**www.livjm.ac.uk**)run MSc courses in subjects allied to clinical pharmacology.

Higher Medical Training

Clinical pharmacology is a core component of the modular training courses (**www.fpm.org.uk**) for Higher Medical Training that lead to accreditation in Pharmaceutical Medicine by the Faculty of Pharmaceutical Medicine.

Physicians employed in academic and hospital clinical pharmacology units can train for accreditation in clinical pharmacology. In addition, there is a joint ABPI and NHS scheme for clinical pharmacology training.

Appendix 2: Contents of the information and consent form

According to ICH GCP[14], the subject information and consent form should state or explain:

- that the trial is research
- the purpose of the trial
- the IMP, and the chance of getting the active one
- the trial procedures
- what the subject must do
- what is experimental and what is standard
- the possible risks or discomforts
- the possible benefits
- the alternative treatments, if any
- the compensation and treatment available to the subject, if harmed
- how much the subject will be paid for completing all or only part of the trial
- what expenses will be paid to the subject for taking part in the trial
- that taking part is voluntary, and that the subject may withdraw at any time without giving reasons and without penalty or loss of benefits
- that the trial monitors and auditors as well as the MHRA and other regulatory authorities worldwide may see the subject's medical records
- that the subject's records will be kept confidential
- that if the results of the trial are published, it will not be possible to identify individual subjects
- that subjects will be informed immediately about anything new that may cause them to change their mind about taking part in the trial
- who subjects should contact if they want more information about the trial, or if they want to know their rights, or if they think they have been harmed by taking part in the trial
- the reasons why the trial might be stopped
- how long it will take the subject to finish the trial, and
- how many subjects will take part in it.

According to the Clinical Trials Directive guidance document on REC applications,[16] the information leaflet should also inform trial subjects about:

- the names and addresses of the researchers
- any conflicts of interest
- that the trial has been approved by a REC
- the subjects' right to privacy and protection of personal data
- the subjects' right to get new information and to correct errors
- the subjects' right to withdraw consent, that no new data will be added to the database, and that all stored samples traceable to them can be destroyed, if they so wish
- the subjects' right to be told of any new analysis of data that can be traced to them, and
- the plans for follow-up.

Appendix 3: Challenge agents

Some examples of challenge agents and their uses**

Challenge agent	Activity	Route of administration
allergens	allergy	skin prick or inhalation (asthma only); to assess anti-allergy activity
AMP	transmitter release	inhalation; to assess anti-allergy effect
capsaicin	villanoid receptor agonist	inhalation; stimulates cough reflex
histamine	H1- & H2-agonis	skin prick; to assess anti-allergy activity
hyoscine	muscarinic antagonist	sc; dementia model
ipecac	causes nausea and vomiting	oral; to assess anti-emetic activity via 5-HT3 or NK1 receptor inhibition
isoprenaline	β-receptor agonist	iv; to assess blocking activity
norepinephrine	α- & β-receptor agonist	iv; to assess blocking activity
methacholine	muscarinic receptor agonist	inhalation; to assess airway responsiveness
substance P	NK-receptor agonist	skin prick; to assess NK blocking activity
serotonin	5-HT agonist	iv, to assess blocking activity
tyramine	norepinephrine release	oral or iv; to assess MAO-B selectivity
P450 probes*	P450 phenotypes	oral; to assess potential for interactions with established medicines

* There are various probes, including 'cocktails',[77-79] to assess the activity of cytochrome P450 enzymes 1A2, 3A4, 2C9, 2C19, 2D6 and 2E1, and N-acetyltransferase-2.

** More details of challenge agents (or non-IMP) will be put on the MHRA website (Section 31).

Examples of radioactive isotopes for PET or SPECT scans

PET		SPECT	
radioisotope	half-life (min)	radioisotope	half-life (min)
^{82}Rb	1	^{99m}Tc	6
^{15}O	2	^{123}I	13
^{13}N	10	^{111}In	67
^{11}C	20	^{201}Tl	73
^{68}Ga	68	^{133}Xe	126
^{18}F	111		

Appendix 4: Abbreviations

ABPI	Association of the British Pharmaceutical Industry
AHPPI	Association for Human Pharmacology in the Pharmaceutical Industry
ALS	Advanced life support
AMS	Accelerator mass spectrometry
AREC	Association of Research Ethics Committees
ARSAC	Administration of Radioactive Substances Advisory Committee
BIA	BioIndustry Association
BLS	Basic life support
CAP	College of American Pathologists
CHM	Commission on Human Medicines
COSHH	Control of Substances Hazardous to Health
CPA	College of Pathology (UK) Accreditation
CPD	Continuing Professional Development
CRF	Case report form
CRO	Contract research organisation
CTA	Clinical Trial Authorisation
DCPSA	Diploma in Clinical Pharmacology of the Society of Apothecaries
DHP	Diploma in Human Pharmacology
Dip Pharm Med	Diploma in Pharmaceutical Medicine
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
EEA	European Economic Area
EMEA	European Agency for the Evaluation of Medicinal Products
ESG	Expert Scientific Group
EU	European Union
EudraCT	European Union database of clinical trials
FDA	Food and Drug Administration of the USA
FFPM	Fellow of the Faculty of Pharmaceutical Medicine
FIBMS	Fellow of the Institute of Biomedical Science
FRCA	Fellow of the Royal College of Anaesthetists
FRCP	Fellow of the Royal College of Physicians
GAfREC	Governance Arrangements for NHS Research Ethics Committees
GCP	Good clinical practice
GLP	Good laboratory practice
GMC	General Medical Council
GMM	Genetically modified micro-organisms
GMP	Good manufacturing practice
GP	General Practitioner (primary care physician or equivalent)
GTAC	Gene Therapy Advisory Committee
HIV	Human immunodeficiency virus
HMT	Higher Medical Training
HSE	Health and Safety Executive
ICH	International Conference on Harmonisation
ICR	Institute of Clinical Research
ILS	Immediate life support
ISO	International Standards Organisation
IMP	Investigational medicinal product
MABEL	Minimal anticipated biological effect level
MD	Doctorate in Medicine

MFPM	Member of the Faculty of Pharmaceutical Medicine
MHRA	Medicines and Healthcare products Regulatory Agency
MIA (IMP)	Manufacturer's Authorisation for an IMP
MRCP	Member of the Royal College of Physicians
NCE	New chemical entity
NEQAS	National External Quality Assessment Service
NHS	National Health Service
NOAEL	No-observed-adverse-effect level
NRES	National Research Ethics Service (formerly COREC)
PET	Positron emission tomography
PhD	Doctorate in Philosophy
PML	Progressive multifocal leukoencephalopathy
QP	Qualified person
RCP	Royal College of Physicians
REC	Research ethics committee
SAE	Serious adverse event
SI	Statutory instrument
SOP	Standard operating procedure
SPECT	Single photon emission computed tomography
SUSAR	Suspected unexpected serious adverse reaction
TOPS	The Overvolunteering Prevention System
UKECA	United Kingdom Ethics Committee Authority

Appendix 5: Glossary of terms

Accelerator mass spectrometry (AMS) – an extremely sensitive and accurate method of analysing a very small dose – a microdose – of an IMP labelled with an isotope (^{14}C).

Accreditation – recognition that a trial-related function meets an official quality standard. Examples are accreditation of a quality system by ISO 9001, a pathology laboratory by a College of Pathology, a Phase 1 unit by MHRA, and a REC by NRES (formerly COREC).

Administration of Radioactive Substances Advisory Committee (ARSAC) – decides if the amount of radioactivity subjects receive in a clinical trial is within acceptable limits.

Adverse event (AE) – an unwanted clinical symptom, sign or disease, or an abnormal laboratory finding, that is related in time to, but is not necessarily caused by, the administration of an IMP to a subject in a clinical trial.

Agonist – binds to a cell receptor and triggers a response by the cell. An agonist often mimics the action of a naturally occurring substance.

Algorithm – procedure for making a series of choices among alternative decisions to reach an outcome.

Anaphylactic reaction – an allergic reaction that is life-threatening.

Antigen – a substance which when introduced into the body stimulates the immune system to make a specific immune response, such as production of an antibody that binds to the antigen. An antigen may cause an allergic reaction.

Appraisal – a review of a person's performance and development needs.

Association of the British Pharmaceutical Industry (ABPI) – a trade association of pharmaceutical, biotechnology, research and development, or associated companies with either their main or subsidiary premises in the UK.

Association for Human Pharmacology in the Pharmaceutical Industry (AHPPI) – a group of people who are involved in commercial Phase 1 trials and hold biannual symposia to educate members.

Audit – a systematic and independent review of trial-related activities and documents, to find out if the activities were carried out, and if the data were recorded, analysed, and accurately reported, according to the protocol, SOP, GCP, GMP and regulatory requirements.

Audit certificate – written evidence that a trial-related function has been audited.

Audit report – an auditor's written report of his or her findings.

Audit trail – documentation of events at each stage of a trial that allows an auditor to trace the source of the data, track changes, and assess if the data are genuine.

Batch – a defined amount of starting material, packaging material or IMP that is prepared in one process or a series of processes and is expected to be uniform within specified limits.

Batch release – the process of signing off a batch of IMP by a qualified person (QP).

Bioavailability – a measure of how well a medicine is absorbed by the body.

Bioequivalence – two medicines are bioequivalent if their bioavailability does not differ significantly when they are used in a trial at the same dose and under similar conditions.

Biological investigational medicinal products – potential new medicines, such as proteins, cytokines, monoclonal antibodies, genetically-modified micro-organisms and gene therapy, resulting from advances in cell biology and in biotechnology.

Biomarker – a laboratory or clinical measure of the body's response to an IMP that might indicate that the IMP is working. When a biomarker can replace a clinical endpoint it is called a surrogate endpoint.

Biotechnology – the application of the biological sciences, especially genetics, to technological or

industrial uses.

BioIndustry Association (BIA) – a trade association for the UK bioscience sector.

Bivalent antibody – antibody with two binding sites.

Blinding – a procedure in which one or more of the parties to a trial do not know which IMP (active, placebo or comparator) is allocated to which trial subject.

Calibration – demonstrating that an instrument or device gives results within specified limits by comparing them with the results obtained with a standard over a range of measurements.

Case report form (CRF) – a printed, optical, or electronic document designed to record all of the information that is required by the clinical trial protocol, and is to be reported to the sponsor, for each trial subject.

Central Office for Research Ethics Committees (COREC) – responsible for coordinating, training and accrediting all UK research ethics committees. (Name changed to National Research Ethics Service [NRES] in March 2007).

Certificate of analysis – a document of the identity, purity and strength of an IMP.

Chief investigator – leads a group of principal investigators.

Clinical (human) pharmacology – the scientific basis of Phase 1 trials.

Clinical Trial Authorisation (CTA) – sponsors must obtain a CTA from the MHRA before they can start a trial of an IMP.

Clinical trial (study) – tests the safety and activities of an IMP in humans.

Clinical trial (study) report) – includes all the results of a trial and an analysis and clinical interpretation of them.

Comparator – a marketed medicine, a placebo, or another preparation of an IMP used for comparison in a trial.

Complement system – many small plasma proteins that work together to clear pathogens, such as bacteria, and promote healing.

Compliance – meeting the relevant requirements for a trial-related function.

Confidentiality – making sure that only authorised people see a sponsor's proprietary information or know a trial subject's identity.

Concentration-response curve – relationship between concentration of the IMP in blood or tissues and its effect.

Continuing Professional Development (CPD) – process by which physicians keep up-to-date, develop new skills and maintain a high standard of professional practice.

Contract – a written, dated and signed agreement among the parties to a trial, such as the sponsor, investigator and CRO, that sets out the duties and responsibilities, including financial, of each party (the protocol can be the basis of the contract).

Contract research organisation (CRO) – a commercial, academic or other type of organisation that may carry out the sponsor's trial-related duties and functions.

Control of Substances Hazardous to Health (COSHH) – regulations to protect workers against any substance in the workplace that might damage their health.

Curriculum vitae (CV) – written details of the researchers' qualifications and experience that enable sponsors, MHRA or REC to assess the eligibility of the researchers to do a trial.

Cyclotron – produces radioactive isotopes of short half-life for research or diagnostic imaging.

Cytokine – small proteins produced by cells, mainly white blood cells, in response to an immune stimulus. They mediate and regulate immunity and inflammation.

Cytokine storm – uncontrolled release of cytokines which react with immune cells. A cytokine storm damages tissues and organs, which may be fatal.

Data Protection Act – legislation to give people the right of control of personal information that

is held about them.

Declaration of Helsinki – guidelines of the World Medical Association that protect the rights, safety and well-being of subjects who take part in clinical trials, and are revised every four years – Directive 2001/20/EC is based on the 1996 version.

Delayed hypersensitivity reaction – a harmful immune response caused by re-exposure to a protein to which the body has become sensitive as a result of a previous exposure.

Deoxyribonucleic acid (DNA) – the substance in cells that carries the genetic code for the individual.

Diploma in Pharmaceutical Medicine (Dip Pharm Med) – a qualification in pharmaceutical medicine awarded by the Faculty of Pharmaceutical Medicine.

Diploma in Human Pharmacology (DHP) – a qualification for principal investigators for Phase 1 trials to be awarded by the Faculty of Pharmaceutical Medicine.

Direct access – permission to examine, analyse, verify and reproduce the relevant records and reports of a clinical trial.

Documentation – the process of creating records, in a written, magnetic, optical or other form, that describes the methods and conduct of the study, factors affecting it, and the action taken. Records include the protocol and any amendments, copies of submissions and approvals from the MHRA and REC, curricula vitae, information and consent forms, monitor's reports, audit certificates, relevant letters, reference ranges, raw data, completed CRF and the final study report.

Dose – the amount of an IMP given to the trial subject on one or more occasions (single- or multiple-dose). A dose may be one or more tablets, capsules, injections or other form of the IMP.

Dose-response curve – relationship between doses of an IMP and their effect.

Efficacy – whether an IMP is effective.

Endoscopy – looking into parts of the body – such as the stomach and windpipes – with an endoscope, a thin fibre-optic telescope with a light at the end.

Essential documents – documents that are kept in the trial master file and enable the sponsor or MHRA to assess if a trial was carried out properly and to judge the quality of the data produced.

European Agency for the Evaluation of Medicinal Products (EMEA) – coordinates the regulatory authorities, such as the MHRA, of all the EU countries.

European Commission (EC) – an institution in Brussels that drafts proposals for EU legislation and does the day-to-day work of running the EU.

European database of clinical trials (EudraCT) – a database in which all EU clinical trials must be registered.

European Economic Area (EEA) – the EU plus Iceland, Norway and Lichtenstein.

European Union (EU) – a group of European countries with common policies.

Exclusion criteria – reasons for excluding a subject from a trial, such as taking another medicine, having an illness or having out-of-range laboratory results.

Expert Advisory Group of the Commission on Human Medicines – The Commission on Human Medicines advises the Government and the MHRA about medicinal products. Expert Advisory Groups – such as the one for higher risk biological IMP – support the Commission.

Expert Scientific Group (ESG) Report on Phase 1 Clinical Trials – report of an enquiry into the First-in-Human trial of TGN1412.

Faculty of Pharmaceutical Medicine – a section of the Royal College of Physicians that sets and maintains standards in pharmaceutical medicine through Higher Medical Training.

Fc receptor – protein found on the surface of certain white blood cells that contribute to the protective function of the immune system.

Finished product – an IMP that has undergone all stages of manufacture, including packaging and labelling in its final container.

First-in-Human clinical trial – a clinical trial in which a potential new medicine is given to humans for the very first time.

General Medical Council (GMC) – registers and regulates UK physicians.

Genes – a biological unit of heredity – a sequence of DNA that codes for one protein. The human genome has about 70,000 genes.

Gene therapy – the deliberate introduction of genetic material into human somatic cells for therapeutic, prophylactic or diagnostic purposes.

Gene Therapy Advisory Committee (GTAC) – reviews proposals to conduct gene therapy research and advises about gene therapy.

Genetic testing – to detect the presence or absence of, or variation in, a particular gene using a DNA, biochemical or other test. The metabolism of many medicines is affected by genetic differences in enzymes.

Genetically modified micro-organisms (GMM) – micro-organisms that have had their genetic material altered by artificial means.

Good clinical practice (GCP) – an international ethical and scientific quality standard for designing, conducting, recording, monitoring and reporting studies that involve human subjects. GCP ensures that the rights, safety and well-being of the trial subjects are protected, and that the trial data are credible and accurate.

Good laboratory practice (GLP) – a set of principles for planning, performing, monitoring, reporting and archiving laboratory studies.

Good manufacturing practice (GMP) – a set of principles which ensures that medicinal products are produced and controlled to the quality standards appropriate to their intended use.

Governance Arrangements for NHS Research Ethics Committees (GAfREC) – guidelines issued by the National Research Ethics Service (NRES) that all REC must follow.

Half-life – time for the concentration of an IMP or medicine to halve in the body.

Health and Safety Executive (HSE) – responsible for enforcing regulations that ensure the health and safety of staff and visitors in the workplace.

Hepatitis viruses B and C (HVB and HVC) – viruses that are transmitted by blood or blood products and cause liver disease.

Higher Medical Training in pharmaceutical medicine – consists of seven advanced training modules in pharmaceutical medicine, of which clinical pharmacology is one, leading to the award of the Certificate of Completion of Specialist Training (CCST) by the Royal Colleges of Physicians.

Higher risk agent – an IMP that the ESG Report deemed more likely to cause harm than other IMPs when tested for the first time in humans: biological molecules with novel mechanisms of action; new agents with a highly species-specific action; and new agents directed towards immune system targets.

Human immunodeficiency virus (HIV) – the virus that causes AIDS.

Human Tissue Act – legislation to regulate the removal, storage and use of human organs and tissues.

Imaging – taking a picture of part of the body using a special detector and a computer.

Immune response – a white blood cell, antibody or cytokine response to an antigen, infection or some other stimulus.

Importing – bringing an IMP into the UK from a third country, such as the USA.

Inclusion criteria – conditions that must be met if a subject is to join a trial.

Indemnity – a guarantee inserted in the protocol, contract or subject information leaflet that the sponsor will compensate a trial subject who is harmed by taking part in a clinical trial.

Informed consent – a process by which subjects voluntarily confirm their willingness to take

part in a trial after having been fully informed about it. Informed consent is documented by means of a written, signed and dated consent form.

Inspection – the act by a regulatory authority of reviewing the documents, facilities, records, and any other resources related to the clinical trial and that may be located at the trial site, at the facilities of the sponsor or CRO or at other establishments.

Insurance – provides cover for the sponsor or investigator in the event of a claim for damages by a trial subject.

International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) – ICH version of GCP, which provides a unified standard for the EU, Japan and USA to facilitate the mutual acceptance of clinical data by the regulatory authorities in those countries.

Investigational medicinal product (IMP) – a potential new medicine, a placebo or a comparator. Includes a marketed product when used or assembled in a way different from the approved form, or when used for an unapproved indication or to gain further information about an approved use.

Investigational medicinal product dossier (IMP dossier) – gives information about the quality, manufacture and control of the IMP, including any comparator or placebo, and pre-clinical data and any clinical data.

Investigator – a researcher who carries out a clinical trial. A principal investigator leads a team of researchers. A chief investigator leads a group of principal investigators. In some units, the chief investigator and the principal investigator may be the same person.

Investigator's brochure – contains all the information and evidence, including non-clinical and any clinical data on the IMP, that support the proposed trial.

in vitro – outside the body, such as in a test tube (the opposite of in vivo).

in vivo – in the living body.

International Standards Organisation (ISO) – responsible for the ISO 9000 and other quality standards.

Isotope – one of two or more atoms having the same atomic number but a different atomic mass. Isotopes, such as 14C and 3H are used as tracers in medical tests.

Ligand – a molecule that binds to a protein or receptor.

Manufacture – any process carried out in the course of making an IMP, except dissolving or dispersing it in, or diluting or mixing it with, another substance used as a vehicle to administer the IMP.

Manufacturer's Authorisation for IMP [MIA (IMP)] – a licence, granted by the MHRA, to import or manufacture an IMP.

Marketing Authorisation – a licence, granted by the MHRA, that enables a manufacturer to sell a medicinal product so that doctors can prescribe it for patients.

Medicines and Healthcare products Regulatory Agency (MHRA) – a body required by law to assess the safety, quality and efficacy of medicinal products and devices, and to enforce GCP, GMP and GLP.

Metabolism – the breakdown of substances, including IMP, by the body.

Microdose – less than one hundredth of the predicted pharmacological dose but not exceeding 100 micrograms.

Monitoring – the act of overseeing the progress of a clinical trial, to ensure that it is conducted, recorded and reported in accordance with the protocol, SOPs, GCP, GMP, GLP, and any regulatory requirements.

Monoclonal antibodies – identical antibodies cloned from a single cell by a biotechnology method. They target a specific cell or protein in the body. Several monoclonal antibodies are in clinical use and many more are under development.

Mutual Recognition Agreement (MRA) – an agreement between the EU and an exporting third

country to allow an IMP to be imported into the EU.

National Research Ethics Service (NRES) – responsible for coordinating, training and accrediting all UK research ethics committees. (Name changed from COREC in March 2007)

Needlestick (sharps) injury – an injury caused by penetration of the skin by a needle or other sharp object, which may result in infection with blood-borne viruses such as hepatitis B and C, and HIV.

New chemical entities (NCE) – potential new medicines that are derived from chemical substances. They are sometimes referred to as small molecules.

No-observed-adverse-effect dose level (NOAEL) – the highest IMP dose level that is free of toxic effects in animal toxicology studies.

Nuclear medicine – use of radioactive isotopes for diagnosing or treating disease.

Nursing and Midwifery Council (NMC) – the organisation that controls nursing in the UK. All nurses must be registered with the NMC to carry out nursing duties.

Pharmaceutical medicine – the discipline concerned with the discovery, development, assessment, registration, monitoring and medical marketing of medicines.

Pharmacodynamics – the study of the effects of an IMP on the body and the mechanisms by which it acts (what the IMP does to the subject).

Pharmacokinetics – the study of the time course of the concentrations of an IMP and related substances in the blood and other parts of the body (what the subject does to the IMP). The concentrations depend on the processes of absorption (from the site of administration of the IMP), distribution in the tissues, metabolism (breakdown) and excretion (getting rid of it).

Pharmacology – information about the activities of an IMP in animals or humans.

Pharmacovigilance – collecting information about the safety of an IMP.

Phase 1 – trials of an IMP in subjects, either healthy subjects or patients, who will not benefit from the IMP.

Phase 2 – early trials of an IMP in subjects with the target disease who are expected to benefit from the IMP.

Phase 3 – late trials of an IMP in many subjects with the target disease who are expected to benefit from the IMP.

Phase 4 – post-marketing trials of a medicine to compare it with other treatments.

Photon – a quantum of electromagnetic radiation.

Placebo – a preparation that looks and may taste like the IMP that is being tested but contains no active substance (a dummy medicine).

Positron – a positive charge emitted from the nucleus of a radioactive isotope.

Positron emission tomography (PET) – a scanner gives a picture of the radioactivity taken up by a 'slice' of an organ, such as the brain, after administration of a radioactive isotope. PET measures metabolism or locates chemical transmitters.

Pre-clinical studies – studies in laboratory animals in vivo or in tissues, cells, components of cells or biological fluids of laboratory animals or humans in vitro before the start of Phase 1 trials. Also called non-clinical studies.

Principal investigator – leads a team of investigators (researchers).

Progressive multifocal leukoencephalopathy (PML) – a rare and fatal infection of the brain and spinal cord caused by reactivation of JC polyoma virus (a normally harmless virus that 80% of people carry) in patients with severely impaired immunity.

Protocol – a document that describes how a clinical trial will be done and includes information about the trial, such as the background, reasons, aims, ethics, design, methods, records, data management and statistics.

Protocol amendment – a document that describes a change to a protocol.

Publication policy – a policy agreed between the investigator(s) and sponsor for publishing the results of a trial in a scientific or medical journal.

Pulse oximetry – a non-invasive and painless way to measure, from the surface of the skin, the amount of oxygen in arterial blood.

Quality assurance (QA) – all those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, recorded and reported in compliance with GCP and with MHRA regulations.

Quality control (QC) – checking the quality of trial-related activities.

Qualified person (QP) – someone who ensures that each batch of an IMP that is made within the EU meets the requirements of GMP and that each batch of an IMP made outside the EU meets GMP requirements at least equivalent to those in the EU.

Quarantine – the status of materials, product or information that is isolated pending a decision on its approval or rejection.

Radioactive isotope – an unstable form of an element that breaks up into other elements and in so doing gives out radiation that can be measured.

Radiolabel – technique of incorporating a radioactive isotope into a molecule.

Radiopharmaceutical product – a product that includes a radioactive isotope.

Randomisation – the process of allocating trial subjects to IMP (active, placebo or comparator) by chance, so as to reduce bias.

Receptor – a structure on the surface of a cell (or inside the cell) that selectively receives and binds a specific substance.

Regulatory (competent) authorities – bodies such as the MHRA that review submitted clinical data and conduct inspections.

Reproductive toxicology – a series of toxicity tests in animals to assess the risk of giving an IMP to a fertile woman or man, or a woman who is pregnant.

Research ethics committee (REC) – an independent group of medical and scientific professionals and members of the public, with no financial interests or affiliations with the sponsor or researchers, who give an opinion on the ethics of a trial.

Rescue medication – treatment given to a subject to relieve a problem brought about by taking part in a clinical trial.

Resuscitation Council (UK) – provides education and reference materials to healthcare professionals and the general public in the most effective methods of resuscitation.

Risk – potential for harm.

Scintillation counter – a machine for measuring radiation, that counts light flashes emitted from a detector substance exposed to radiation.

Serious adverse event (SAE) or serious adverse drug reaction (serious ADR) – any untoward medical event that at any dose of a medicinal product:

- results in death
- is life-threatening
- requires a stay in hospital or prolongs an existing stay in hospital
- results in persistent or significant disability or incapacity or
- is a congenital anomaly or birth defect.

Shipping (dispatch) – packing and sending trial-related material somewhere.

Sievert – a unit of radiation exposure. The average person in the UK receives about 2.5 milliSievert of 'background' radiation annually from the environment. A chest X-ray represents about 10 days of 'background' radiation.

Signature – a distinct record (initials, or full handwritten or electronic signature) of the person who was responsible for a particular action or review.

Single photon emission computed tomography (SPECT) – similar to positron emission tomography but uses an isotope with a longer half-life (hours rather than minutes) that does not have to be made by a cyclotron machine.

Single photon emitters – radioactive isotopes that mainly emit gamma or X-rays.

Small molecules – see new chemical entities.

Somatic cells – cells other than egg or sperm cells.

Source data – all information in original records, and certified copies of original records, of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are found in source documents.

Source documents – original or certified copies of documents, data and records such as charts, laboratory notes, memoranda, diaries, checklists, dispensing records, printed output from instruments, and records kept at the pharmacy, laboratories and other departments involved in the trial.

Sponsor – an individual, company, institution or organisation that is responsible for the initiation, management and/or financing of a clinical trial.

Standard operating procedures (SOP) – detailed, written instructions to ensure that trial-related procedures are done in the approved way by everybody.

Statutory instrument (SI) – a power delegated by Parliament. Parliament can delegate its power to make and amend law to a person or organisation. A statutory instrument is one of these powers and is used by government ministers to amend legislation.

Sterility – the absence of living organisms.

Subject identification code – a unique identifier assigned by the investigator to each trial subject and used instead of the subject's name when the investigator reports adverse events and/or other trial-related data.

Subrogation – substituting one person or organisation for another, including all rights and responsibilities.

Suspected unexpected serious adverse (drug) reaction (SUSAR) – a serious adverse event considered by the investigator or sponsor to be possibly or probably related to the IMP under test and for which the nature and/or severity differs from the information in the investigator's brochure.

Target disease – the disease for which a potential new medicine is being developed.

Technical agreement – agreement between sponsor and investigator for the IMP.

TGN1412 – a monoclonal antibody that differs from those in clinical use in that it activates rather than blocks the body's immune response – so it is called a 'superagonist'.

Third country – countries, such as Japan and the USA, that are members neither of the EU nor the EEA.

TOPS (The Overvolunteering Prevention System) – an internet-based system to prevent subjects from taking part in Phase 1 trials too often.

Toxicokinetics – the toxicity of an IMP in animals expressed as the amount that gets into the bloodstream (exposure) rather than the dose.

Toxicology – studies in animals or on tissues to test the safety of IMPs before they are tested in humans.

Trial master file – file that contains essential documents for the trial filed in a logical way.

Trial site – place where the clinical trial is done.

Trial subject – someone who takes part in a clinical trial and either receives the IMP or is a control and receives placebo or active comparator.

QT interval – a component of the ECG which if prolonged by a medicine can lead to a potentially fatal abnormal heart rhythm called torsade de point.

Unit – the premises in which clinical trials are carried out.

United Kingdom Ethics Committee Authority (UKECA) – responsible for recognising NHS research ethics committees to review clinical trials.

Unblinding – finding out in an emergency or at the end of the trial which IMP (active, placebo or comparator) a subject has been allocated in the randomisation process.

Validation – documented programme to make sure that any equipment or specific process, method or system works correctly and gives the expected results.

Vulnerable subjects – people at risk of being persuaded against their will to take part in a clinical trial. Examples are medical students and staff of the investigator.

Appendix 6: Consultation responses

Feedback from the following organisations were received, either on the 2007 edition, or in response to the ABPI consultation on the draft 2012 revision. The list is not exhaustive and many more organisations were invited to comment.

ABPI member companies

ABPI Expert Networks – in particular the Experimental Medicine Expert Network and Legal Expert Network.

Authorising Authority for Phase 1 Ethics Committees (AAPEC)

Cancer Research UK

Clinical Contract Research Association (CCRA) members

Department of Health (DH)

Independent Ethics Committees for Medical Research (Edinburgh, Plymouth)

Good Clinical Practice (GCP) Inspectorate, MHRA

Medicines and Healthcare products Regulatory Authority (MHRA)

Medical Research Council (MRC)

National Research Ethics Service (NRES)

Royal College of Physicians (RCP)

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