Introduction to the EQIPD Quality System

Anton Bespalov[1]*, René Bernard[2]*, Anja Gilis[3]*, Björn Gerlach[1]*, Javier Guillen[4], Vincent Castagné[5], Isabel A. Lefevre[6], Fiona Ducrey[7], Lee Monk[8], Sandrine Bongiovanni[9], Bruce Altevogt[10], María Arroyo-Araujo[11], Lior Bikovski[12,13], Natasja de Bruin[14], Esmeralda Castaños-Vélez[2], Alexander Dityatev[15,16,17], Christoph Emmerich[1], Raafat Fares[18], Chantelle Ferland-Beckham[19], Christelle Froger-Colléaux[5], Valerie Gailus-Durner[20], Sabine M. Hölter[21], Martine Hofmann[14], Patricia Kabitzke[22,23], Martien J. Kas[11], Claudia Kurreck[2], Paul Moser[24,25], Malgorzata Pietraszek[1], Piotr Popik[26], Heidrun Potschka[27], Ernesto Prado Montes de Oca[28,29,30], Leonardo Restivo[31], Gernot Riedel[32], Merel Ritskes-Hoitinga[33,34], Janko Samardzic[35], Michael Schunn[36], Claudia Stöger[20], Vootele Voikar[37], Jan Vollert[38], Kim Wever[33], Kathleen Wuyts[39], Malcolm Macleod[40], Ulrich Dirnagl[2,41], Thomas Steckler[3]

* these authors contributed equally to this work

[1]PAASP, Heidelberg, Germany; [2]Department of Experimental Neurology, Charité Universitätsmedizin, Berlin, Germany; [3]Janssen Pharmaceutica NV, Beerse, Belgium; [4]AAALAC International, Pamplona, Spain; [5]Porsolt, Le Genest-Saint-Isle, France; [6]Rare and Neurologic Diseases Research, Sanofi, Chilly-Mazarin, France; [7]Integrity and Global Research Practices, Sanofi, Chilly-Mazarin, France; [8]Research and Clinical Development Quality, UCB, Slough, UK; [9]Quality Assurance, Novartis Institutes for BioMedical Research, Novartis Pharma, Basel, Switzerland; [10]Pfizer, Silver Spring, MD, USA; [11]Groningen Institute for Evolutionary Life Sciences, University of Groningen, Groningen, The Netherlands; [12]The Myers Neuro-Behavioral Core Facility, Sackler School of Medicine, Tel Aviv University, Israel; [13]School of Behavioral Sciences, Netanya Academic College, Netanya, Israel; [14]Fraunhofer Institute for Molecular Biology and Applied Ecology IME, Branch for Translational Medicine and Pharmacology TMP, Frankfurt am Main, Germany; [15]Molecular Neuroplasticity, German Center for Neurodegenerative Diseases, Magdeburg, Germany; [16]Center for Behavioral Brain Sciences, Magdeburg, Germany; [17]Medical Faculty, Otto-von-Guericke University, Magdeburg, Germany; [18]Charles River Laboratories, Safety Assessment, Lyon, France; Current affiliation: Etisense SAS, R&D department, Lyon, France; [19]Cohen Veterans Bioscience, Boston, MA, USA; [20]German Mouse Clinic, Institute of Experimental Genetics, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany; [21]Institute of Developmental Genetics, Helmholtz Zentrum München, German Research Center for Environmental Health, and Technical University Munich, Germany; [22]PAASP US, Ridgefield, CT, USA; [23]The Stanley Center for Psychiatric Research, Broad Institute of MIT & Harvard, Cambridge, MA 02142; [24]Cerbascience, Toulouse, France; [25]PAASP France, Toulouse, France; [26]Maj Institute of Pharmacology, Polish Academy of Sciences, Krakow, Poland; [27]Institute of Pharmacology, Toxicology and Pharmacy, Ludwig-Maximilians-University, Munich, Germany; [28]Research Center in Technology and Design Assistance of Jalisco State, National Council of Science and Technology, Guadalajara, Jalisco, Mexico; [29]Scripps Research Translational Institute, La Jolla, CA, USA; [30]Integrative Structural and Computational Biology, Scripps Research, La Jolla, CA, USA; [31]Neuro-BAU, Department of Fundamental Neurosciences, University of Lausanne, Lausanne, Switzerland; [32]Institute of Medical Sciences, University of Aberdeen, Scotland, UK; [33]SYRCLE, Department for Health Evidence, Radboud

University Medical Center, Nijmegen, the Netherlands; [34]Department for Clinical Medicine, Aarhus University, Denmark; [35]Institute of Pharmacology, Medical Faculty, University of Belgrade, Serbia; [36]Institute of Science and Technology, Klosterneuburg, Austria; [37]Neuroscience Center and Laboratory Animal Center, Helsinki Institute of Life Science, University of Helsinki, Finland; [38]Pain Reearch, Department of Surgery and Cancer, Faculty of Medicine, Imperial College London, London, UK; [39]Avertim, Brussels, Belgium; [40]Centre for Clinical Brain Sciences, University of Edinburgh, Scotland, UK; [41]QUEST Center for Transforming Biomedical Research, Berlin Institute of Health, Germany

Abstract

While high risk of failure is an inherent part of developing innovative therapies, it can be reduced by adherence to evidence-based rigorous research practices. Numerous analyses conducted to date have clearly identified measures that need to be taken to improve research rigor. Supported through the European Union's Innovative Medicines Initiative, the EQIPD consortium has developed a novel preclinical research quality system that can be applied in both public and private sectors and is free for anyone to use. The EQIPD Quality System was designed to be suited to boost innovation by ensuring the generation of robust and reliable preclinical data while being lean, effective and not becoming a burden that could negatively impact the freedom to explore scientific questions. 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 Quality System is the set of 18 core requirements that can be addressed flexibly, according to user-specific needs and following a user-defined trajectory. The EQIPD Quality System proposes 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. EQIPD has also developed tools (for optional use) to support users in implementing the system. Further, EQIPD is preparing training support and assessment services for those research units that successfully implement the quality system and would like to seek formal accreditation. Building upon the feedback from users and continuous improvement, a sustainable EQIPD Quality System will ultimately serve the entire community of scientists conducting non-regulated preclinical research, by helping them generate reliable data that are fit for their intended use.

Word count - 321

The challenge: Discovery of novel therapies requires rigor in research practices

The success rate in the discovery of novel, safe and effective pharmacotherapies has been declining steadily over the last few decades (Scannell et al., 2012). There are several factors likely accounting for this unfortunate record (DiMasi et al., 2016; Waring et al., 2015; Shih et al., 2018). While some of these factors (e.g., deeper knowledge of disease biology or clinical trial methodology) will take years, if not decades, of continued research to be properly addressed, others can be readily controlled today (Bespalov et al., 2016; Landis et al., 2012). One area requiring immediate attention is research rigor, which is estimated to be lacking in 50-90% of preclinical studies (Freedman et al., 2012).

High risk of failure is an inherent part of developing innovative therapies (DiMasi et al., 2016). However, some risks can be greatly reduced and avoided by adherence to evidence-based rigorous research practices. Indeed, numerous analyses conducted to date have clearly identified measures that need to be taken to improve research rigor (Begley and Ioannidis, 2015; Landis et al., 2012; Ritskes-Hoitinga and Wever, 2018; Vollert et al., 2020; Volsen and Masson, 2009).

The EQIPD consortium: Enhancing research quality as the main objective

Improving research rigor has biomedical, societal, personal, economic and ethical benefits for academia and industry alike, since the development of novel therapies is often rooted in academic discoveries and requires a highly specialized effort of industry to translate these discoveries into clinically useful applications. Moreover, this simple dichotomy between purely academic research and large industry/big pharma efforts is currently being replaced by networks of biotechs, spin-offs, private and public funders, contract research organizations (CROs), academic institutions engaging in drug discovery projects and manufacturers of research tools. It is therefore important that strategies to increase the robustness and reliability of preclinical research, both in terms of conduct and reporting, involve all these different stakeholders.

To address this challenge in preclinical biomedical research in a collaborative manner, the Enhancing Quality in Preclinical Data (EQIPD; originally called European Quality in Preclinical Data) consortium was formed in 2017 with founding members from 29 institutions across 8 different countries (https://quality-preclinical-data.eu). The consortium works closely with a large group of associated collaborators, advisors and stakeholders representing research institutions, publishers, funders, learned societies and professional societies, from nearly 100 organizations in Europe and the US.

Supported through the European Union's Innovative Medicines Initiative (IMI), the EQIPD consortium, among other deliverables, aimed to develop a novel preclinical research quality system that can be applied in both the public and private sectors. Such a quality system should be suited to boost innovation by ensuring the generation of robust and reliable preclinical data while being lean, effective and not becoming a burden that could negatively impact the freedom to explore scientific questions.

EQIPD defines research quality as the extent to which research data are fit for intended use (for related definitions and explanations, see Juran and Godfrey, 1999; Gilis, 2020). Fitness, in this context, is defined by the stakeholders, who can be scientists

themselves, but also patients, funders, sponsors, publishers and collaboration partners (e.g., peers in a multi-site research project).

The EQIPD consortium has developed a quality system that is free for anyone to use. Further, EQIPD is preparing training support and assessment services for those research units that successfully implement the quality system and would like to seek formal accreditation.

A *new* quality system to boost innovation

Quality systems usually appear as a response to an existing need (Table 1). For example, the development of the Good Laboratory Practice (GLP) standards, introduced first by the Food and Drug Administration (FDA) in the late 1970s, was triggered by poor research practices that compromised human health, such as mis-identification of control and experimental animals, omitted, non-reported or suppressed scientific findings, data inventions, dead animal replacements and mis-dosing of test animals (Bongiovanni et al., 2020; Marshall, 1983). In the Organisation for Economic Co-operation and Development (OECD) Principles (https://www.oecd.org/chemicalsafety/testing/overview-of-good-laboratory-practice.htm), GLP is defined as "a quality system concerned with *the organisational process and the conditions* under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported".

GLP is a standard approach to quality in the regulated areas of preclinical drug development (which largely relate to non-clinical safety and toxicology studies rather than efficacy; see Supplement S1 Glossary for a definition of regulated research), where trained personnel perform mainly routine analyses, following defined Standard Operating Procedures (SOPs), and deliver data ultimately supporting patient safety.

There have been attempts to develop a quality system based on GLP – i.e., taking GLP as the basis and eliminating elements that are seen as excessive for the purposes of non-regulated drug discovery. However, GLP does not provide explicit guidance regarding those aspects of study design, conduct, analysis and reporting that are important to minimize the risk of bias and make research robust. In other words, even if it were made less demanding, conventional GLP cannot address some of today's key challenges in non-regulated preclinical research.

In contrast, the EQIPD Quality System is a novel system specifically aimed at supporting innovation in preclinical biomedical research. While the direct consequence of installing a quality system will be the generation of research data that are of higher rigor, the ultimate goal is to improve the efficiency of developing novel effective and safe therapies.

Development of a new quality system by EQIPD

EQIPD was started in October 2017 and during the first phase (until June 2018), three work packages of the EQIPD consortium have delivered:

- A systematic review of guidelines for internal validity in the design, conduct and analysis of research involving laboratory animals (Vollert et al., 2020);

- An inventory of current practices and expectations towards quality management in non-regulated preclinical research (based on interviews with 70 consortium members and stakeholders);
- A review and analysis of governance in existing quality management systems (AAALAC International; ASQ Best Quality Practices for Biomedical Research in Drug Development; BBSRC Joint Code of Practice; ISO 9001, ISO 17025, ISO 15189; Janssen discovery quality system; Novartis research quality system; OECD Principles of GLP; RQA – Quality Systems Workbook).

During the second phase (July 2018 - January 2019), a working group was assembled from the EQIPD consortium members (n=20). Based on the collected information, the working group nominated 75 statements that could define a functional quality system in non-regulated research. After three Delphi feedback rounds and two consensus meetings, these statements were revised, resulting in a final list of 18 core requirements (Table 2; see below for details).

During the third phase (February 2019 – September 2019), a supporting framework was developed (see below) and pilot implementation of the quality system started at four independent research sites.

Based on the feedback from those pilot implementation sites and interactions with the stakeholder group, an updated version of the framework was released for beta-testing in November 2019. The official launch of the final version of the quality system is scheduled for September 2020.

The EQIPD Quality System: Key features

Flexible: Driven by the needs of an individual research unit

Research environments are highly diverse: the needs of researchers at a big pharma company are different from those at a biotech; the needs of CROs are 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 Quality System is flexible: researchers are not confronted with a long and ultimate A-to-Z list of what should be done and in what sequence. Instead, implementation of the EQIPD Quality System is characterized by:

- user-specific content – i.e., the exact nature of the individual elements of the EQIPD Quality System 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 Quality System; and
- no deadlines or fixed timelines – i.e., each unit adopts the EQIPD Quality System 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 (Figure 1). 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 (see Support Tools below).

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 Quality System. 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 (Table 2; 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 quality system. 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" (https://osf.io/vduze).

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 Quality System 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 Quality System. 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 (Guillén and Steckler, 2020). The EQIPD team has developed a concise checklist that allows scientists to review if their animal care and use processes meet at least a minimum standard that supports the implementation and maintenance of the EQIPD Quality System. 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 (Supplement S2 Animal care and use checklist).

EQIPD-defined principles, user-defined content

Implementation of the EQIPD Quality System 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 Quality System 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 Quality System 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 (see Supplement S1 Glossary for definition). 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 (Dirnagl, 2016; Hooijmans et al., 2014). 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; see Table 3). 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 (Kimmelman et al., 2014);
- 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 (Nosek and Errington, 2020);
- 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 (Deming, 1986). 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 the 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 Quality System, 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; see Box 1), 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 Quality System (core requirement #17; see Box 2).

Defining the user of the EQIPD Quality System

The ultimate mission of the EQIPD Quality System is to serve the entire community of scientists conducting non-regulated preclinical biomedical research. To achieve this goal, EQIPD has developed and is executing a dissemination strategy that will *initially* focus on early adopters, i.e., research groups and scientists who:

1. See the value of higher standards of rigor in research to achieve more robust and reliable results, are willing to learn about and adopt a quality mindset and are prepared to invest effort to set up the EQIPD Quality System;
2. Consider their standards of rigor are already good, but strive to improve them further, and would like to establish the EQIPD Quality System as an independent *seal of quality*;
3. Can use the EQIPD Quality System to strengthen a grant application, to support decision-making in drug discovery and /or to promote their services (e.g., CROs or academic labs active in the contract research domain) and bolster their reputation;
4. Are motivated by their funders, publishers and collaboration partners to secure high-rigor research standards (e.g., as a condition for funding or collaboration).

Such early adopters are known to be of critical value in every field where a cultural change is under discussion. For instance, academic initiatives have successfully addressed research data management and sharing of best practices by introducing Data Champions that serve as local advocates for good data practices (e.g., https://www.data.cam.ac.uk/intro-data-champions). Peer-to-peer learning eventually supports the dissemination of good practices beyond the early adopters.

The early adopters of the EQIPD Quality System, through their feedback to the EQIPD consortium, will help optimize the balance between the benefits of implementing such a system and any potential adverse consequences (e.g., resources allocated, reduction in conventional indices of scientific productivity). A positive balance will support further dissemination of the EQIPD Quality System and help broader research communities take advantage of the work done by the EQIPD team and the early adopters.

Since the scientists themselves will be the main users of the EQIPD Quality System, their leading and proactive role in improving the quality of their own scientific data is a cornerstone of the strategy to improve the utility of preclinical research.

Implementation of the EQIPD Quality System

Even a lean and user-friendly quality system requires effort and resources to be implemented and maintained. This consideration makes it important to emphasize that a decision to start implementing the EQIPD Quality System should be well justified and regularly checked by the Process Owner and discussed with the research team.

Size of the research unit

Ideally, the EQIPD Quality System should be implemented at the level of an organization (university, research institute, or a company). While this is the desired case, EQIPD encourages the transition towards better quality practices at the level of individual labs, departments or research groups, no matter how small they are, provided that there is a researcher capable, authorized and willing to take on the role of Process Owner.

The EQIPD Quality System is not intended to be used at the level of individual projects. Otherwise, it may create confusion and increase the risk of errors as the same people within a research unit may follow separate research quality practices depending on the project that they are working on.

Implementation path

There are several ways in which the EQIPD core requirements can be introduced within a research unit in terms of timing and sequence. Whether supported by the EQIPD Tools or not, any of the possible implementation scenarios are acceptable as long as the outcome is the same – i.e., a quality system implementing all 18 core requirements.

The implementation path suggested by EQIPD envisions three phases (Supplement S3 Implementation path):

Phase 1– A short list of cornerstone actions that are the same for all research units to help users understand why things are done, as well as ensuring that efforts triggered by the EQIPD framework have immediate impact (e.g., best practices to support data integrity and traceability).

Phase 2 – Users develop solutions for challenges directly connected to their environment or needs communicated by their funders, publishers and collaboration partners. During this phase, users meet most of the EQIPD core requirements while developing a habit of working towards a quality system.

Phase 3 – Completion of the remaining core requirements enabling formal recognition of a functional quality system.

The implementation is concluded with an important sustainability checkpoint: the Process Owner is expected to estimate the required resources and make them available for maintaining the EQIPD Quality System (core requirement #18).

Supporting tools

EQIPD has developed several tools (Figure 2; Supplement S4 Key tools) to support the implementation and maintenance of the Quality System:

- The Toolbox is a structured collection of information that enables users to build or select solutions for customized research needs. This Toolbox is built using wiki principles. The Toolbox contains a growing body of information about existing guidelines, recommendations, examples, templates, links to other

resources, literature references, or just guidance on how to address a specific topic and will be regularly updated.

- The Planning Tool is a user interface, designed to review the needs of researchers and is specific to their environment and focus of their research. Summarized expectations of funders, publishers, and collaboration partners can be entered in the Planning Tool either directly or using a special template called the Creator Tool.
- The Dossier is a structured collection of customized documents and information related to research quality in a given research unit.

EQIPD does not intend to insist that researchers use these tools and rather sees their application as optional.

Enhancing Quality in Preclinical Data (EQIPD): The Outlook

At the end of the IMI funding period on September 30, 2020, the EQIPD Quality System 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, the EQIPD team is developing a governance model (Figure 3). 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 Quality System 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 Quality System with a certificate of EQIPD compliance;
- Launch of an educational platform that will support both the use of the EQIPD Quality System 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 Quality System and that may require adaptations in the associated framework;

- Evaluation of the impact of implementation of the EQIPD Quality System on research quality, to inform further development of the EQIPD framework.

The EQIPD Quality System was developed with the focus on the users and their needs. The EQIPD collaborators will maintain and expand this focus further.

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 Quality System.

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

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Disclosures

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FIGURE 1

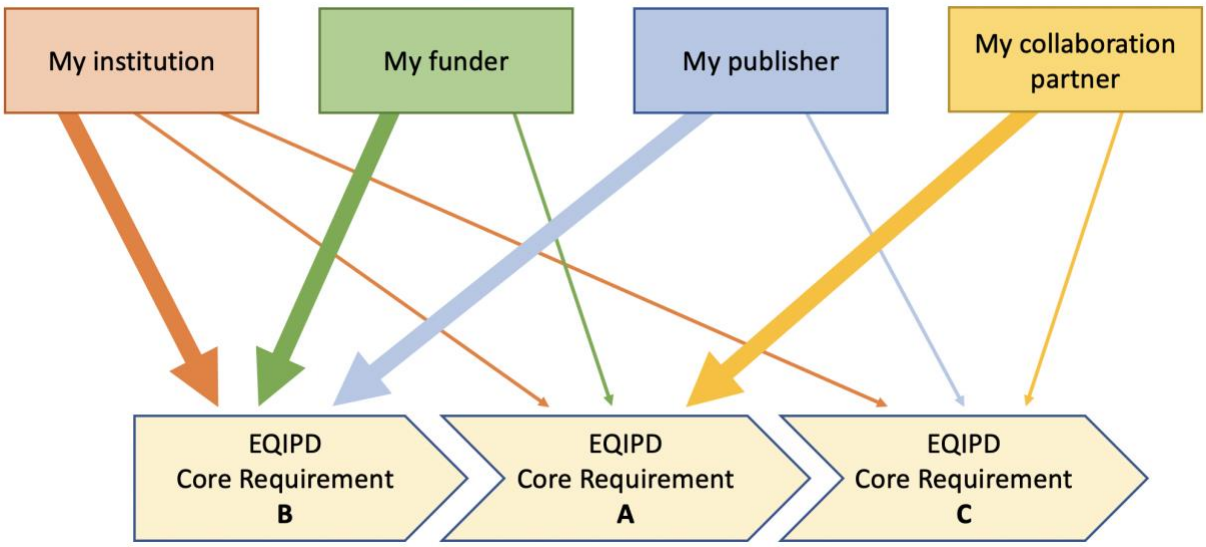


Figure 1: Flexible sequence of implementation of the EQIPD core requirements. Depending on the current needs, a research unit may prioritize implementation of one or another core requirement. For example, tasks related to core requirement “B” are highly relevant for the research unit’s parent institution, the funding organization and a scientific journal where the research team plans to publish the results of their work. In contrast, core requirement “C” is of lower importance and can, therefore, be addressed at a later timepoint. The EQIPD Planning Tool can be used to sort challenges and activities based on their importance for the individual research unit.

FIGURE 2

Figure 2: EQIPD tools to support the implementation and maintenance of the EQIPD Quality System. The EQIPD consortium has developed and intends to maintain a growing collection of research quality-related information, called a Toolbox, a wiki-based collaboration platform. The Planning Tool is operationally an interface between the users and the EQIPD framework, allowing to navigate to relevant information in the Toolbox, to sort and prioritize various core and user-specific needs, and to keep track of activities related to the performance of the quality system. The Dossier is a repository of documents and information that are specific to the user's research unit and that is organized according to a structure suggested by EQIPD (to keep all research quality-related information in one place and make it easily findable).

FIGURE 3

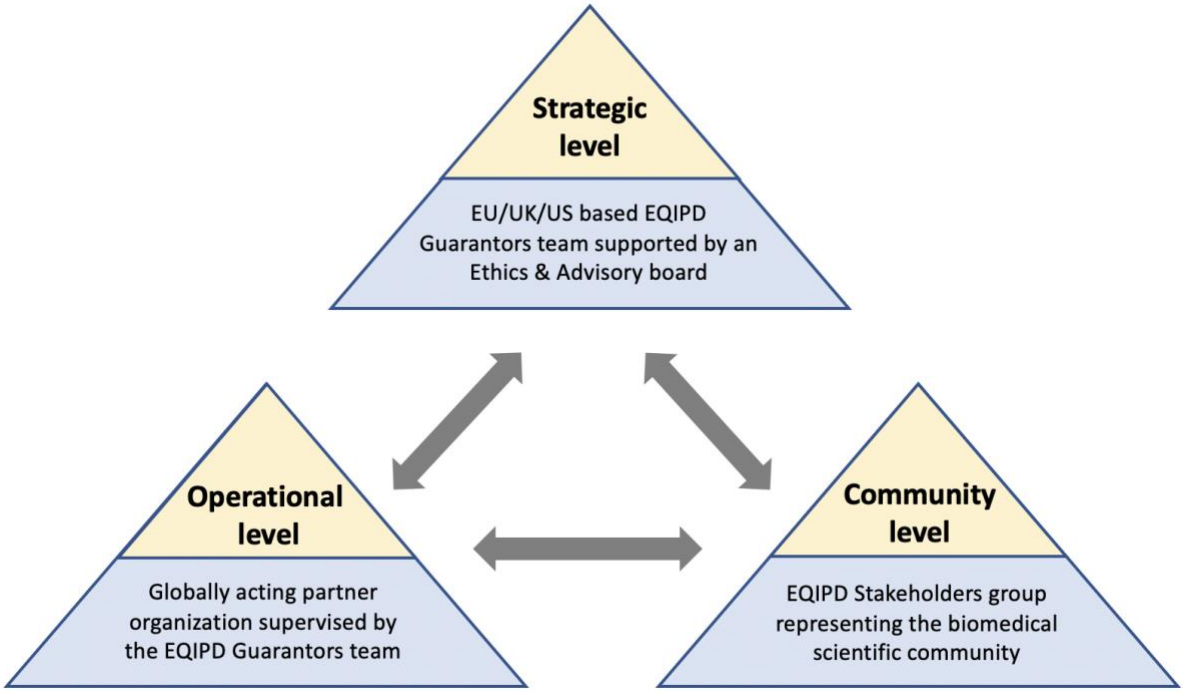
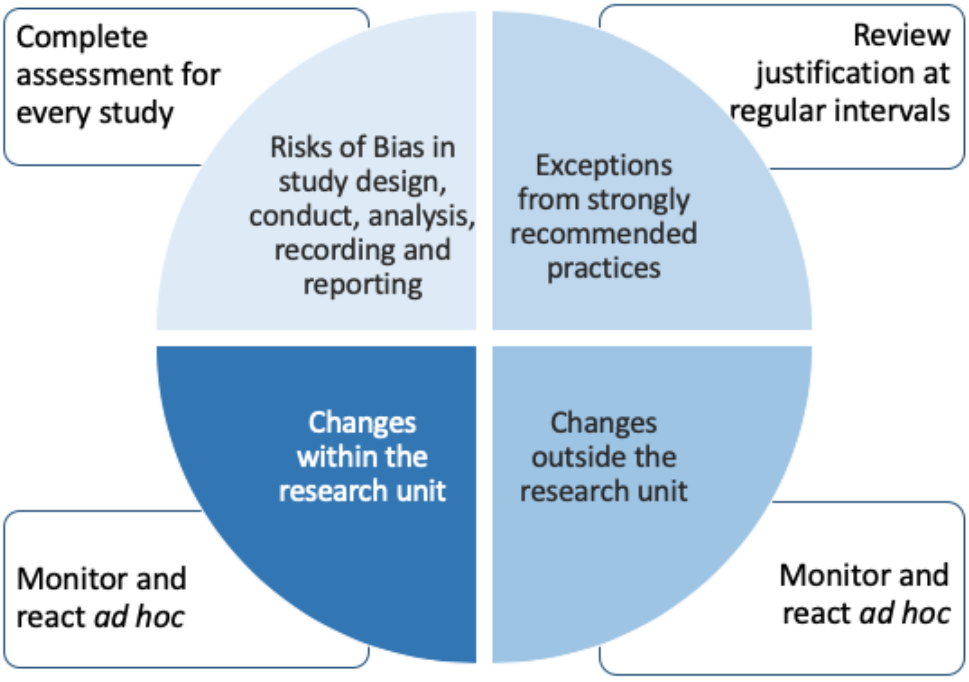


Figure 3: The proposed future governance model of EQIPD. The EQIPD Guarantors group and the EQIPD Ethics & Advisory Board are responsible for the overall guidance, administration of academic and educational programs, as well as dissemination of the EQIPD vision (*Strategic level*). An independent partner organization, commissioned by the EQIPD Guarantors, will provide the operational support and the day-to-day services for the EQIPD community (*Operational level*). The EQIPD Stakeholder group, composed of scientists, funders, quality professionals, manufacturers of research tools, and publishers, provides feedback on the practical aspects of the EQIPD Quality System and facilitates connections to a broader biomedical research community (*Community level*).

BOX 1 --- Managing risks to data quality

Even under the best circumstances, not all recommended practices and protection measures can be applied to a working environment or research study, leaving a potential risk of failure. The EQIPD Quality System recognizes three main areas where risk assessment should be conducted with risks made transparent and, if appropriate, documented:

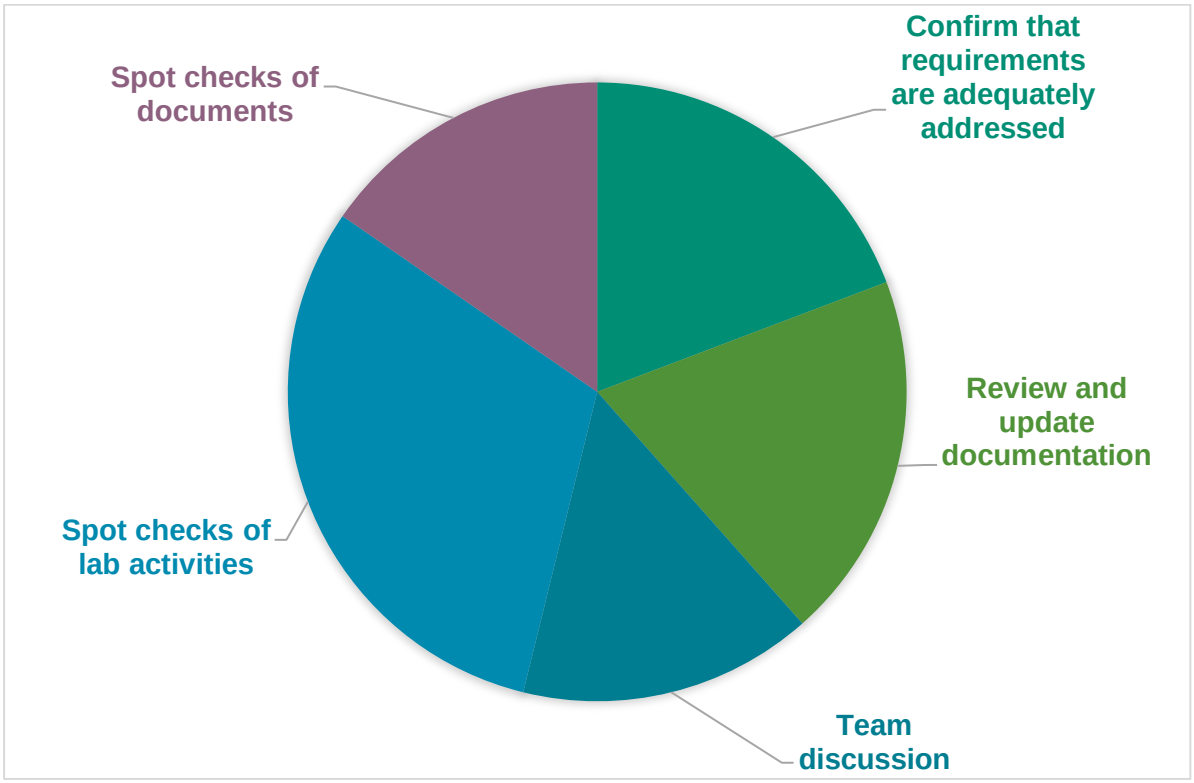
1. alterations from strongly recommended practices (i.e., situations in which the language of the EQIPD guidance includes “should“ and the research unit justifies why it does not or cannot apply). These assessments are done at regular intervals by the Process Owner;
2. key and support processes that are inherently associated with risks endangering the validity of the results (e.g., risk of unblinding; emergency access to blinding codes). These assessments are done by scientists responsible for a study plan;
3. changes in the environment both inside and outside of the research unit (colleagues leaving; facility changes, etc.). These assessments are done or initiated *ad hoc* by the Process Owner.



BOX 2 --- Self-assessment

The primary objectives of the self-assessment are to confirm that the research unit has everything in place for proper performance of the fit-for-purpose EQIPD Quality System, and to set the basis for internal or external quality checks / accreditation mechanism.

The process owner is responsible for defining the scope and frequency of this self-assessment, which is expected to involve all members of the research unit to ensure that all quality goals in the research unit have been considered and achieved.



As part of the self-assessment, there are spot checks conducted on selected documents (core requirements ## 11, 12, 16, 17; Table 2) and laboratory activities (core requirements ## 6, 7, 8, 9, 10, 13, 14, 15). The Process Owner completes a paperless assessment of several solutions being up-to-date (core requirements ## 1, 2, 4, 5), reviews and, if necessary, updates documentation (core requirements ## 2, 3, 6, 7, 8), and engages the team in the discussion and review of certain processes (core requirements ## 3, 5, 13, 16). The self-assessment itself is a core requirement (#17) and can be conducted using a template provided in the Toolbox.

TABLE 1 --- Comparison of quality systems

Quality system	ISO 9001	GLP (FDA, OECD)	EQIPD
Year Launched	1987, 2015	1976, 1981	2020
Application area	A general QMS that can be applied to all aspects of organizations (not focused on biomedical research)	Non-clinical health and environmental safety studies upon which hazard assessments are based	Non-regulated preclinical (non-clinical) biomedical research
Initial stimulus to be developed	Procuring organizations needed a basis of contractual arrangements with their suppliers (i.e., basic requirements for a supplier to assure product quality)	Regulators such as FDA aimed to avoid poorly managed or fraudulent non-clinical studies on safety of new drugs	Biomedical research community (industry and academia) recognized the negative impact of lacking research rigor on the development of novel therapeutics, and the need for a comprehensive practical solution to help enhance preclinical data reliability
Objectives	To certify that a product (which can be preclinical data) or a service is provided with consistent, good-quality characteristics, which satisfy the stated or implied needs of customers	To ensure the quality, integrity and reliability of data on the properties and/or safety of test items concerning human health and/or the environment	To facilitate generating robust and reliable preclinical data and thereby boost innovation
Customers	Typically outside of the organization (anyone who requires a product or service)	Typically outside of the organization (patients, regulators, sponsors, etc.)	In most cases, both inside (scientists themselves) and outside (patients, funders, collaboration partners, publishers, etc.) of the organization

Main focus	Standardization of processes The organizational overall performance is continuously improved (process approach) to enhance customer satisfaction and development initiatives are done on a sound basis for sustainability	The organizational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported	The outcome of research activities that is robust, reliable, traceable, properly recorded, reconstructible, securely stored and trustworthy (generated under appropriately unbiased conditions)
Dedicated quality professionals	Not required (advisable for larger organizations)	Required	Not required (advisable for larger organizations)
Formal training on implementation and use	Not required	Required	Advisable, but not required
Assessments	External (ISO auditors) and internal (internal auditors)	External (health authorities / governmental inspectors) and internal (QA auditors)	Self-assessment (by Process Owner), external (by EQIPD)[1]

1 additional internal assessments may be conducted by qualified colleagues (e.g., dedicated quality professionals) outside the research unit but within the same organization (advisable for larger organizations)

TABLE 2 --- EQIPD Core Requirements

Categories	#	Item
Research team	1	Process Owner must be identified for the EQIPD Quality System
	2	Communication process must be in place
Quality culture	3	The research unit must have defined quality objectives
	4	All activities must comply with relevant legislation and policies
	5	The research unit must have a procedure to act upon concerns of potential misconduct
Data integrity	6	Generation, handling and changes to data records must be documented
	7	Data storage must be secured at least for as long as required by legal, contractual or other obligations or business needs
	8	Reported research outcomes must be traceable to experimental data
	9	Reported data must disclose all repetitions of a study, an experiment, or a test regardless of the outcome
Research processes	10	Investigator must declare in advance whether a study is intended to inform a formal knowledge claim
	11	All personnel involved in research must have adequate training and competence to perform assigned tasks
	12	Protocols for experimental methods must be available
	13	Adequate handling and storage of samples and materials must be ensured
	14	Research equipment and tools must be suitable for intended use and ensure data integrity
Continuous improvement	15	Risk assessment must be performed to identify factors affecting the generation, processing and reporting of research data
	16	Critical incidents and errors during study conduct must be analyzed and appropriately managed
	17	An approach must be in place to monitor the performance of the EQIPD Quality System, and address identified issues
Sustainability	18	Resources for sustaining the EQIPD Quality System must be available

TABLE 3 --- Expectations towards rigor in study design

	All research	**Research informing a formal knowledge claim (i.e., research requiring maximal rigor)**
Study plan	Should be defined and documented before starting the experiments	Must be defined and documented before starting the experiments
Study hypothesis	Advised to define	Must be pre-specified
Blinding	Advised to implement	Should be implemented, exceptions must be justified and documented
Randomization	Advised to implement	Should be implemented, exceptions must be justified and documented
Sample size calculation	Advised to define and document before starting the experiments	Must be defined and documented before starting the experiments (e.g., included in the study plan)
Data analysis	Advised to define and document before starting the experiments	Must be defined and documented before starting the experiments (e.g., as a formal statistical analysis plan and/or included in the study plan)
Inclusion and exclusion criteria	Advised to define and document before starting the experiments	Must be defined and documented before starting the experiments (e.g., included in the study plan)
Deviations from study plan	Advised to document	Must be documented
Preregistration	-	Should be implemented

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