

Insurance and compensation in the event of injury in Phase I clinical trials

Guidance developed by the Association for the British Pharmaceutical Industry, the BioIndustry Association and the Clinical Contract Research Association in consultation with the Department of Health and the National Research Ethics Service



1. Background

- 1.1 Sponsorship by industry of Phase I studies conducted in the UK has, for many years, been the subject of specific industry guidance aimed at protecting the interests of healthy volunteers and enhancing the reputation of the UK as a place to conduct research. Such guidance has included special arrangements for the payment of compensation that would apply in the rare cases where volunteers suffer adverse health consequences from participation in industry sponsored studies.
- 1.2 The record of the industry in meeting these aims has been very good; relatively few adverse events leading to claims for compensation have arisen and even fewer relate to serious injury. To assist Ethics Committees in satisfying themselves that the interests of volunteers are properly protected, both industry and the Department of Health recognised the need to review the existing guidance on compensation issues and to consider what further recommendations should be implemented by Sponsors.
- 1.3 For the avoidance of doubt, the guidance set out below applies only to Phase I studies sponsored by industry involving healthy volunteers and covered by the 1988 Association of the British Pharmaceutical Industry (ABPI) guidelines entitled “Guidelines for Medical Experiments in Non-Patient Human Volunteers”, subsequently incorporated into the 2007 ABPI “Guidelines for Phase I Clinical Trials”. Notwithstanding the title, these guidelines also apply to subjects who are patient volunteers in the sense that they suffer from a chronic but stable condition, and 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. Where, because of the inherent toxicity of the medicine, an industry sponsored study is carried out in patients with the disease which the medicine under research is intended to treat, the guidance below does not apply as the compensation arrangements are those described in the 1991 ABPI Guidelines entitled “Clinical Trials Compensation Guidelines”.
- 1.4 The resulting guidance does not change the well-established approach on these issues, but does provide more detailed recommendations on several matters and, in particular, where insurance is taken out by Sponsors to back undertakings to compensate volunteers, on the levels of insurance and on other policy terms that are considered reasonable. The guidance below does not amend wider industry guidance on other matters relating to the performance of Phase I studies.

1.5 The aims of this guidance, which has been developed by the ABPI, the BioIndustry Association (BIA) and the Clinical Contract Research Association (CCRA) in consultation with the Department of Health and the National Research Ethics Service, are:

- to provide authoritative recommendations to clinical trial sponsors, clinical research organisations and ethics committees on the level of insurance and other aspects of insurance cover for industry sponsored Phase I clinical trials;
- to assure volunteers in clinical trials and ethics committees that adequate insurance is in place for industry sponsored Phase I clinical trials; and
- to accelerate the ethics committee review process, enabling clinical trials to start more quickly, and thereby enhancing the early stage clinical development environment in the UK, but without compromising the protection of volunteers.

2. **The legal framework**

2.1 Clinical Research takes place on the boundaries of scientific knowledge and, therefore, if a healthy volunteer suffers injury as a result of participation in the study of a new medicine, the volunteer will not find it easy to establish an entitlement to compensation under general principles of the law. A claim for damages based upon negligence or (for producers) based upon strict liability under the Consumer Protection Act 1987 are the likely bases for asserting a right to compensation. However, injury can arise in research studies without evidence of fault by either Sponsor or Investigator. Moreover, a volunteer will find it hard to establish strict liability against the producer of the medicine because the safety that the volunteer is entitled to expect (the focus in strict liability) will ordinarily have been heavily qualified by the informed consent process and the producer may also be able to rely upon the development risks defence.

2.2 The relevant European Directives (2001/20/EC and 2005/28 EC) and the Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended) that implement the EC Directive requirements do not establish any absolute requirements in relation to arrangements for payment of compensation to injured research subjects. The focus of the EU provisions¹ is a requirement for transparency as to the arrangements that exist in the event of injury or death of a trial subject and of any insurance or indemnity

¹ Articles 3.2(f) and 6.3(h) and (i) of Directive 2001/20/EC

arrangements covering the liability of the Sponsor and Investigator. The provisions do not establish an obligation to compensate injured volunteers unless legally liable to do so, nor that any commitment to compensate is backed by insurance. However, Ethics Committees have an obligation to consider all such arrangements and have discretion to decide whether the arrangements represent adequate protection for the interests of volunteers.

3. Compensation arrangements in practice

3.1 Notwithstanding the formal legal position, the pharmaceutical industry in the UK has, for over 30 years, accepted on ethical grounds, an obligation to compensate even where legal liability under general law could not be established. Under prevailing guidelines of the ABPI, before the start of a Phase I study the Sponsor must have agreed with the research subject to provide compensation for injury whenever a causal relationship with participation is demonstrated. This undertaking can be provided directly by the Sponsor to individual volunteers through the consent process, or through authorising the Contract Research Organisation (CRO)/Investigator to give such an undertaking for and on behalf of the Sponsor. In either case the intention is to create a contractually binding commitment.

3.2 The essence of the undertaking is as follows:

- If the health or wellbeing of the volunteer deteriorates significantly as a result of taking part in the study, the Sponsor will compensate the volunteer, irrespective of the ability of the volunteer to prove fault on the part of the Sponsor or anyone else connected with the study;
- The amount of compensation should be calculated by reference to the amount of damages that would commonly have been awarded for similar injuries by an English court had liability been proven. The amount of compensation may be reduced if the volunteer is partly responsible for the injury or if the volunteer is separately compensated under any other insurance policy;
- The Sponsor and volunteer agree to refer any dispute about whether compensation is payable or the amount of such compensation to an arbitrator with power to consult a barrister of ten years' standing on any issue of law, including the amount of damages to be paid. If the Sponsor and volunteer

cannot agree on the identity of an appropriate arbitrator, the President of the Royal College of Physicians of London will be invited to appoint an arbitrator;

- The undertaking to compensate the volunteer will be construed in accordance with English law and, subject to the provisions above, the English courts have sole jurisdiction over any dispute that may arise out of it. The nature of the Sponsor's compensation policy should be made clear to the volunteer as part of the consent process. Volunteers should be given a copy of the relevant ABPI guidelines and should be invited to seek clarification of any aspect of the undertaking that is not clear to them.

3.3 Volunteers may make a claim through the Investigator. The Sponsor should aim to respond sympathetically and promptly to any properly particularised claim and should involve the Investigator in any discussion with a volunteer about the right to compensation. The volunteer information sheet for the study should explain how to make a claim and where to seek further information. The volunteer should be given contact details for the trade association(s) (ABPI, BIA and/or CCRA) that may be the most appropriate association(s) to assist the volunteer initially in identifying persons who may be able to help the volunteer in assessing the validity of a possible claim or progressing it.

4. Insurance

4.1 The Medicines for Human Use (Clinical Trials) Regulations 2004 state that a clinical trial may be undertaken only if provision has been made for "insurance or indemnity" to cover the liability of the Investigator and Sponsor in relation to the trial (see Regulation 28.1 and Schedule 1, Part 2, paragraph 14). The current advice from the Department of Health is that this requirement is not met by the Sponsor providing evidence of his financial ability to meet a claim made in response to the contractual undertaking given under the ABPI compensation guidelines. The Department argues that insurance or an indemnity by a third party is required and "self-insurance" does not suffice. This matter is unlikely to be resolved in the immediate future. In the meantime, the Medicines and Healthcare products Regulatory Agency (MHRA) has stated that, unless the European Commission advises Member States to adopt a different interpretation, a requirement for insurance or indemnity will continue to be enforced by MHRA GCP inspectors.

4.2 In any event, many Sponsors, in practice, already choose to take out specific clinical trial insurance that will indemnify the Sponsor in respect of claims made by volunteers, either pursuant to general principles of law or pursuant to the contractual liability accepted in accordance with the ABPI compensation guidelines. The ABPI policy for Phase I studies is that the subject is entitled to compensation if the injury arises through participation in the study. To meet this requirement the policy of insurance should not exclude cover where the volunteer is injured through the negligence of the Investigator. This does not exclude the Sponsor (and by subrogation to the Sponsor's rights, the insurer) separately seeking contribution or full indemnity from the Investigator for any payments made in respect of claims that are attributable to the Investigator's negligence.

5. Limits of indemnity and other aspects of insurance cover

5.1 An Ethics Committee will wish to satisfy itself that the nature and amount of the Sponsor's insurance cover represents adequate protection for volunteers. Whether the insurance cover is adequate involves a judgment to be made in all circumstances of the case. However it is possible to suggest reasonable indemnity limits, taking into account relevant factors. These include the history of claims in this field over the last 30 years, the level of compensation commonly awarded (under English law or under compensation arrangements in place in other parts of the EU) for injuries that may be suffered by the categories of persons commonly volunteering to participate in Phase I studies, and the practices and capacity of the insurance market.

5.2 Having regard to these factors, it is recommended that a distinction be made between "first into man" studies and studies where experience has already been gained from studies where the product in question has been administered in comparable doses. One cannot exclude adverse events in both situations being serious, but the risk of an event in "first into man" studies is inevitably greater, even if they are subject to a higher level of regulatory scrutiny. There is inadequate evidence to justify distinguishing between different types of products in these two categories when providing broad guidance of this nature. However, it will be appreciated that the level of premium paid to obtain cover at any given aggregate limit will vary according to all the circumstances of the study and where the risks are manifestly low, the premium fixed will reflect this.

5.3 For these purposes "first into man" studies is defined as the administration of a new molecule to man (healthy subjects and or patients) for the first time by dose (single

and repeated) and /or by route of administration. A new molecule is a unique molecular structure irrespective of whether the molecular class or the therapeutic target is known. For insurance purposes, it is not proposed to treat a study of a new fixed combination of known active substances, used already in the composition of single ingredient authorised medicinal products, but not hitherto used in a fixed combination, as a “first into man” study.

- 5.4 It is thought justified to provide a minimum level of cover of £5 million in aggregate per protocol for “first into man” studies, with such cover reduced to a minimum of £2.5 million in aggregate per protocol in respect of other studies. This is viewed as likely to be sufficient to cover a volunteer’s claim for compensation including ancillary expenses such as legal costs. Some Sponsors, carrying out a large number of different types of studies, may purchase, for a single premium, insurance for all protocols conducted over one year. This is not objectionable provided the Sponsor is still able to confirm before the commencement of each study to which this guideline applies that the required level of aggregate cover is still available in respect of the protocol in question. In each case the aggregate level of indemnity should exclude reasonable legal costs and expenses incurred by the insured. Whether the insurance policy also indemnifies the insured for legal costs and expenses incurred (and if so, any applicable limit and conditions attaching) is a matter of negotiation between insurer and insured and should not affect the level of indemnity available to meet the volunteer’s claim.
- 5.5 It should be explained to volunteers that there can be no guarantee that this level of indemnity will cover every conceivable set of circumstances, but that the relevant level is viewed as reasonable, particularly as the requirement for insurance is only additional protection for the volunteer. The level of indemnity is only relevant in the rare case in which the Sponsor is unable to meet the full claim from his assets due to insolvency. It is not thought appropriate that there be any limit in the indemnity available per individual volunteer within that aggregate sum. Nevertheless the minimum level suggested will be subject to periodic review that will take into account any relevant changed circumstances.
- 5.6 In all cases the insurance should be written in a way that includes an obligation to respond to claims made consistent with the ABPI Compensation Guidelines, i.e. in circumstances where the claimant need not prove negligence or strict liability, but only that the injury arose through participation in the study. In principle, the Investigator has an independent obligation to ensure that he has adequate insurance

or indemnity, but for an additional premium (likely to be modest) a policy may be extended by the Sponsor to cover claims for negligence made directly against the Investigator which would not ordinarily be covered by the indemnity given to the Investigator by the Sponsor .

5.7 Insurance today is generally written on a “claims made” basis, i.e. the claim must be made in the policy period during which the insurance is in force. As it is conceivable that a volunteer’s injury will only become manifest more than one year from the commencement of the study, the insurance arrangements should ensure that cover continues in respect of any claim made within a reasonable period after the completion of the study (defining this event as the date the final volunteer receives the final dose of the medicine). It is recommended that this period be not less than 3 years. This can be achieved by purchasing an extended discovery period of three years in the individual policy covering the study in question.

5.8 Insurance policies of all types invariably contain appropriate conditions and clinical trial insurance policies are no exception. The following conditions for liability are normal, but are unlikely to be an issue in practice in the specialised field of clinical trial insurance:

- Absence of intentional misconduct on the part of the insured;
- Meeting the regulatory requirement that the study be authorised by the competent authorities;
- Making proper disclosure of background facts of the proposed study that would be material to the insurer’s willingness to accept the risk or his setting of the premium;
- Making timely notification of a claim to the insurer and not compromising it without the agreement of the insurer.

5.9 We recommend that Ethics Committees accept the presentation by a Sponsor of a declaration of insurance that summarises details of the available insurance cover and other information of the type Ethics Committees might reasonably require. A template for such a document is provided alongside this guidance. The Sponsor’s declaration should include a statement to the effect that the insurance in place contains no conditions or exclusions that would not normally be found in clinical trial insurance of this type. If it does, this should be noted and justified on the basis of the facts of the

particular study. It is reasonable for Ethics Committees to rely upon such a statement rather than being required to undertake detailed scrutiny of policy terms and conditions. However, if a specific issue arises and an Ethics Committee wishes to review a particular policy, the Sponsor should make it available.

6. Insurance or indemnity of the Investigator

- 6.1 Before the start of a Phase I study, the Sponsor must indemnify the Investigator (and any CRO providing the Investigator) against any loss incurred by the Investigator (including the cost of legal representation) as a result of claims arising from the study, except to the extent that such claims arise from the negligence of the Investigator, in respect of which the Investigator remains responsible, as between the Investigator and the Sponsor. For these purposes the Investigator is the person responsible for the conduct of a study at a trial site and, if the study is conducted by a team of individuals, the Principal Investigator.
- 6.2 It is important to recognise that the exclusion from the indemnity given by the Sponsor of claims due to negligence only affects the relationship between the Sponsor and Investigator. It preserves the Sponsor's right of recourse against the Investigator in circumstances where the Sponsor pays compensation to a volunteer for injury caused by the Investigator's negligence. In the case of Phase I trials, the right of the volunteer to claim compensation from the Sponsor is not affected because, as described in paragraph 2 above, the Sponsor's undertaking to pay compensation is given on a "no fault" basis. It arises wherever the volunteer can show that the volunteer suffered injury through participation in the trial, even if the injury was due to the negligence of a person other than the Sponsor. However, having paid such compensation, the Sponsor is free to seek full indemnity or (depending upon the circumstances) a contribution from any person whose negligence caused the injury. In such circumstances the Sponsor has a legitimate interest in establishing that such other persons have appropriate insurance cover.
- 6.3 The Phase I unit must have insurance to cover claims for negligence in respect of its employees or sub-contractors, or must provide evidence of financial resources to meet any such claim. The aggregate level of protection for each study in respect of negligence should, in principle, be equivalent to that recommended in respect of a Sponsor purchasing insurance cover.

- 6.4 The Investigator and other physicians involved in Phase I studies must have appropriate insurance or indemnity against claims based upon negligence. This could be provided under the insurance of the Sponsor or of the CRO or through personal membership of a medical defence organisation or a policy of insurance purchased personally by the Investigator and other relevant physicians. The aggregate level of protection in respect of negligence should, in principle, be equivalent to that recommended in respect of a Sponsor purchasing insurance cover. Care should be taken to establish that membership rights in respect of medical defence organisations extend to cover claims made in the context of commercially sponsored studies.
- 6.5 Nurses and other qualified persons involved in Phase I studies must hold medical professional liability insurance, for example that provided by membership of the Royal College of Nursing.

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The Association of the British Pharmaceutical Industry

The Association of the British Pharmaceutical Industry (ABPI) is the trade association for the research-based biopharmaceutical industry in the UK, representing companies both small and large. Our member companies research, develop, manufacture and supply more than 80 per cent of the branded medicines prescribed through the National Health Service (NHS). For further information visit: www.abpi.org.uk

BioIndustry Association

Founded over 20 years ago at the infancy of biotechnology, the BioIndustry Association (BIA) is the trade association for innovative enterprises involved in UK bioscience. Members include emerging and more established bioscience companies; pharmaceutical companies; academic, research and philanthropic organisations; and service providers to the bioscience sector. The BIA represents the interests of its members to a broad section of stakeholders, from government and regulators to patient groups and the media. Our goal is to secure the UK's position as a global hub and as the best location for innovative research and commercialisation, enabling our world-leading research base to deliver healthcare solutions that can truly make a difference to people's lives. For further information, please go to www.bioindustry.org

Clinical Contract Research Association

The Clinical Contract Research Association (CCRA) is the trade association, established in 2003, for all organisations which provide clinical contract development services for the pharmaceutical and biotechnology industries, and their service providers.

CCRA also helps ensure that patients and volunteers receive the very best professional attention and information through every stage of their participation in trials. In adopting the CCRA Code of Practice, a company is guaranteeing to be at the leading edge of study design and to subscribe to a benchmark of excellence. For further information please visit: www.ccra.org.uk