Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Comment sheet for MHRA draft document:

MHRA GxP Data Integrity Definitions and Guidance for Industry

Deadline for comments: 31 October 2016

Send comments in Word format to: inspectorate@mhra.gsi.gov.uk

Comments from:

Name of organisation or individual
ACRO (Association of Clinical Research Organizations)

Please be aware that information submitted may be made public under a Freedom of Information Act request. Please highlight any information considered commercially sensitive.

1. General comments:

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 welcomes the opportunity to comment on the draft version for consultation (July 2016) of the MHRA GxP Data Integrity Definitions and Guidance for Industry. ACRO welcomes and supports the overall approach that does not expect organisations to implement a forensic approach to data checking on a routine basis, but instead to design and operate a fully documented system that provides an acceptable state of control based on the data integrity risk with supporting rationale. ACRO is concerned, however, that this message does not always come across within the body of the document, where details suggest that a more forensic approach, rather than a risk-based approach, is required.

Additionally, ACRO considers that the intent of the MHRA guidance is not clarified sufficiently and may lead to confusion at an international level. ACRO notes that, in May 2016, the World Health Organization published WHO Technical Report 996 which, as Annex 5, includes guidance on good data and record management practices applicable to GxP matters. The

MHRA guideline addresses some topics not covered in detail in the WHO document (computer system transactions, flat files, relational databases, and cloud/virtual service providers) but the WHO guidance otherwise covers, in substantially more detail, essentially the same subject matter and principles as the proposed MHRA guideline. It is therefore not clear why the MHRA intends to duplicate this guidance, rather than simply adopt the WHO guideline, unless it is with the aim of explaining how the MHRA plans to implement the WHO guidance in the UK. ACRO was therefore surprised that the MHRA guideline makes no reference to the WHO guidance. We recommend that it should be referenced in the MHRA guideline, and the role of the MHRA guideline relative to the WHO guidance explained. Given that both guidelines embody the same principles, many of ACRO's detailed comments below are designed to ensure clarity of alignment of the two guidelines, in order to avoid confusion.

2. Specific comments on text:

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale	Proposed Change (if any) *(If changes to the wording are suggested, please highlight using 'track changes')*
91 - 92	ACRO agrees with this statement, but recommends it should also emphasise that users should be adequately involved in defining critical data.	"Different data has varying importance to quality, safety and efficacy decisions. Data criticality may be determined by considering the type of decision influenced by the data. Users should be adequately involved in defining critical data."
153	For the avoidance of confusion at an international level, ACRO recommends replacing this definition of "Data" with that in WHO Technical Report 996 Annex 5.	"Data means all original records and true copies of original records, including source data and metadata and all subsequent transformations and reports of these data, which are generated or recorded at the time of the GXP activity and allow full and complete reconstruction and evaluation of the GXP activity. Data should be accurately recorded by permanent means at the time of the activity. Data may be contained in paper records (such as worksheets and logbooks), electronic records and audit trails, photographs, microfilm or microfiche, audio- or video-files or any other media whereby information related to GXP activities is recorded."
214	For the avoidance of confusion at an international level, ACRO recommends replacing this definition of "Data integrity" with that in WHO Technical Report 996 Annex 5.	"Data integrity is the degree to which data are complete, consistent, accurate, trustworthy and reliable and that these characteristics of the data are maintained throughout the data life cycle."
253 - 255	For the avoidance of confusion at an international level, ACRO recommends replacing this definition of "Data life cycle" with that in WHO Technical Report 996 Annex 5.	"All phases of the process by which data are created, recorded, processed, reviewed, analysed and reported, transferred, stored and retrieved and monitored until retirement and disposal."

315 - 317	For the avoidance of confusion at an international level, ACRO recommends replacing this definition of “Original data” with that in WHO Technical Report 996 Annex 5.	“Original data include the first or source capture of data or information and all subsequent data required to fully reconstruct the conduct of the GXP activity.”
336 - 340	For the avoidance of confusion at an international level, ACRO recommends replacing this definition of “True copy” with that in WHO Technical Report 996 Annex 5. Additionally, ACRO believes that the WHO wording is preferable in referring to “the entire content and meaning of the original record” rather than “having all of the same attributes as the original.” The term “attributes” includes, for example, colour, which means that photocopies or scans should have the same look and feel as the original. However, technology may not be available at a clinical trial investigator site to ensure this. Further, it is unlikely to be possible (and unnecessary) for all attributes, e.g. pH of the paper used, to be replicated.	“A true copy is a copy of an original recording of data that has been verified and certified to confirm it is an exact and complete copy that preserves the entire content and meaning of the original record, including, in the case of electronic data, all essential metadata and the original record format as appropriate.”
359 - 367	ACRO agrees that this approach would be onerous. It also appears unnecessary when it can be demonstrated that data generated by electronic means can be retained in an acceptable paper or pdf format using a process that maintains the integrity of the original data. The current text takes no account of the application of a risk-based approach and does not consider the criticality of the data (impact on data reliability) or risk to the data (deletion or alteration).	“Data must be retained in a dynamic form where this is critical to its integrity or later verification. However, a risk-based assessment of criticality (impact on data reliability) and risk to the data of alteration or deletion may allow for some data generated by electronic means to be retained in an acceptable paper or pdf format, where it can be justified that a static record maintains the integrity of the original data. In the absence of such risk assessment, the data retention process must be shown to include verified copies of all raw data, metadata, relevant audit trail and result files, any variable software/system configuration settings specific to each record, and all data processing runs (including methods and audit trails) necessary for reconstruction of a given raw data set. It would also require a documented means to verify that the printed records were an accurate representation. This approach is likely to be onerous in its administration to enable a GxP compliant record.”
403 - 404	For the avoidance of confusion at an international level, ACRO recommends replacing this definition of “Audit trails” with that in WHO Technical Report 996 Annex 5. Additionally, ACRO believes that the WHO wording is preferable in that it makes clear than an audit trail covers the creation, addition, deletion or alteration of information in a record (as is noted later in lines 426 – 427).	“The audit trail is a form of metadata that contains information associated with actions that relate to the creation, modification or deletion of GXP records. An audit trail provides for secure recording of life-cycle details such as creation, additions, deletions or alterations of information in a record, either paper or electronic, without obscuring or overwriting the original record. An audit trail facilitates the reconstruction of the history of such events relating to the

		record regardless of its medium, including the “who, what, when and why” of the action.”
425	This is not consistent with WHO Technical Report 996 Annex 5, which allows for a risk-based approach to the inclusion of audit trial review in routine data reviews. ACRO therefore recommends that the statement is amended.	“Routine data review should include a documented audit trail review unless there is a documented risk-based justification for omission of audit trail review.”
456 -476	Except in relation to assessment of a contractor’s quality system, no mention is made in this section of a risk-based approach. It is therefore not clear that a risk-based approach to data review will be acceptable. ACRO recommends adding the relevant paragraph from WHO Technical Report 996 Annex 5 to this section.	Add the following: “The approach to reviewing specific record content, such as critical data fields and metadata such as cross-outs on paper records and audit trails in electronic records, should meet all applicable regulatory requirements and be risk-based.”
559 - 560	For the avoidance of confusion at an international level, ACRO recommends replacing this definition of “Backup” with that in WHO Technical Report 996 Annex 5.	“A backup means a copy of one or more electronic files created as an alternative in case the original data or system are lost or become unusable (for example, in the event of a system crash or corruption of a disk). It is important to note that backup differs from archival in that back-up copies of electronic records are typically only temporarily stored for the purposes of disaster recovery* and may be periodically overwritten. Such temporary back-up copies should not be relied upon as an archival mechanism.” *actual text in Annex 5 is “Annex 5 disaster recovery”
Currently omitted – ACRO recommends inclusion:	As noted in our General Comments, ACRO recommends that WHO Technical Report 996 Annex 5 should be referenced in the MHRA guideline, and the role of the MHRA guideline relative to the WHO guidance explained.	Reference WHO Technical Report 996 Annex 5 in the MHRA guideline, and explain the role of the MHRA guideline relative to the WHO guidance.
Currently omitted – ACRO recommends inclusion:	Line 298 refers to “dynamic storage” but this concept has not been explained at this point in the document (it is briefly summarized in lines 319 – 322). ACRO recommends adding before this point the definition of “Dynamic record format” given in WHO Technical Report 996 Annex 5.	“**Dynamic record format**. Records in dynamic format, such as electronic records, that allow for an interactive relationship between the user and the record content. For example, electronic records in database formats allow the user to track, trend and query data; chromatography records maintained as electronic records allow the user (with proper access permissions) to reprocess the data and expand the baseline

		to view the integration more clearly."
Currently omitted – ACRO recommends inclusion:	The guideline does not address the management of laboratory notebooks and blank forms, which may be used, for example, as worksheets. ACRO considers that this is an important omission and proposes additional text should be inserted in a relevant section of the document. Section 9 (Recording data) is suggested.	"If used, blank forms (including, but not limited to, worksheets, laboratory notebooks, and master production and control records) should be controlled by the quality unit or by another document control method. For example, numbered sets of blank forms may be issued as appropriate and should be reconciled upon completion of all issued forms. Similarly, bound paginated notebooks, stamped for official use by a document control group, allow detection of unofficial notebooks as well as of any gaps in notebook pages."
	ACRO thanks the MHRA for the opportunity to comment on this Comment sheet for MHRA draft document: MHRA GxP Data Integrity Definitions and Guidance for Industry. Please do not hesitate to contact ACRO if we can provide additional details or answer any questions at all (knoonan@acrohealth.org)	

Please add more rows if needed.