New FDA Draft Guidance on Informed Consent

COLIN WILSHER

This FDA draft guidance (‘FDA Informed Consent Information Sheet Guidance for IRBs, Clinical Investigators and Sponsors’ draft guidance July 2014), when finalised, will supersede ‘A Guide to Informed Consent’ issued in September 1998, by the Office of Health Affairs, FDA. This new draft guidance combines various bits of guidance on consent issued by the FDA since 1998.

The FDA starts with a very clear and useful statement: ‘to many, the term informed consent is mistakenly viewed as synonymous with obtaining a subject’s signature on the consent form...FDA believes that obtaining a subject’s oral or written informed consent is only part of the consent process’. Of great interest is the fact that this new guidance contains some new definitions from the FDA that may influence clinical trial conduct.

There is an interesting definition from the FDA of when a review of a potential subject’s record is part of the clinical investigation. Surveys of patient records, to determine the number of potential subjects at site (ICH E6 4.2.1), are not part of the clinical investigation (’such a survey is in preparation for a clinical investigation and does not fall within the definition of a clinical investigation and, therefore, does not require informed consent under FDA’s regulations’). Preliminary review of subjects records to determine eligibility, (and the recording of limited information), are not part of the clinical investigation (’a patient’s records may be reviewed to determine whether the patient is eligible for a clinical investigation...this preliminary review of the patient’s record and recording of limited information is considered preparation for a clinical investigation, does not fall within the definition of a clinical investigation, and does not require informed consent’).

Requesting additional information (in addition to what already exists in the subject’s medical history) is part of the clinical investigation and requires consent (’obtaining informed consent may be required prior to obtaining the additional information’).

It remains to be seen if the EMA agree with this approach. The EMA may argue that determining subject eligibility and collecting data (that will be used in the trial), is part of the clinical investigation.

One possible danger of extrapolating from this FDA guidance, is that sponsor’s clinical departments may be tempted to claim all sorts of things are just ‘preparation for a clinical investigation’, and not part of the investigation and therefore do not require prior consent. There will be a need for vigilance by clinical QA departments, to make sure this is not abused, as the FDA says; ‘whether the record review is considered part of the clinical investigation, as defined under FDA’s regulations at 21 CFR 50.3(c) and 21 CFR 56.102(c), is determined on a case-by-case basis...if the record review is part of the clinical investigation, then informed consent from the subject for the record review is required under 21 CFR part 50’.
This FDA guidance also defines what can be done retrospectively. Retrospective review of subjects’ files (after the subject’s participation in the trial) for parameters which were covered by the protocol/consent form, does not require additional consent. Retrospective review of subjects’ files after the trial, for parameters which were not covered by the protocol/consent form, does require additional consent (in cases where the additional information goes beyond what was identified in the original protocol and disclosed in the original consent form, obtaining informed consent for the additional information would be required).

The FDA provides useful definitions of two important phrases, ‘coercion’ and ‘undue influence’.

The guidance says: ‘according to the Belmont Report, ‘coercion occurs when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance. Undue influence, by contrast, occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance’’. The FDA provides an illustrative example: ‘coercion and undue influence may be situational... for example, in a clinical investigation involving the surgical insertion of an investigational device, waiting to obtain informed consent until the potential subject is in the preoperative area may fail to minimise the possibility of undue influence’. A useful lesson from this is that there might be many situations where the investigator (and their staff) may inadvertently put subjects in a position of undue influence and care should be exercised to avoid this, before, during and after clinical trials.

IRBs should make sure they are constituted properly when reviewing clinical investigations involving vulnerable populations; ‘the IRB membership should include individuals with knowledge about and/or experience working with such subjects, in order to provide expertise and identify techniques for ensuring informed consent’.

IRBs should decide about financial disclosure to subjects: ‘IRBs should determine whether subjects should be provided with information regarding the source of funding, funding arrangements, financial interests of parties involved in the clinical investigation and any financial interest management techniques applied. The IRB should consider the kind, amount and level of detail of information to be provided to subjects’.

The IRB must ensure that investigators seek consent from subjects under circumstances that minimise the possibility of coercion and undue influence (21 CFR 50.20 and 56.111(a)(4)); FDA considers this to include ensuring investigators allow sufficient time for subjects to consider the information, provide time and opportunity for the subjects to ask questions and have those questions answered and allow time and opportunity for the subjects to consider fully whether to participate’.

Interestingly this new guidance does not mention the 1998 guidance requirement that: ‘the IRB should also be informed of... the timing of obtaining informed consent and of any waiting period (between informing the subject and obtaining the consent) that will be observed’. In contrast requiring a ‘prior interview’ is being emphasised in the new European Clinical Trial Regulation (536/2014).

‘A useful lesson from this is that there might be many situations where the investigator (and their staff) may inadvertently put subjects in a position of undue influence and care should be exercised to avoid this, before, during and after clinical trials.’

A situation that often occurs is where subjects both consent and begin participation in the trial, on the same day. The FDA offers some advice on this: ‘in those cases where the subject provides consent on the same day that he/she begins participation in the clinical investigation, the subject’s case history must document that the subject provided consent prior to their participation in the research [see 21 CFR 312.62(b) and 21 CFR 812.140(a)(3)]. Of course, many sponsors solve this problem by having the date and time of consent recorded on the consent form and the date and time of participation in the study documented in the source documents.

The FDA also has more guidance about the requirements for ethical oversight (institutional review board (IRB)/independent ethics committees (IECs)). ‘IRBs must review all materials used in the informed consent process... This includes recruitment materials and information provided in addition to the informed consent document (for example, a chart explaining what to expect at each study visit or a document explaining the costs to subjects). These last two documents might not have been routinely forwarded to IRBs in the past.

**Collin Wilscher**

Colin is a freelance GCP expert and frequently presents at the Brookwood International Academy training courses. He has spent the last ten years working for the clinical auditing group of Pfizer Medical as a GCP auditor and then as a Director and Regulatory Intelligence Lead, in the Inspection Management group of Medical Quality Assurance at Pfizer. He joined RQA as a member in 1994; was twice elected Chairman of the GCP Committee and is a Fellow of Research Quality Assurance (FRQA). He was honoured with the ‘RQA Award’ in 2013. He is an active member of the Audit Working Party of EFGCP (European Forum for Good Clinical Practice) and was on the editorial board of the Quality Assurance Journal (QAJ) and is a senior correspondent of the CQ Advisor.

Colin has served on the Regulatory Authority MHRA GCP Consultative Committee from its inception until 2010. He has also served on the MHRA Risk Based Inspection Stakeholder group and the MHRA Risk Adaptation Consultative Group.