

## CLINICAL TRIALS DIRECTIVE: “FLEXIBILITY”

1. DH, MHRA and others have made statements to the effect that the Directive has been “flexibly” interpreted in the UK, in accordance with the risks associated with different types of trial. It is important to remember that this is a generalisation and that there is a difference between interpreting the provisions of the Directive “flexibly,” and using an option or flexibility allowed explicitly by the Directive. There is a danger when referring to “flexible interpretation” that this is taken to imply either—
  - that the UK will enforce the Directive in reliance on a ‘flexibility’ which the Directive itself does not permit; or
  - that the UK will apply the Directive in an unfairly discriminatory manner.

We need to be wary of giving this false impression, and avoid using the phrase as a catch-all description of the UK approach to the Regulations. This note gives examples of areas where there is a risk that this misunderstanding could arise and an explanation of how risk affects the application of the Directive.

*Is the Directive applied by reference to the risks associated with each trial?*

2. The point is not that the Directive will be “interpreted” in line with the risk of each trial. Rather, the risks of a trial will affect how the Directive’s rules are applied. This occurs in a number of different ways.
3. First, the Directive itself makes different provision for different types of trial or types of subject. In essence, in the Directive the Member States and the European Parliament have made an assessment of the risks and adopted particular rules for particular cases. For example, competent authorities are given more time to assess requests for authorisation to conduct particular types of trial, such as trials involving gene therapy or biological products. To take another example, particular rules apply for trial subjects who are children or adults incapable of consent.
4. Second, where there is scope for different rules for different types of trial, the UK has considered the nature and risks of such trials and made different provision in national legislation accordingly. For example –
  - The provisions concerning the IMP dossier to be submitted to competent authorities. In accordance with similar provision in Commission guidance, the content of the dossier depends on the nature of the trial. For newly developing products, for example, a full dossier is required. But in the case of a marketed product, where much is already known about safety & efficacy, less information is required.
  - Labelling – for trials of marketed products dispensed by a retail pharmacist, the normal labelling rules apply, rather than the specific rules relating to labelling of ‘ordinary’ clinical trial products.

5. Third, competent authorities and ethics committees are clearly required to consider risk when they are considering applications for authorisation and ethical approval. Competent authorities must consider the risk posed by the investigational medicinal products being used; ethics committees are specifically required to consider whether the evaluation of risks and benefits made by the sponsor/investigator is satisfactory.
6. Fourth, sponsors and investigators clearly need to consider risk when designing the trial and drawing up the clinical trial protocol. This can affect how the requirements of the legislation apply. For example, the reporting requirements for non-serious adverse reactions are that investigators must report adverse events “identified in the protocol as critical to evaluations of the safety of the trial” (this is the requirement specified in the Directive and the UK’s Regulations).
7. Finally, risk may affect monitoring and enforcement arrangements. The competent authority must monitor safety and compliance with GCP; it is entirely appropriate for the authority to prioritise their work and to focus on trials posing the greater safety risk.

*‘Flexibility’ on liability and indemnity*

8. The question of liability (i.e. who is liable for product failures or negligence) is not a question of “flexibly” interpreting the Directive. It is simply our clear view that the Directive does not affect such liability issues. So, for example, it is not the case that the Directive is being interpreted “flexibly” in order to ensure that non-commercial sponsors are somehow less liable for claims of drug-induced damage than commercial sponsors. On the contrary, their liability remains as it was before the Directive was implemented.
9. As for insurance or indemnity to cover the liability of the sponsor, there is no flexibility, in the sense that the rule applies to all trials. But the Directive is “flexible” in that different arrangements may be appropriate for different types of trial. For example, NHS trials are covered by the NHS’ own arrangements, rather than commercial insurance.

*What provisions of the Directive are most open to “flexible” interpretation?*

10. Certain provisions of the Directive specifically allow Member States (MS) to choose different approaches or options. In particular –
  - Article 2, definition of “informed consent” – national legislation determines the exceptional cases where informed consent may be given orally (in UK see paragraph 3(1)(b)(ii) of Part 1 of Schedule 1 to the Regulations)
  - Article 2 – an “investigator” is either a doctor or “a person following a profession agreed in the Member State” (for the UK, see the definition of “investigator” and “authorised health professional” in regulation 2(1))

- Article 3(1) - MS may have national provisions for the protection of clinical trial subjects which are more comprehensive than the Directive's rules (UK has not used this option however)
- Article 6(1) – MS must take measures necessary for establishment and operation of ethics committees; but MS decide the form of that system and the detailed rules for operation (in UK see regulations 5 to 10 and Schedule 2)
- Article 7 – MS must have a procedure for the adoption of a single ethics committee opinion; but they decide what that procedure is (for UK we have imposed rules as to which committee an investigator may apply and limited them to one committee – see regulation 14(2))
- Articles 8 and 9(8) – the Directive does not specify the format or content of applications to ethics committees or requests for clinical trial authorisation; the Commission must publish guidance, but the UK's view is that although this must be taken into account, it would not be legally binding, and individual MS can have national rules (provided they comply with the provisions of the Directive) (see Schedule 3)
- Article 19 – MS may set conditions for when a charge may be made for supply of IMPs (in UK see regulation 29(4)).

11. In addition, as with all Directives, Member States are required to comply with the requirements of the Directive, but have a choice as to the form and methods to achieve the necessary results. So, for example, -

- (a) it is for MS to make detailed procedural rules, such as provision for appeals (see regulations 16 and 26) and
- (b) subject to the rules in Article 12, it is for MS to make detailed rules about enforcement of obligations, offences and penalties (see regulations 47 to 52).

12. The two other main examples where the UK takes the view that the Directive permits a “flexible interpretation” are: -

- The provisions regarding sponsor. The Directive defines “sponsor” in a broad manner and makes no further detailed rules for identifying the sponsor of a trial. The UK's view is that the provisions leave sufficient scope for either one individual or body to be the sponsor, or for a group of individuals or bodies to take on that role.
- Article 13(5) – provision regarding persons carrying out QP functions in relation to IMPs before implementation of the Directive. The UK's view is that MS are permitted to impose additional qualification/experience requirements on such individuals (see definition of “qualified person”).