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1. Introduction

Within the Work package 4: 'Accelerate excellence, innovation and translation, and foster exchange by promoting Open Science' six tasks addressed the relevant areas. Specifically, task 4.6: Promoting quality assurance in research aimed for the implementation of standards in the design of (animal/biomedical) experiments that should reflect the contemporary good practice in research. Those standards are important for ethical and economic reasons and to obtain the best possible scientific results. As a formal step towards a common European normative regarding research quality, the EBRA project regards unified criteria as necessary that will support both, funding bodies and researchers across Europe, in their grant proposals, review procedure standards, and consequently the quality of the scientific projects. The key will be the implementation of a set of minimum standards for quality assurance including ethical aspects beyond the 3Rs (replacing, reducing, refining animal experiments), and comprising preclinical as well as clinical research. Such standards enable the research community as well as EC services, and national funding agencies to foster confidence and facilitate collaboration.

This task involved thus two parts:

- A survey among funders about the implementation of quality assurance criteria in national funding measures.
- The organization of workshops on the implementation of standards in actual research projects.

2. Quality Assurance Survey: "Safeguarding quality of research in frame of the European Brain Research Area (EBRA) project"

The survey: 'Safeguarding quality of research in frame of the European Brain Research Area (EBRA) project' aimed to collect information regarding the quality assurance procedures in funding organizations (FO) and the implementation of the main criteria of quality assurance in preclinical studies in the respective FO.

A call-for-tender to conduct the survey was launched by DLR-PT in November 2018, and the contract with QUEST (Quality, Ethics, Open Science, Translation, Center for Transforming Biomedical Research, Berlin, Germany) finalized in February 2019.

The content of the survey was consented with DLR-PT and was open between May and September 2019.

A draft report was presented to DLR-PT in September 2019, and the final version presented on December 5th, 2019, by Prof. Dirnagl at the EBRA public meeting in Brussels. The report, and slide-kit for the information of *ad hoc* reviewer panels were well received. A summary of the report can be found here below.

Promoting quality in preclinical research proposals

Summary

Raising the minimum standards of preclinical research is crucial for the proliferation of reliableand translatable results. In the past decade, guidelines and checklists have been developed, but the actual impact of guidelines and checklists on published preclinical research quality is limited. Improving overall study quality requires improving more than just the quality in the published literature, but an ex ante evaluation of study design quality. Moreover, appraisal of preclinical evidence is only possible if all evidence is actually available. This is impeded by a publication bias where results remain unpublished that do not confirm a hypothesis. This white paper summarizes a set of widely applicable, prospective criteria to evaluate preclinical research quality and ensure timely and complete communication of results.

Quality assurance of preclinical studies includes four main domains. First, clearly separating confirmatory from exploratory research is a key aspect of assuring quality with regards to the scope of preclinical research. Second, explicit study planning can assure basic aspects of quality in research. Third, statistical aspects of studies need to be explicitly justified and evaluated before conducting the study, in order to provide valid and efficient statistical results. Fourth, reporting is the bottleneck for quality in any kind of study, hence, needs to be optimized and guaranteed.

Funders need to publicly communicate their implemented quality standards. Based on a survey within the EBRA project (18 responses from funding organisations [FO]), we note that implementation of the main quality criteria is mixed. Funding institutions can mandate a minimum standard in their grant conditions, explicitly encourage applicants to budget for quality assurance, actively implement these standards by asking applicants about whether they adhere to these standards and implement a two-stage evaluation process to reduce reviewer load and

turnover times. Retrospective evaluation of the quality in previously funded proposals by the applicant can inform the evaluation of the current proposal. New funder-owned communication models potentially reduce the negative effects of the current, selective publication process on the funded research.

The aforementioned points should inform reviewer guidelines to support reviewers participating in the process of improving the minimum quality standard of funded proposals. For quality improvement, reviewers should assess whether a proposal fulfills the minimum quality criteria and make specific and actionable improvements to quality assurance of the proposal. In case a reviewer's expertise is not sufficient to judge the proposal on a specific criterion this should be noted as well."

3. Q-EBRA Workshops: Quality assurance in pre-clinical research.

The workshops on "Quality assurance in preclinical research" aim to raise awareness for and knowledge of reproducible experimental project design, and thus enhanced validity of obtained results. As more national and European funding organisations including the EU itself request detailed information of research proposals on the design and statistical analysis of preclinical studies, and evaluate the proposals along respective criteria, the need for accordingly oriented training rises constantly. EBRA set its major interest in supporting and promoting enhanced reproducibility in preclinical research and thus bridging the translational gap. The workshops were organized by Era-NET NEURON in cooperation with the QUEST Center.

The QUEST Center was founded in 2017. It conducts research on research (meta research) (see projects) and derives from it offers (see services and courses & workshops) for the scientific community. With this mission, the QUEST Center is unique in Europe. Through its projects and services, the QUEST Center also examines the role of an academic institution in enhancing the trustworthiness, usefulness, and ethical accountability of biomedical research. The QUEST Center aims to overcome the roadblocks of translational medicine to foster innovation that contributes to improved healthcare. To do this, they want to make biomedical research more trustworthy, useful, and ethical. They maximize the quality of research at the BIH by making sure that its results are accessible, reproducible, and generalizable and thus have a high value. They want to create an awareness of the need to rethink biomedical research and to initiate a culture change in academic biomedicine.

NEURON conducted the participant management including registration platforms, invitations, exchange with participants, collection of project descriptions as basis for participation, program development, and presentations, dissemination via report on EBRA's website and social media. The QUEST part comprised the teaching personnel, the in-depth analysis of submitted project descriptions, presentations at the workshop, and not least the individual consultation sessions with the researchers on their study design. The workshops were held on the QUEST premises or organized via ZOOM. The invitation addressed Early Career Researchers (ECRs) of the EBRA clusters, the ERA-Net NEURON and JPND funded researchers and Principial Investigators (PI's).

Five workshops were held of which 3 were virtual because of the covid-19 pandemic. The interactive format in discussing each project (individual consultation) strongly relies on physical meetings. Therefore, two more in-person workshops were planned when pandemic restrictions were lifted in 2021 and 2022.

3.1. Pilot Quality Assurance Workshop, January 2019, Berlin

A pilot workshop for quality assurance was conducted by the European Brain Council (EBC) in cooperation with NEURON on January 19th, 2019, in Bonn, Germany. The workshop comprised a series of lectures complemented by interactive session, from pre-registration of preclinical studies to challenges in multicenter clinical studies. With 220 participants the workshop was very well attended. Here below, the event report can be found.

Event report

Within EBRA's portfolio one task aims to broadly inform and support the research community in the implementation of future (pre-clinical) research. The combination of a strong bias toward statistically significant findings and flexibility in data analysis results in irreproducible research. In view of this reproducibility crisis in pre-clinical and clinical research it is essential to develop and implement measures for enhanced adherence to standards, e.g., ARRIVE, and 3Rs.

EBRA and NEURON are fully committed to the highest possible standards of quality assurance, including working to nationally and internationally recognized best practices. NEURON's implementation of standards in the design of animal research and full implementation of the 3Rs reflects contemporary good practice for all research using animals and reinforces that these standards are important for ethical reasons and to obtain the best possible scientific results.

In acknowledgement of these common goals EBRA and NEURON co-organized a specific thematic workshop on the issue of transparency, reproducibility, and independent verification in biomedical research on January 22nd, 2019, in Bonn, Germany. Within a series of keynote lectures and specific break-out sessions a number of renowned researchers focused on biomedical preclinical research, experimental design, data analysis, infrastructural support for clinical studies (ECRIN), open access to research including publication and data management plan policies, and challenges in multicenter clinical studies on TBI.

Prof. Dr. Ulrich Dirnagl as the Director of the Department of Experimental Neurology, and founding director of the QUEST – Quality, Ethics, Open Science, and Translation Center at the Berlin Institute of Health addressed in his keynote 'Reducing bias and improving science by transforming biomedical research' the problem of non-reproducible research findings and failure to translate bench findings into effective therapies as 'vicious cycle of academic biomedical research'. Where scientists need to publish new, positive, and spectacular results for professional advancement, journals need to publish new, positive, and spectacular results to promote their Impact Factor (IF), and institutions and funders support researchers who publish new, positive, and spectacular results in high IF journals. To break this vicious cycle, he suggested a number of measures: distinguishing between exploratory and confirmatory pre-clinical research, publication of NULL results, and preregistration of confirmatory pre-clinical studies to promote an open science policy (http://osf.io).

David Mellor, from the "Center for Open Science" reflected in his keynote 'Increasing impact, reproducibility, and credibility through open science' on the mission to increase the reproducibility and transparency of science. He introduced the Transparency and Openness Promotion (TOP) Guidelines that are promoted by the Center for Open Science. These comprise eight policy statements for increasing the transparency and reproducibility of the published research.

Pre-registration of the study design is one of the standards defined in the TOP Guidelines. In the break-out session 'Practical steps for implementing policies to improve study design and transparency' it was highlighted how pre-registration helps improving the study design, mitigate the publications bias and clearly delineates exploratory from confirmatory research. In fact, pre-registration is strongly recommended for the confirmatory pre-clinical studies.

The registered reports publication format offers an approach to the scientific community that emphasizes the importance of the research question and the quality of the methodology prior to data collection. The format requires authors of empirical studies to pre-register their study protocols including hypotheses, details on the sample size and sampling methods, and the analysis plan. The submission of an empirical study outline is followed by a standard peer review process determining the quality of research methodology. If the study is accepted as a registered report, publication is granted to the authors irrespective of the outcomes. The presentation and workshop materials can be accessed here: https://osf.io/9qw53/

Prof. Dr. Christian Ohmann, former Head of the Coordination Centre for Clinical Trials (KKS) at the Medical Faculty, University Düsseldorf presented in his keynote 'ECRIN – Facilitating European Clinical Research' the European Clinical Research Infrastructures Network (ECRIN). , former Head of the Coordination Centre for Clinical Trials (KKS) at the Medical Faculty, University Düsseldorf presented in his keynote 'HYPERLINK "https://www.ecrin.org/" ECRIN – Facilitating European Clinical Research' the European Clinical Research Infrastructures Network (ECRIN). ECRIN focuses on the connection of European national networks of clinical research centres and clinical trials units and developed a sustainable infrastructure able to support the set-up, conduct, and analysis of multinational trials in Europe. ECRIN provides integrated support to multinational clinical research projects through information and consultancy, and a set of flexible services during the conduct of the project. ECRIN currently supports around 40 multinational clinical trials (mostly academic) with services and developed a series of open tools to support clinical trials. ECRIN aims to structure the landscape of clinical research via funded capacity projects.

'Assessing quality of research practice: From manuscript checklists to auditing: Practical issues in preclinical study design' Breakout Session:

Prof. Dr. Anton Bespalov, co-chair of the ECNP Preclinical Data Forum, and CEO of Partnership for Assessment and Accreditation of Scientific Practice GmbH Heidelberg (PAASP) addressed the issues of randomization, blinding, and research hypothesis generation with an engaged audience. To increase the internal validity of any preclinical study the challenges of randomization (may create selection bias), blinding interventions and outcome assessments (may create performance bias and detection bias), and predefined in and exclusion criteria (may create attrition bias) must be carefully considered and were discussed in a hands-on session.

'Practical issues in preclinical data analysis' Breakout Session:

Prof. Dr. Martin C. Michel, of the Pharmacology department at the Johannes Gutenberg University in Mainz (Germany) elaborated on how to reduce bias in data analysis. With the participants the issues of implementing the difference between exploratory and hypothesis-testing (confirmatory) studies, randomization and blinding which can also be applied to data analysis, and where unblinding should be done only after database lock (as in clinical trials), and the pre-specification of analysis strategies were discussed. For confirmatory (hypothesis testing) studies a scientifically plausible hypothesis exists, a pre-specification of null-hypothesis is required, and the experimental methods including sample size and analytical methods lead to statement of significance regarding the null-hypothesis. Exploratory studies can generate scientifically plausible hypotheses, do not necessarily need P-values, and have a lower prior probability. He pointed out that both types of study have a place in science, but serve different roles, and – importantly – elements of both can be combined in a single study. For instance, a study can be confirmatory for primary (and key secondary) endpoint, and exploratory for other endpoints.

'Challenges in multicenter clinical studies on TBI' Breakout Session:

Prof. Dr. Ari Ercole, a clinical anesthetist and researcher at the University of Cambridge, and Prof. Dr. Andrew Maas, Prof Em. of Neurosurgery, Antwerp University Hospital and University of Antwerp, Belgium focused on studies in the area of traumatic brain injury (TBI). Four domains comprise epidemiological research, studies on acute, hospitalized patients, rehabilitation studies for moderate/severe TBI, and on mild TBI, concussion research, respectively. The many questions of the audience were well matched since Dr. Ercole has a particular research focus on applications of systems biology in intensive care medicine and anesthesia after TBI and both, he and Dr. Maas are involved in CENTER-TBI (Comparative European NeuroTrauma Effectiveness Research in TBI). CENTER-TBI is a large European project that aims to better characterize TBI as a disease, and describe it in a European context, identify the most effective clinical interventions for managing TBI, and it forms part of the larger global initiative **InTBIR**: International Initiative for Traumatic Brain Injury Research with projects currently ongoing in Europe, the US and Canada.

3.2. EBRA Spring school on Open Research, March 2020, online

On March 19-20th, 2020, the EBRA Spring school on Open Research in collaboration with the QUEST Institute Berlin was conducted as online conference. 51 applications were received, of which 30 were eligible and finally 22 participants attended the virtual meeting and discussed the presentations. From 'Quality and Robustness in Biomedical Research' via 'Experimental Design (Strategies against Biases, Exploration to Confirmation)', and 'What is N? Experimental, observational, and measurement units' to 'Statistics and p-value' the lectures detailed a tremendous amount of information and support for experimental preclinical research. The attendees honored the online workshop with specific questions also in regard to own projects. Originally planned as physical conference the Corona pandemic necessitated an alternative approach and EBRA highly appreciates the effort taken by our collaboration partner. Consecutive events are intended for 2021.

3.3. Early Career Researcher workshop, October 2020, virtual

The next workshop took place on October 22nd - 23rd, 2020, with altogether 17 participants as virtual conference. The program comprised lectures and well-prepared interactive session among the ECRs. The interactive sessions were lively and very well received. The feedback by both, participants, and lecturers, was positive.

3.4. Workshop on Neuroethics and Quality Assurance, January 2021, virtual

The workshop on 'Neuroethics and quality assurance' (video link here) welcomed - Prof. Ulrich Dirnagl (Charité, QUEST, Berlin, Germany) and his talk: Your bench is closer to the patient bed than you think! - Prof. Daniel Strech (Charité, QUEST, Berlin, Germany) and his talk: How to safeguard the value of animal research. Scientific and technological developments are crucial for brain research and treatment of brain disorders, so it is not surprising that exactly these gains in knowledge play a central role in ethical issues and associated consequences from that research. The brain plays a fundamental role in our psycho-social makeup and so it is natural that although ethical questions are not unique to neuro-technologies, they take on greater significance. Therefore, the workshop enthused a contribution on 'Recommendation on Responsible Innovation in Neurotechnology' by Dr. David Winickoff, from the Working Party on Bio-, Nano- and Converging Technologies (BNCT), OECD.

3.5. Robust evidence in translational biomedicine workshop, November 2021, Berlin

The workshop on 'Robust evidence in translational biomedicine' took place on November 10th – 12th, 2021. The workshop addressed experienced researchers, post-doctoral researchers, and Principal Investigators (PIs) with own projects and was attended by 12 participants. It was a 2-days presence event at the BIH QUEST Center – Charité in Berlin, Germany. Besides presentations on e.g., translational validity, reliability, and robust evidence a major part of the program concerned interactive rounds to discuss these complex issues. Participants expressed high interest in the topic for their own projects and appreciated the inspiring workshop indeed as support for running and future projects.

3.6. Your next grant application – methodological workshop, April 2022, Berlin

The workshop 'Your next grant application – methodological approach' took place from April 27th -29th, 2022, at the BIH QUEST Center – Charité in Berlin, Germany as an in-person event. For this workshop a modified approach in communication was applied, instead of approaching the six cluster heads. In a first step ALL researchers in the six clusters did receive the invitation. In addition, a modified approach in branding did utilize a broader and more future/funding-oriented title. Of the 58 applications, 22 participants were selected. The program was extended for sessions with external speakers on 'Data sharing in brain research (pre-clinical & clinical data)' (EBRAINS), 'The ethical self-assessment for preclinical animal studies, human tissue studies, and human clinical studies' (NEURON), 'Public and patient involvement (PPI) in research: how to' (MS UK Society), and 'When a project is selected: Data management plans (DMP), the RDM kit, and the Data Stewardship Wizard' (ELIXIR) each followed by an extended interactive practicing session. Here below, the event report can be found.

Event report

The ERA-NET NEURON, as partner of EBRA, would like to strengthen the support of researchers in Responsible Research Innovation and Open Science. As fifth event of a series of successful workshops since 2019, the group collaborated again with the Quality, Ethics, Open Science, and Translation Center, QUEST at BIH/Charité to conduct an intense three-day workshop aimed at preparing the clinical and preclinical Principal Investigators (PIs) as well as Early Career Researchers (ECRs) to safely navigate Public and Patient Involvement (PPI), data sharing, data management plans (DMP), ethical self-assessments, justification of animal experimentation, as well as detailed and statistically sound experimental design of projects.

The workshop agenda was developed in close cooperation with QUEST, EBRAINS, ELIXIR and the MS Society, UK. The face-to-face event took place in Berlin, Germany on Wednesday 27th to Friday 29th of April 2022. The participants included 22 PIs and ECRs of EBRA clusters (PSMD, TRISOMY21, and BRAINFOOD) and of ERA-NET NEURON funded projects from nine different countries.

The event involved plenary lectures, practical breakout sessions, group discussions, individual consultations and an eLearning session on DMP generation with the Data Stewardship Wizard.
Day one started with an overview of the program by Hella Lichtenberg (ERA-NET NEURON), and Ulf Toelch (QUEST) and project pitches by the participants.

Day two provided overviews on experimental design by Hella Lichtenberg (ERA-NET NEURON), Ulf Toelch and Natascha Drude (QUEST, Germany), and Patient and Public Involvement (PPI) across health research by Annessa Amjad (MS Society, UK), PPI expert and trainer, followed by a hands-on case study training on how and when to involve people in research projects. The afternoon sessions were devoted to the ELIXIR infrastructure and the DMP development with the Data Stewardship Wizard guided by Laura Portell (ELIXIR, Spain) and Jan Slifka (University of Prague, Czech Republic). The day was rounded up with a plenary lecture by Ulrich Dirnagl, past Director of the Department of Experimental Neurology, and founding director of the BIH QUEST.

Day three comprised plenary lectures on robust evidence and translational validity by Ulf Toelch and Natascha Drude, and on data sharing and governance in the brain research area by Damian Okaibedi Eke (EBRAINS, De Montfort University, Leicester, UK). Both, day two and three had intense interactive sessions with individual project consultations of the participants by QUEST.

The response to the workshop was overwhelmingly positive, with participants reporting a clear benefit of DMP generation, understanding of the data sharing challenges and options in brain research, and of the benefits of Patient and Public Involvement in research, as well as greatly improved confidence in the conduction of the scientific projects.

4. EBRA cluster QA activities coordinated by the European Brain Council

In addition to joining one or more Q-EBRA workshops, the EBRA clusters also focused on Quality Assurance during their meetings.

4.1. EPICLUSTER

Representatives from the QUEST centre attended the EPICLUSTER consensus meeting to address quality assurance and ethics in epilepsy research.

4.2. Predictive Model Systems (PREMOS) cluster

The PREMOS cluster is formed based on several large networks and current EU funded consortia, which join forces to propel disease modelling capacities and expertise for neuroscience research in Europe and beyond. One of those networks is the European Quality in Preclinical Data (EQIPD).

The IMI2 EQIPD consortium is addressing the urgent need for lean, sustainable solutions to improve preclinical data quality. The overarching goal of EQIPD is to deliver simple recommendations to facilitate data quality without impacting innovation. The EQIPD consortium defined components of an EQIPD quality management system and achieved a consensus among different academic and industry stakeholders on quality management recommendations for research. EQIPD also assessed the feasibility of the quality management system in prospective studies in the fields of neuroscience and safety. EQIPD also sets up an online educational platform that will deliver certified courses in the principles and application of data quality and rigor. This will pave the way for a cultural change in approaches to data quality in the medical research and drug development field.

The EQIPD consortium builds on the existing ECNP Network “Preclinical Data Forum”, which is part of a global Preclinical Data Forum. The current membership includes 42 regular and 6 associate members, representing EU and US Universities, publishers and journal editors, funding agencies (NIH), non-profit advocacy and PPP groups.

EQIPD representatives took actively part in each PREMOS meeting.

1. 1st PREMOS cluster event: 3 working groups on the translational Models of Animal Models
    - Working Group 1, March 19th, 2021, online
    - Working Group 2, July 1st, 2021, online
    - Working Group 3, October 11th, 2021, in-person (Brussels)
2. Stakeholder meeting on translational value of animal models, April 1st, 2022, online
3. Policy meeting, September 22nd, 2022, hybrid (Brussels and online)

5. Conclusions

In summary, six workshops with 293 participants were conducted and successfully completed. Due to very positive feedback by the attending researchers, this format will be implemented by the ERA-Net NEURON Cofund2 from 2023 - 2025.