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The Decommissioning of Computerised Systems Used in Clinical Trials

A white paper written by a joint task force from
the European CRO Federation and the eClinical Forum

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About EUCROF

The European Contract Research Organisation Federation (EUCROF) consists of members from most European countries and partner members from nearby countries with the aim of promoting clinical research of high quality in Europe in general and in the European Union in particular. EUCROFs objectives include supporting discussions with European bodies (EMA/EU Commission), promoting discussions on selected topics with representatives of the pharmaceutical industry to enhance business relations and identify common concerns, and endeavouring to develop transcontinental relationships with other associations e.g., with ACRO (Association of Clinical Research Organisations) in the USA and JCROA (Japanese Clinical Research Organization Association) in Japan. For further information visit the website at www.eucrof.eu.

About the eClinical Forum

The eClinical Forum (eCF) is a global, technology independent group representing members of industries engaged in clinical research. The eClinical Forum's mission is to serve these industries by focusing on those systems, processes and roles relevant to electronic capture, handling, and submission of clinical trial data. The eClinical Forum has sought out opportunities to promote electronic Clinical Trials since its inception in 2000. The cross-industry forum has a broad view of research with members - Sponsors, Contract Research Organizations (CROs), Technology vendors (both clinical research and healthcare), Academia, and Investigators - and with invited outreach opportunities with global Regulatory representatives. For further information visit the website at www.eclinicalforum.org.

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The information presented in these works draws upon the combined current understanding and knowledge of EUCROF and the eClinical Forum on this topic and is provided as an aid to understanding the environment for electronic clinical research. The opinions of the author(s), EUCROF and the eClinical Forum do not necessarily reflect the position of individual companies. Users should assess the content and opinions in the light of their own knowledge, needs and experience as well as interpretation of relevant guidance and regulations.

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1 Executive Summary

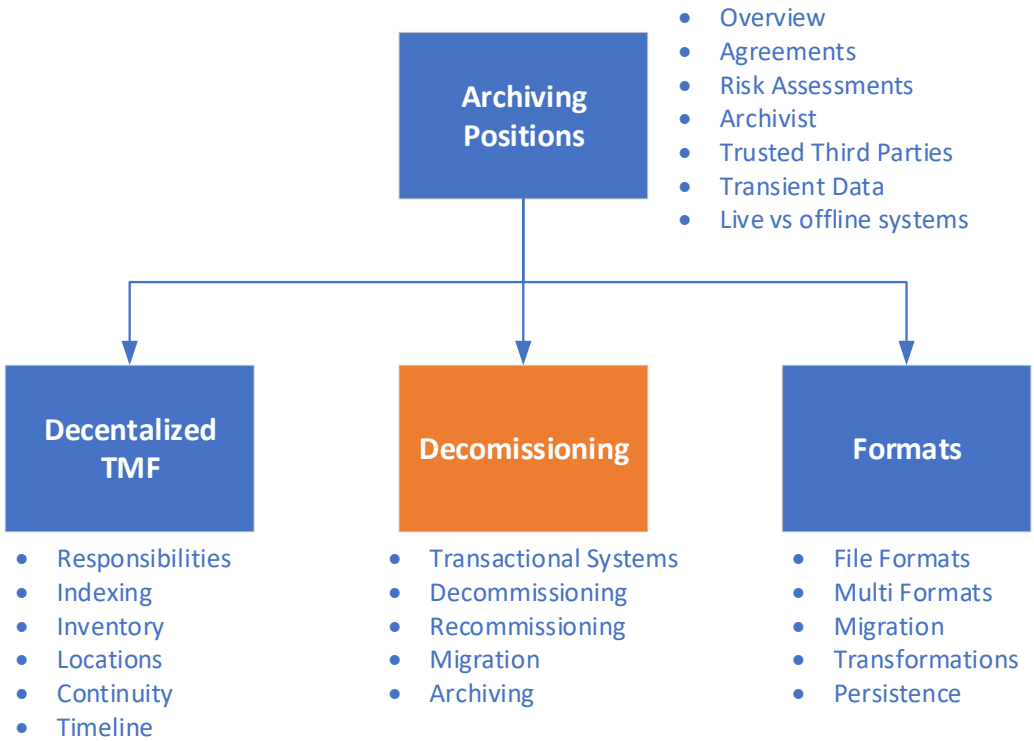
Many of the computerised systems employed in a clinical trial are only used during the active data collection stage of the trial. This is often a shorter duration than the retention period for the essential trial documents. Systems in this context means either a whole computing system, or a clinical trial schema within a larger computing system.

It is being proposed that those computerised systems be decommissioned when they are no longer being used in the trial. This decommissioning should be preceded by archiving all required data and metadata by sponsors and sites that is required for the reconstruction of the clinical trial.

2 Introduction

Clinical trials typically involve the use of multiple computerised systems and many of these systems are rarely developed for use in one trial alone. Instead, specific trial configurations are built on common platforms used by multiple sponsors and contract research organisations (CROs).

This white paper addresses the decommissioning of computerised systems such as EDC/eCOA systems used in clinical trials and is one of a series of white papers detailing aspects of the positions described in a position paper titled “Decentralized TMF Archives and The Decommissioning of Computerised Systems Used In Clinical Trials”.[1]



[1] Published by the eClinical Forum and EUCROF, see their websites for more information

Decommissioning of a computerised system is withdrawing or taking the system out of use. For systems that include hardware components (servers, network switches, firewalls, etc.) this can even include taking the hardware components out of use. For cloud-based or "Software-as-a-Service" (SaaS) solutions this normally does not include the withdrawal of hardware components from use.

For dedicated trial systems, the computerised system is traditionally decommissioned when the trial is completed and the trial itself is closed, submitted to regulators as appropriate and archived. However, multi-tenanted computerised systems are becoming commonplace, and these computerised systems are rarely decommissioned when the trial is closed. Instead, it is more correct to talk about the decommissioning of the trial itself, which involves the archiving of all trial specific data and metadata and the removal of that information from the computerised system used in the clinical trial.[2]

While decommissioning of a trial encompasses other aspects such as trial specific services and equipment used for the trial, these are not topics addressed in this white paper.

On completion of a clinical trial, it is the responsibility of the trial sponsor and the investigators/institutions to archive copies of the collected trial-related data from any computerised systems. Historically the archives generated from these systems have consisted of PDF files (static files) containing copies of the data entry forms. However, only archiving the data in this format is no longer considered to be sufficient by regulators to permit evaluation of the conduct and quality of a clinical trial. Thus, the archival format should allow dynamic interrogation of the information being archived and should include the patient data, audit trails, the query history, users' access log and other relevant metadata. Controls should exist to preserve the integrity of the data held in the archive consistent with ALCOA+ principles.

3 Definitions and Abbreviations

The meaning of terms as they are applied in this position paper are presented below. Definitions that are inherited from other sources are noted using footnotes.

- **ALCOA+:** Acronym referring to Attributable, Legible, Contemporaneous, Original, and Accurate (ALCOA) plus Complete, Consistent, Enduring, and Available.
- **Archive (*noun*):** A designated secure area or facility (e.g. cabinet, room, building or computerised system) for the long term, retention of data and metadata for the purposes of verification of the process or activity.[3]
- **Archive (*verb*):** Arrangements to permit recovery and readability of the data and metadata throughout the required retention period.
- **Audit Trail:** Provides for secure recording of life-cycle details such as creation, additions, deletion or alteration of information in a record, either paper or electronic without obscuring or overwriting the original record.

[2] For more information on data formats, metadata formats and reader tools, see the white paper on Formats from this series.
[3] MHRA GXP Data Integrity Guidance and Definitions, March 2018

- **Backward- (or Reverse-) Compatibility:** A property of a system, product, or technology that allows for interoperability with an older legacy system, or with input designed for such a system, especially in telecommunications and computing.[4]
- **Decommissioning Systems:** Decommissioning of a computerised system is withdrawing or taking the system out of use.
- **Dynamic Archive Formats:** File formats that allow the contents to be sorted, filtered and queried.
- **Essential Documents:** Documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced.[5] For the purpose of this position paper the term "essential documents" is used to cover all records, data and documents retained in the TMF.
- **Metadata:** Metadata refers to data that describe the attributes of other data and provide context and meaning. Typically, these are data that describe the structure, data elements, inter-relationships and other characteristics of data. Metadata also permit data to be attributable to an individual.[1] The Audit Trail is included in the metadata.
- **Recommissioning:** The restoration of an electronic trial system to a transactional state following the decommissioning of such systems. Recommissioning may involve the restoration of trial data that was originally held in the decommissioned electronic trial system.
- **Static Archive Formats:** File formats that do not allow the contents to be sorted, filtered and queried (e.g. PDF/A).
- **Transactional:** A state of an electronic trial system that permits interaction with data maintained in such systems as limited by system functionality and user permissions. Transactional interactions include data entry, update, querying, source data verification or audit trail review.
- **Trial Master File (TMF):** The collection of essential documents that is used by sponsors, CROs and investigators/institutions for the management of the trial and by monitors, auditors and inspectors to review and verify whether the sponsor and the investigators/institutions have conducted the trial in line with the applicable regulatory requirements and the principles and standards of GCP.[6]
- **Trusted Third Party (TTP):** A service provider that is a separate legal entity from the sponsor, CRO or investigator. A contract should be in place defining the tasks to be performed by the service provider, enabling the sponsor and/or investigator to contract specific tasks, but to retain control of their responsibilities.[7]

[4] Petersen, J.K. (2002), The Telecommunications Illustrated Dictionary (Second ed.), CRC Press, ISBN 9781420040678
[5] Integrated Addendum to ICH GCP E6(R1): ICH Guideline for Good Clinical Practice E6(R2)
[6] EMA/INS/GCP/856758/2018 Guideline on the content, management and archiving of the clinical trial master file (paper and/or electronic), December 2018
[7] EMA/INS/GCP/454280/2010 Reflection paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials, 09 June 2010

4 Obligations to Maintain Electronic Trial Systems in a Transactional State

Regulators expect trial sponsors and investigators to retain archival copies of trial data generated by the investigational site or the trial subjects. Regulatory agency inspectors have further expressed a desire to be able to interrogate such data for purposes of trend and issue analysis and may wish to evaluate or interact with operational deployments of trial systems for current or completed trials. This latter requirement poses technical and operational challenges, particularly over the full legal retention period for trial data/records. EUCROF and the eClinical Forum have evaluated the feasibility of this requirement and established the following position in line with their understanding of legal requirements and regulatory need.

5 EUCROF/eClinical Forum Position Statement

EUCROF and the eClinical Forum have established the following position statement regarding recommissioning of electronic trial systems, see "Decentralized TMF Archives and The Decommissioning Of Computerised Systems Used In Clinical Trials"[1]:

> *With the implementation of archival processes for trial data/meta-data and system documentation, electronic trial systems which are no longer being used in a trial are not required to be maintained in a (live) transactional state for the full retention period.*

By transactional state it is meant access to, and dynamic interaction with, the electronic trial system as it was used when active during the trial and as limited by system functionality and user permissions.

6 Justification

6.1 Clinical Regulatory Considerations

While the ICH E6 (GCP) R2 guideline does not specify a need for system recommissioning, regulators are continuing to request such activities based on a consideration that electronic trial systems allow users to interact to a high degree with the electronic records held in the system. This approach leverages the concept of "static" and "dynamic" records. Both the United Kingdom MHRA[3] and World Health Organization (WHO) have indicated that "*A static record format, such as a paper or electronic record, is one that is fixed and allows little or no interaction between the user and the record content*" whereas "*Records in dynamic format, such as electronic records, allow an interactive relationship between the user and the record content.*"

Electronic trial systems may permit users to view and report on electronic records. These source records should not be manipulated or changed after they have been extracted for analysis and reporting. Once extracted these are not considered to be truly "dynamic" and therefore there is limited benefit in resurrecting the data within the original system to enable users to conduct transactional interaction with the system and data within it.

The retention of the records in a file format that permits analysis by software tools (e.g. statistical or spreadsheet programs) allows for flexible analysis capabilities beyond that found in electronic trial systems and offers more benefit to regulatory inspectors.

6.2 Information Security & Privacy Considerations

Operating systems, databases and programming languages have all evolved over time. Entire technical solutions such as remote data hosting and access to data over the internet did not even exist 25 years ago. Systems were not interconnected then as they are today, and information security is currently an entirely new sector. Older browsers, programming languages and operating systems might not be compatible with future systems. In any event these would have security issues that cannot be fixed and are not maintained by software companies/developers.

The absence of security patches for unsupported software increases the risks of security threats impacting systems and their data, and there are well documented cases of malware impacting unpatched systems or those dependent on current unsupported operating systems. As security threats evolve, recommissioning legacy technology may introduce unacceptable security risks. This is a significant concern as stricter data privacy regulations have been implemented in many countries around the world since 2015, including the European Union (EU), Japan, US, and China. These regulations drive increasing sponsor liability for data breaches under data privacy legislation which can be punitive.

Information security and privacy concerns make it inadvisable today to use a 25-year-old computerised system. Even if the system could be kept operational, the information security issues alone could mean that any data in the system may not be secure and could be compromised, and therefore untrustworthy.

6.3 Technology Considerations

The technology landscape and the level of outsourcing undertaken by trial sponsors is constantly evolving. Historically, electronic trials systems operated principally on single tenant basis where data/meta-data were held in a single installation configured to meet customer requirements. Typically, these were on premise installations where application and other required software was licenced by sponsors and installed in their own or contracted facilities. The current trend is to utilize applications within cloud computing environments in a multi-tenant model, in essence a single application which may share identity or other services with specific sponsor configurations. The multitenant model reduces the maintenance associated with multiple application installations facilitating easier deployment of updated software versions and patches.

In addition, electronic trial systems are increasingly integrated. Digital health devices, such as wearable devices, are transmitting data via cellular phone networks/Wi-Fi through gateways and portals which may perform data aggregation into centralised data warehouses or into specific data fields within electronic case report forms (eCRFs).

The complexity of current ecosystems for electronic trial systems may have a significant impact on the ability to recommission such systems to a fully transactional state. As the level of integration increases, the challenges associated with recommissioning also rise accordingly.

6.4 User and Developer Competence

Over time, whilst it may be possible to source consulting expertise to assist in running legacy applications on outdated technology platforms in a timely manner in accordance with regulatory expectations, the necessary skill sets will become increasingly difficult to source. This may be coupled with the absence of necessary software patches resulting in a significant shift in the risk profile around the hosting of such electronic trial systems.

6.5 Technology Challenges

While maintenance activities can support the ongoing use of electronic trial systems for many years, it should be recognised that electronic systems do have defined operational life and that system retirements will be a necessity at some point in the system lifecycle. System vendors also rely on the availability of compatible and supported third party software (e.g., operating systems, databases, middleware) and infrastructure. Consequently, while the cost of physical or Cloud based memory now plays a smaller role in decision-making around decommissioning and archiving, external and other factors will impact the ability of vendors to support trial systems into the future including ongoing costs.

The integration of data from digital health devices or other data sources typically requires customised mapping of data points and a defined routine for extraction, transformation and loading (ETL) from one database to another. Such integrations add further complexity when seeking to keep electronic trial systems in a transactional state as multiple vendors/parties would need to ensure the ongoing operation of a multitude of systems.

Virtualisation technologies which are commonly used to enable hardware to host multiple operating systems and associated applications, also have constraints on their longevity. Virtual machines using proprietary operating systems, such as MS-Windows and applications or databases may require software licenses even if the electronic trial system is no longer in general use, adding levels of complexity. The virtualization technology also requires licensing, ongoing maintenance and qualification for any updates.

6.6 Alternatives to keeping computerised systems in operation

There is much to consider when attempting to retain data/meta-data in live systems into the future. Realistically, many of these factors are out of the control of a trial sponsor or a CRO. The most practical options open to sponsors are:

- Migration of all required data/meta-data into a new electronic trial system when the existing one is to be decommissioned.
- Archiving the data and metadata from the system with the required longevity.

Hardware devices, be they handheld or less portable, can be stored relatively easily. However, as time progresses, it will become increasingly difficult to operate and retrieve data off such devices because of hardware degradation. Practically, these factors limit the effectiveness of storing infrequently used hardware/software in the hope it can be powered up should the need arise, for example during a regulatory inspection.

6.6.1 Migration

The transfer of data/meta-data from one electronic trial system to another offers a route to maintaining for the long term such data on a technology platform. Migration can occur between systems hosted by sponsors or now typically involves

cloud environments, which reduces the IT infrastructure and application management demands placed on the sponsor.

Migration requires extensive planning, testing and qualification and does not alleviate the need for ongoing maintenance, change control, software patching, user management and software licencing. Migration can facilitate ongoing access but the use of vendor specific database schema, vendor specific data standard extensions and system specific functionality make such migration a significant effort.

Larger electronic trial systems used on-premise are typically highly embedded in sponsor/CRO work practices with associated IT support staff and data management teams. Such systems often host data from multiple customers and trials requiring the migration of significant data volumes which ramps up the complexity of the task.

Considering all the factors above which add complexity and cost to the migration approach, the joint task force recommends that archiving is adopted as the principal accepted means for enabling access to records from electronic trial systems into the long term.

6.6.2 Archiving

Archiving, as opposed to migration, offers the ability to transition data/meta-data from an electronic system to an appropriate file format which may be read by other software applications. Archiving provides the ability to access data/meta-data over an extended period, however, the intent with archiving is not to provide a user with the same features and functionality in the original electronic trial system.

Successful archiving is reliant on the following:

a) The availability of suitable data storage environments and periodic assessment of the archived data.
b) The use of appropriate file formats which facilitate future access to the data/meta-data.
c) Maintaining the integrity of stored data/meta-data over the required retention period.
d) The implementation of operational processes to support any requirements to extract data/meta-data in a suitable format in order to address legal retention and inspection requirements; for example, CRF retention by clinical investigators.

6.7 Archiving Environments

The selection of appropriate archiving technologies and implementation of archiving workflows and processes dictate how long files can be retained and how quickly they can be accessed. Environments need to be secure and protected against physical threats such as fire, flood and pests. The environments and the means to retrieve files should also be periodically assessed. Storage media will change over time as can be seen in the decreased use of optical media. Consideration must be given to determining if the technology in use is the current state of the art or is it necessary to copy archived data from one medium/format to a new or more modern one to ensure continued preservation. As technology is evolving at a high frequency, this should be a dynamic process. Considerations should also be given to duplicating or backing up archival copies of files to reduce the

potential for a single point of failure (e.g., hardware failure) impacting continuing availability of the data/meta-data.

6.8 File Formats

The choice of file formats for the archiving of data/meta-data is vitally important for ensuring ongoing access to the information. File formats exist as both open and vendor specific standards. Open standards are designed to permit data interchange or access across systems whereas vendor specific standards may require vendor specific software applications to open any files encoded using vendor standards. Open standards (e.g. ASCII, XML) may be laid down by ISO, IEEE, ANSI or other standards bodies for technology and specific industry bodies such as CDISC and DICOM may define domain requirements around the way that technology should be used.

Vendor specific file formats are a valid method of archiving providing that the sponsor/CRO has accepted that the means to read and access the data/meta-data may be associated with licensing costs and are dependent on the vendors ability to offer software/support into the future. If the technical formats the sponsor wishes to use for archival are not documented or not based on open standards, then they should consider having a suitable technical description as part of a contractual or service agreement to enable access independent of the existing software service.

As time progresses, vendor support for certain file types or formats may be retired. Hence consideration should be given to ensuring that data/meta-data is held in a supported file format depending on the tools vendors have to offer to access such data.

Regulators may identify specific file formats in legislation which are acceptable for submission purposes (such as PDF/A for submission to agencies of PDF representations of eCRFs). Usually, the file format will be required to be of a type that enables access by legacy software applications to ensure backwards compatibility.

Vendor specific file formats may include database dump files for electronic trial systems which typically store records within proprietary database schema. Vendor involvement may be required to create any required output from such files. Database dump files can potentially allow for the reinstatement of data/meta-data into recommissioned transactional systems. Changes over time to underlying applications, integrations, cloud environment and security remediation will limit the ability to mimic the original environment such as selection drop down items, navigation options and reporting capability). Cost of recommissioning may also be substantive.

Whether for the purposes of recording clinical data/meta-data, log files or system development or maintenance documentation, appropriate file types should be chosen to maximize the ability to retrieve information at a subsequent time point. It may be necessary to store data/meta-data in different formats to address evolving regulator needs to analyse trial data for the purposes of identifying intra/inter site trends, fraud or poor compliance practice.

6.9 Integrity

Archiving necessitates the provision of suitable mechanisms to ensure the integrity of any data/meta-data over the required retention period. Sponsors/CRO should ensure that there

are adequate measures in place to cover the retention period bearing in mind that rate of technology change may limit the practical life of a particular technology.

Integrity can be assured through various means. Hashing algorithms can generate hash values unique to individual files. Such values need to be retained and a means to rerun the hashing algorithm on these files should be available.

Data warehousing platforms can facilitate integrity with audit trails around stored files and current blockchain technology also offers the capability to confirm the authenticity and integrity of files. If audit trails are not sufficient and more digital trust is required, blockchain is suited to deployment across an enterprise as part of automated workflow processes. This approach may result in significant ongoing costs for maintenance of the blockchain infrastructure.

Files may be encrypted to protect against update/edit. Caution should be employed as the loss of the ability to decrypt the data would mean that the data is no longer available.

6.10 Operational Processes

To ensure that archived data/meta-data are retained appropriately and retrievable in usable format, responsible organizations should assess the risks associated with the data/meta-data and develop decommissioning, data archiving and retention plans supported by standard operating procedures/policies and good life cycle practices. The focus of such plans should be on the confidentiality, integrity and availability of the records with consideration to the potential data privacy needs of patients/consumers for data amendment or destruction.

Regardless of the file formats selected for archiving, suitable tools must be available to facilitate the periodic review, analysis or processing of data/meta-data. Open standards do permit files to be opened in a range of free or licensed software applications. For example, video, audio, PDF and text files can all be usually opened easily with a multitude of software. Once encryption, electronic signature or other technologies are applied to the files, specific technologies may be needed to successfully access the data/meta-data. The use of open standards to drive archiving is advantageous. However, careful thought must be given to how users will access data as it may be necessary to acquire/use file reader applications.

The use of open standards provides a possibility that file readers can be developed by a range of vendors or indeed the user population themselves.

The CDISC ODM standard is one example of an open standard, which has been created to permit the interchange of clinical data/meta-data and electronic signature information. The use of file readers in conjunction with a standards-based data export provides an approach that enables investigators, sponsors, CROs, regulatory and other interested parties to access clinical trial data/meta-data, while permitting a degree of navigation and querying.

Within the clinical research domain there may be a range of consumers of data/meta-data. Investigators, in particular work across multiple electronic trial systems as driven by sponsor/CRO demands. This variety of systems creates a diverse landscape of file types that need to be handled by investigators albeit the Portable Document Format (pdf) is frequently

used due to its versatility. The content of PDF files can vary to reflect both feature / functionality differences across systems and protocol driven requirements and as such there is variation in the way data/meta-data are presented.

7 Conclusions

Investigational sites are obliged to maintain records of data collected during the trial and reported to sponsors using electronic trial systems. A similar requirement is placed on sponsors. Historic practices have resulted in data being retained in static formats such as pdf, but this limits the ability of regulatory agency inspectors to perform dynamic reviews.

The export of data/meta-data to suitable archiving formats provides a practical and realistic alternative to migration or the recommissioning retired systems. The archiving of trial data/meta-data in conjunction with the availability of system documentation supports the premise that “live” transactional electronic trial systems are not required for the full retention period.

Migration of data/meta-data to alternate operational electronic trial systems offers a potential solution to retain data in an accessible and inspectable manner in the long term. However, this approach has a substantial effort/cost for ongoing maintenance and change control, and may need to be repeated multiple times.

The recommissioning of systems to facilitate regulatory investigation offers significant technical challenges and is seen as a risk filled approach, the reasons for this have been elaborated in this white paper.

8 About the Authors

This white paper was authored by the EUCROF and eClinical Forum Joint Task Force on Archiving and Decommissioning.

You can contact the task force via the EUCROF and eClinical Forum websites (www.eucrof.eu and www.eclinicalforum.org) if you would like more information or if you have any comments on the contents of this white paper.

Although the Task Force was initiated as a joint effort by EUCROF and the eClinical Forum, team members representing the following organisations have also participated in the authoring of this white paper:

- ECRIN - https://ecrin.org/
- The ePRO Consortium - https://c-path.org/programs/eproc/
- Medicines for Europe - https://www.medicinesforeurope.com/
- RQA - https://www.therqa.com/

We would also like to thank the many organisations and individuals who reviewed and commented on this white paper before we released it.

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