30 September 2015

To: Bill Davidson, HRA Policy Projects Lead – HRA

cc: Catherine Blewett, HRA Improvement & Liaison Manager – HRA
Susan Sandler, ACRO Representative to HRA Phase 1 Advisory Group
John Poland, ACRO Representative to HRA Phase 1 Advisory Group

From: Karen Noonan, ACRO

RE: ACRO Response to Informal Call for Comments:
"UK policy framework for health and social care research"
Version 1.0 (February 2015)

Thank you for your 20 August email to Phase 1 Advisory Group members in which you welcomed continued feedback related to the informal call for comments on the draft that was issued earlier this year. Thank you, in particular, for your efforts to ensure there is clarity on the role of CROs.

The Association of Clinical Research Organizations (ACRO) represents the world's leading, global clinical research organizations (CROs). Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics and medical devices – from discovery, pre-clinical, proof of concept and first-in-man studies through post-approval and pharmacovigilance research. With more than 110,000 employees engaged in research activities around the world (including 30,000 in Europe), ACRO advances clinical outsourcing to improve the quality, efficiency and safety of biomedical research. Each year, ACRO member companies conduct more than 9,000 clinical trials involving nearly two million research participants in 142 countries. On average, each of our member companies works with more than 500 research sponsors annually.

ACRO is delighted to have been invited to participate in the review and fully supports this initiative to create an up-to-date policy framework for health and social care research in the UK.

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Purpose, section 1.1: The final bullet reads "research projects get registered, the data and tissue they collect can be made available, where appropriate and with safeguards, for future analysis and research findings get published and also summarised for those who took part in them." With regard to tissue, it is an offence under the Human Tissue Act (2004) and equivalent legislation in Scotland to remove, store or use human tissue for Scheduled Purposes without appropriate consent, and to store or use human tissue donated for a Scheduled Purpose for another purpose. With regard to data, the Data Protection Act (1998) establishes rules for compliance with data protection principles to ensure that information is accurate, used fairly and lawfully, used for limited, specifically stated purposes, used in a way that is adequate, relevant and not excessive, is kept for no longer than absolutely necessary, is kept safe and secure and not transferred outside the UK without adequate protection, and is handled according to the subject's data protection rights. The latter, as in the case of human tissue, is based on the consent of the subject. Consequently, ACRO recommends that the phrase "where appropriate and with safeguards" in the final bullet of section 1.1 should include a specific reference to the need for consent, e.g. "where appropriate and with adequate consent and safeguards".

Purpose, sections 1.2 and 1.3, and Part 2, Scope: Section 1.2 includes the sentence "Research involves staff in our universities, hospitals and social services in something that develops their skills" and makes no reference to the commercial sector. Section 1.3 includes a general reference to "The UK policy framework for health and social care research sets out policy and standards for the ethical conduct and proportionate, assurance-based management of research in health and social care". In these sections, and throughout the document, the framework appears heavily (but not exclusively) focused on non-commercial research. Despite this, it is noted that in Section 8.20 it is stated that a sponsor may be the funder of commercial research. Consequently, it is not clear whether the document applies to all research (including commercial research) carried out within the relevant organisations or only to non-commercial research. ACRO recommends that the scope of research to which the policy framework applies is very clearly stated in the Scope section of the document.

Section 1.2 also states that "Research … removes uncertainties". ACRO proposes that this statement be deleted since no research can provide guarantees regarding outcome for an individual.

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Implementation, section 3.2: Among other factors, the policy states its intent to encourage the pursuit of high-quality research that "ensures safety and confidentiality". Given that research is defined as "the attempt to derive generalisable and/or transferrable4 new knowledge by addressing clearly defined questions with systematic, rigorous and repeatable methods", safety, especially in medical (and particularly interventional medical) research can never be ensured as there may always be unknown or unrecognised risks. Rather than "ensures safety", ACRO recommends use of an alternative phrase such as "minimises the risk of harm to participants". ACRO also considers that the term "confidentiality" as used here needs greater definition of its meaning in this context. For instance, the TOPS healthy volunteer database managed by the Health Research Authority (HRA) shares information on volunteer subjects between UK clinical trial units conducting Phase I healthy volunteer studies on investigational medicinal products, and ACRO understands that a similar system for interventional clinical trials of medicines in patients is under consideration. Is personal data that is shared in this way still considered confidential? In this case (and others), data sharing is possible through the consent of the trial subject, and therefore ACRO recommends use of an alternative phrase such as "ensures confidentiality in accordance with the consent of the participant."

UK wide responsibilities, section 4.1: The draft policy states that "the policy framework references and interprets, as required, the relevant legislation in the EU and UK and sets out the application of this legislation in each country". ACRO proposes that it be clarified that applicable legislation is the relevant national legislation, as appropriate. It is also stated that the policy framework is relevant for research with participants including people who could be identified. It is recommended that it be clarified that it also applies to people who might not be identified.

Principles that apply to all health and social care research, section 7.5 ACRO suggests that it be clarified that publication of research should also be undertaken in compliance with any applicable regulatory requirements.

Principles that apply to all health and social care research, section 7.6: ACRO notes the use of a protocol "conforming to a standard template where applicable". Regulation (EU) No. 536/2014 governing clinical trials on medicinal products for human use includes in section D of Annex I a description of the required protocol content. Following implementation of the Regulation, ACRO recommends that, for consistency, this should be adopted as the standard UK protocol template for clinical trials subject to the Regulation. ACRO also recommends that, for other studies where protocol requirements are not established in law, UK templates should align with recognised international standards.

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Principles that apply to all health and social care research, section 7.10: This section states that information about research projects must be made publicly available "normally before they start". ". ACRO proposes that this section be concluded with the following statement: "This should be undertaken in compliance with applicable legal requirements and in accordance with the terms and conditions of the HRA website."

Principles that apply to individuals and organisations, section 8.2: This section lists the responsibilities of the chief investigator. However, they exceed those responsibilities defined in UK law and appear to conflate the chief investigator's responsibilities with those of the sponsor. The term "chief investigator" is used in The Medicines for Human Use (Clinical Trials) Regulations 2004 (Statutory Instrument No. 2004/1031) to mean "(a) in relation to a clinical trial conducted at a single trial site, the investigator for that site, or (b) in relation to a clinical trial conducted at more than one trial site, the authorised health care professional, whether or not he is an investigator at any particular site, who takes primary responsibility for the conduct of the trial." Further, these Regulations state the following additional responsibilities for the chief investigator: (a) initial application and signatory for research ethics committee (REC) opinion, (b) appealing against an unfavourable REC opinion, and (c) ensuring the trial master file (TMF) and the medical files are retained for at least 5 years (jointly with the sponsor). ACRO notes that the latter responsibility under UK law is not currently included in section 8.2 and recommends that it is added. We also recommend adding that the chief investigator must understand the relevant legislation governing the particular study.

Additionally, ACRO notes that the primary responsibility of the chief investigator defined in UK law is similar to that of the term "coordinating investigator", defined in the ICH (E6) Good Clinical Practice (GCP) guideline as "an investigator assigned the responsibility for the coordination of investigators at different centres participating in a multicentre trial." Under the ICH GCP guideline, an international standard for the conduct of clinical trials recognised in the UK, it is the sponsor, rather than the coordinating investigator, who is responsible for trial design and management. This principle is followed by the Medicines and Healthcare products Regulatory Agency (MHRA) when inspecting clinical trial sponsors for verification of compliance with ICH GCP. It should also be noted that the list of chief investigator responsibilities stated in this section is not consistent with those stated in the MHRA Good Clinical Practice Guide (2012), which is likely to cause confusion. The list of responsibilities of the chief investigator in this section may be valid for a chief investigator who also takes on the role of sponsor (a Sponsor-Investigator, as defined in the ICH GCP guideline) but confuses the two roles in the case of other chief investigators. To avoid confusion, ACRO therefore recommends that the listed responsibilities of the chief investigator and (in section 8.10) those of the sponsor are modified to align with the requirements of UK law and (in the case of clinical trials on investigational medicinal products) ICH GCP.

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Principles that apply to individuals and organisations, section 8.4. ACRO proposed that it be noted that in research undertaken in compliance with Good Clinical Practice, non-compliance with the protocol is a breach of GCP and may result in legal sanctions.

Principles that apply to individuals and organisations, section 8.9: Among other things, the funder is stated to be responsible for establishing the value for money of the research as proposed. It is not clear whether this applies only to funding by the Department of Health, its non-Departmental Public Bodies, the National Health Service, and social care agencies or also to commercial funders of research. While commercial organisations will always conduct a cost-benefit analysis before undertaking research projects, it is unclear to what extent they would need to demonstrate this (should this requirement apply to them) and to whom, or how the responsible party/parties within the research government framework will verify that this was done (including how value for money will be defined). ACRO therefore recommends adding greater clarity about the requirement for establishing the value for money of a research proposal, while recognising that commercial confidentiality considerations may apply in the case of commercial sponsors. As noted earlier, ACRO would be concerned if the UK policy framework failed to recognise commercial considerations that would lead to commercial sponsors conducting studies outside the UK, to the detriment of the UK research base.

Principles that apply to individuals and organisations, section 8.10 and 8.11: Section 8.10 defines the responsibilities of the sponsor and section 8.11 notes that sponsors of clinical trials of investigational medicinal products have particular legal duties. As noted above in comments on section 8.2, there appears to be confusion between the responsibilities of the chief investigator and of the sponsor with regard to such trials. ACRO therefore recommends that section 8.10 is modified to align with the requirements of UK law and (in the case of clinical trials on investigational medicinal products) ICH GCP.

Principles that apply to individuals and organisations, section 8.21: ACRO notes that the Human Tissue Authority also has a remit as regards UK research.

Principles that apply to individuals and organisations, section 8.22 and 8.23: ACRO expresses concern that, in the context of the policy, the sponsor is regarded as the employer and, in particular, is responsible for the personal development of research staff. Any action provided as a consequence of an error or breach should be appropriate to the relevant research.

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Recommended additions:
ACRO notes that the document is silent on how compliance with the framework will be monitored, and recommends that this is added.
Additionally, using the above comments on section 8.2 as an example, ACRO recommends that the complete document is reviewed to ensure that, in all sections, a clear distinction is made between UK legal requirements, which are mandatory, and best practices encouraged by the HRA.

ACRO thanks the Health Research Authority for the opportunity to submit comments during this informal call for comments. Please do not hesitate to contact us if we can provide additional information (knoonan@acrohealth.org or +1 202 464 9340).

Respectfully submitted,

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