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Final version of quality assurance system ready for implementation in industry and academia in non-regulated research

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European Quality In Preclinical Data

WP5 – New quality management system in emerging and classical technologies to improve preclinical robustness

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V2.0	28 Sep 2020	Draft sent to PMO team for review
V3.0	01 Oct 2020	Final Version

Publishable Summary

The EQIPD Quality System (QS) has been designed by the EQIPD WP5 / WP6 / WP7 teams to facilitate generation of robust and reliable preclinical data while being lean, effective and not becoming a burden for the user.

EQIPD defines research quality as the extent to which research data are fit for their intended use. Fitness, in this context, is defined by the stakeholders, who are the scientists directly involved in the research, but also their funders, sponsors, publishers, research tool manufacturers and collaboration partners such as peers in a multi-site research project.

The essence of the EQIPD QS is the set of 18 core requirements that can be addressed flexibly, according to user-specific needs and following a user-defined trajectory. These core requirements reflect the following principles:

- Management and research units recognize the need to implement high research quality standards and commit to development and maintenance of scientific quality.
- Functional fitness of scientific quality is promoted through built-in continuous improvement mechanisms.
- Optimal quality scientific data requires competent teams to actively engage in the implementation, maintenance and further development of a QS at all times.
- Scientific and data integrity must be ensured at all times.

The EQIPD QS proposes guidance on various quality-related measures, defines criteria for adequate processes (i.e., performance standards) and provides examples of how such measures can be developed and implemented. However, EQIPD does not prescribe any pre-determined solutions.

EQIPD has developed basic tools (for optional use) to support users in implementing the QS:

- Planning tool (with the Creator tool): primary user interface to review the needs specific to their environment and focus of research.
- Toolbox: structured collection of information enabling users to build or select solutions for customized research needs.

The EQIPD QS can be applied in both public and private research sectors and is free for anyone to use.

While the present report describes the final version of the QS, the EQIPD team continues to work on various efforts to enable the maintenance and further development of the EQIPD QS framework beyond the IMI project phase: a novel governance model, external assessment mechanisms, an educational platform, analysis of geographical and cultural aspects of the EQIPD QS implementation, and evaluation of the impact of implementation of the EQIPD QS on research quality.

Final version of the Quality System

The Quality System has been developed by the WP5 team in a close collaboration with WP6 (governance aspects) and WP7 (training materials).

The following table provides an overview of various elements of the final version of the EQIPD QS framework:

No.	Description	Type	Location
1	White paper introducing the EQIPD QS (main text and supplementary information)	Text files (preprint)	link
2	A set of core of requirements	List	link
3	Toolbox	Wiki site	link
4	Planning tool	Excel file	link
5	Creator tool	Excel file	link
6	Glossary	List	link
7	Why quality matters?	Presentation	link
8	EQIPD QS: Why, what and how?	Presentation	link
9	A set of “external needs” (concise summaries of quality expectations of various stakeholder groups)	Excel files	link
10	A set of templates for addressing various core requirements and recommendations of the EQIPD QS: - self-assessment - risk assessment - study (experimental) plan - protocol for experimental methods - animal care and use - mission statement - communication plan - documentation plan - error reporting - guidance for experimental record keeping under contract research - implementation diary		link

The EQIPD Quality System: Key features

Flexible: Driven by the needs of an individual research unit

In the context of the EQIPD QS, a research unit can be a lab or part thereof, a department, an institute, a company or another institution performing research.

Research environments are highly diverse: the needs of researchers at a big pharma company may be different from those at a biotech; the needs of CROs may be different from those of academic labs, etc. Thus, improving data quality is a challenge that cannot be tackled using a one-size-fits-all solution and flexibility is a critical requirement for future success.

The EQIPD QS is flexible: researchers are not confronted with a long and ultimate A-to-Z list of what must or should be done and in what sequence. Instead, implementation of the EQIPD QS is characterized by:

- user-specific content – i.e., the exact nature of the individual elements of the EQIPD QS are defined largely by the users and their environment;
- a variable trajectory – i.e., there are very limited expectations regarding the sequence of introducing the different elements of the EQIPD QS; and
- no deadlines or fixed timelines – i.e., each unit adopts the EQIPD QS at its own pace, depending on the existing needs and available resources.

EQIPD has developed tools (for optional use) that help scientists identify and organize information to address their own customized needs (e.g., related to *my* research funding source, *my* national regulations for the use of animals, expectations of *my* collaboration partners, policies set by *my* institution, *my* own commitment to research rigor, etc.). Being unique to a research unit or a researcher, such needs can be very specific to local or personal circumstances (i.e., essential for *my* success, *my* funding, *my* career, for instance because of the requirements of *my* preferred funder), and as such may be addressed with a higher or lower priority. Based on these factors, each research unit or researcher can determine their sequence of actions. EQIPD tools offer examples and ready-to-use solutions as well as information to develop new user-specific solutions.

For example, EQIPD has reviewed research quality expectations of several major public funders and pharmaceutical companies. Summaries of these expectations as well as examples of how these expectations can be met are available for downloading and can be imported directly into EQIPD tools to organize the EQIPD Quality System information that is relevant for them.

Team effort: Understanding and endorsing research quality objectives

The focus on the specific needs of an individual research unit is ensured by the Process Owner, a person within the organization who has access to the necessary resources, and the competence and the authority to implement all steps needed to establish the EQIPD QS. Typically, the Process Owner should be someone who directs the work of the research unit (e.g., group leader, principal investigator, CEO or department head) and is knowledgeable about the importance of quality in research. EQIPD expects the Process Owner to be identified at the very first step of implementing the EQIPD Quality System (core requirement #1).

In the second step, the Process Owner defines the scope - i.e., the research unit (lab, territory, organization or part thereof) where the EQIPD Quality System will be applied - and identifies colleagues who will be actively involved in working on the implementation, as well as those who will be informed and may need to be trained about the new process (core requirement #2). To that end, the Process Owner sets up a communication plan to support the team's buy-in and to facilitate two-way information flow, in order to also capture feedback related to performance of the existing and newly introduced practices.

EQIPD also expects research units to define quality objectives (core requirement #3). Although it may sound formal, this core requirement is indispensable and should be articulated at a level understandable and meaningful to everyone in the research unit.

Why are quality objectives needed? Once the Process Owner has decided to accept the role and responsibilities and has defined the research unit where the EQIPD Quality System will be implemented, it is worth getting prepared to answer questions that will likely come from colleagues inside and outside of the research unit: why are we doing this if, at least today, no such quality system is required by funders or collaboration partners and

if, at least on first sight, we can successfully meet the goals without changing anything?

The answer to these questions helps justify the efforts and time to be invested in the implementation and maintenance of the QS. It also provides an argument by balancing the potentially negative impact on traditional metrics of scientific success (e.g., fewer positive results generated, more time needed to complete projects) against the value of higher quality research (greater confidence in the results and scientific interpretations when results are shared with peers or published, improved rigor in decision making, publication in high-profile journals, etc.).

In EQIPD terms, the answer should be documented as a mission statement, i.e., a concise summary of why quality matters for that specific research unit. EQIPD provides examples of how scientists working in different roles and at various types of organizations may answer the question "why quality matters".

It is important that the mission statement is understood, willingly accepted and followed by all members of the research unit.

If a Process Owner, alone or together with the research team members, cannot generate a clear and convincing answer to this question, no further steps should be taken and the implementation of the quality system is best postponed until a good answer is found and the research team is willing to accept a quality mindset.

EQIPD Quality System as part of the overall organizational quality culture

The Process Owner may also be asked and should be prepared to explain that the EQIPD Quality System does not replace and does not intend to re-interpret any of the existing rules, policies and other quality systems (which focus on specific areas) that apply to the research unit's environment.

EQIPD mandates that "all activities must comply with relevant legislation and policies" (core requirement #4) and that a "research unit must have a procedure to act upon concerns of potential misconduct" (core requirement #5). If, for the vast majority of organizations, no additional effort will be required to meet these expectations, why are they included in the list of core requirements?

First, EQIPD does not want to be associated with organizations that engage in or tolerate unacceptable ethical practices or legal violations.

Second, the EQIPD QS is focused on quality, not legislation. Legislation may differ from country to country and for different research activities; hence, it is not possible to specify these individually in the EQIPD QS. Furthermore, EQIPD cannot oversee the way an organization deals with the legal requirements of, e.g., handling hazardous substances, but emphasizes the need for compliance with such regulations as a basis on which all other quality measures rest.

Another example concerns the care and use of laboratory animals that play a pivotal role in the research process. Society has granted the biomedical research community with the privilege to use laboratory animals in research under very specific conditions, all aiming to prevent inappropriate use of these ethically highly sensitive resources. Clearly, it is not acceptable to waste animals due to poor study design, conduct or analysis.

Ethical concerns on the use of animals in research have promoted the creation of a legal framework in almost every country (e.g. Animal Welfare Act in the US; Directive 2010/63 in the EU). Scientific evidence demonstrates that many aspects of animal care and use that are beyond the legal requirements have a direct impact on research results. The EQIPD team has developed a concise checklist that allows scientists to review whether their animal care and use processes meet at least a minimum standard that supports the implementation and maintenance of the EQIPD QS. This review could optionally serve as the basis for further, more specific accreditation of the animal care and use program (i.e., AAALAC International accreditation) to ensure the implementation of high standards of animal care and use that would further contribute to increasing the quality of research.

EQIPD-defined principles, user-defined content

Implementation of the EQIPD QS does not require researchers to stop or reduce ongoing experimental work. It is designed so that it takes only minimal effort to sign up and begin the journey towards a quality system that should help researchers gradually improve certain quality aspects of their work.

The EQIPD QS gives guidance on expectations for quality-related measures, defines criteria for adequate processes (i.e., performance standards) and provides examples of how such measures can be developed and

implemented. However, it does not prescribe any pre-determined solutions. Rather, users define their own specific solutions tailored to their individual settings.

For example, integrity of research data is one of the central concepts that the EQIPD QS aims to support. Four core requirements define the desired outcomes for raw data generation and handling (core requirement #6), data storage (core requirement #7), data traceability (core requirement #8), and transparency of reported data (core requirement #9). Thus, the "what" is clearly described. However, there are various ways to fulfil these requirements. For instance, secure data storage could be achieved by using conventional paper-based laboratory notebooks, electronic laboratory notebooks, custom-built electronic solutions or paper-based controlled-access archives. Thus, there is flexibility in how integrity of research data could be achieved, and it is for the users of the system to decide on the best solution for their specific situation.

Focused on the generation of fit-for-purpose research data

In general, EQIPD recommends that scientists apply protection against risks of bias for every study and unambiguously disclose the protective measures used. Each study has a particular purpose and the rigor applied to the study should be defined, documented in advance and be commensurate with the purpose of the study.

There are modes of research that can tolerate a certain level of uncertainty and do not lead to a formal knowledge claim. Such work is an essential part of the research process and may be used to generate hypotheses or to provide evidence to give the investigator greater confidence that an emerging hypothesis is valid, to develop new methods or to "screen" compounds for potential effects prior to more formal testing.

There are also modes of research where researchers cannot accept inadequate control of the risks that can bias the research results. For research that is conducted with the prior intention of informing a knowledge claim, EQIPD requires that maximal possible rigor is applied (and exceptions explained and documented in the study plan). Such research will usually (but not always) involve some form of null hypothesis statistical testing or formal Bayesian analysis. Here, hypotheses are articulated in advance of data collection, with pre-specified criteria defining the primary outcome measure and the statistical test to be used.

Examples of research requiring maximal possible rigor may include:

- Experimental studies to scrutinize preclinical findings through replication of results;
- Research aimed at generating evidence that enables decisions which will invoke substantial future investment (e.g., a decision to initiate a new drug development project or to initiate GLP safety assessment of a new drug candidate);
- Studies for which any outcome would be considered diagnostic evidence about a claim from prior research;
- Labour-, resource- and/or time-intensive studies that cannot be easily repeated.

EQIPD requires that investigators assert in advance whether a study will be conducted to inform a formal knowledge claim (core requirement #10), and that they explicitly state this in the study (experimental) plans prepared before studies and experiments are conducted.

Further, it is required for all types of research that everyone in the research unit is adequately trained and competent (core requirement #11), has access to protocols for experimental methods (core requirement #12), follows adequate procedures for the handling and storage of samples and materials (core requirement #13), and uses research equipment and tools that are suitable for the intended use (core requirement #14).

A system, not just a collection of guidelines and recommendations

Development and implementation of flexible and fit-for-purpose solutions are usually enabled by introducing a continuous improvement process. Within the EQIPD environment, the improvement cycle is rooted in the following workflow:

- Understand the rationale for introducing something new or modifying the current work routine (Why - the Need);
- Understand what is needed to achieve it (What - the Challenge);
- Propose a solution for achieving it (How - fit-for-purpose Solution);

- Evaluate the success of the implementation (Assessment).

As an example, a research organization is seeking a collaboration with a biopharmaceutical company (Why). The company informs the research organization about its expectations regarding raw data record generation, handling and storage. The research organization recognizes challenges associated with the storage of raw data as defined by the company (What). The EQIPD Toolbox provides information on what is the raw data and what are the best practices in recording and handling the raw data (How). In many cases, the new way of working is applied and has the desired effect. In some cases, there may be deficiencies identified that require remediation such as changes in the protocols, additional communication, educational and training efforts. Evaluation of the success in implementation of new processes concludes the cycle (Assessment).

In addition, the successful use of a new method or procedure often requires training, adequate and timely communication, feedback on incidents and errors, etc. To fully establish the EQIPD QS, several corrective or feedback mechanisms have to be included. These mechanisms identify factors affecting the generation, processing and reporting of research data *before* a study is done (core requirement #15), to analyze and manage the incidents and errors that may occur *during* the study (core requirement #16), and to monitor the performance of the EQIPD QS (core requirement #17).

Enhancing Quality in Preclinical Data (EQIPD): The Outlook

The EQIPD QS will be released for broad deployment and unrestricted use by the research community.

To enable the maintenance and further development of the EQIPD framework beyond the IMI project phase (after 30 September 2021), the EQIPD team is developing a governance model. The proposed model comprises three closely interacting levels:

- A strategic level represented by the EQIPD Guarantors, a group of the EQIPD project team members responsible for the overall guidance, administration of academic and educational programs, and the dissemination of the EQIPD vision. The EQIPD Guarantors will be supported by an Ethics & Advisory Board, a consultative body composed of current EQIPD consortium members, associate collaborators and advisors as well as key opinion leaders in the field of good research practice.
- An operational level represented by an independent globally acting partner organization, to be commissioned by the EQIPD Guarantors to provide the operational support and services required for day-to-day business management (including technical support and training for the research units during the implementation and maintenance of the EQIPD Quality System).
- A community level that is represented by the EQIPD Stakeholder group, a diverse group of scientists, funders, quality professionals, manufacturers of research tools, and publishers that provide feedback on practical aspects of the EQIPD QS and facilitates connections to a broader biomedical research community.

The next milestones for the EQIPD team are:

- Implementation of external assessment mechanisms that will provide those research units that successfully implemented the EQIPD QS with a certificate of EQIPD compliance;
- Launch of an educational platform that will support both the use of the EQIPD QS and provide a more general training in the field of good research practice;
- Analysis of geographical and cultural differences that may affect the acceptance of the EQIPD QS and that may require adaptations in the associated framework;
- Evaluation of the impact of implementation of the EQIPD QS on research quality, to inform further development of the EQIPD framework.

The EQIPD QS was developed with the focus on the users and their needs.

The EQIPD team is actively engaged in discussions with funders (public and private) and publishers to develop instruments and mechanisms that will allow scientists to further benefit from the use of the EQIPD QS.

All scientists engaged in preclinical biomedical research are invited to join the growing community of the EQIPD QS users and supporters (www.eqipd.org).