European Federation of Pharmaceutical Industries and Associations

Draft ✱ Final ☐

Workshop: Experimental Design - 20 March 2019 - Brussels

Overview

The pharmaceutical industry works to ensure high-quality science and high standards of animal welfare that ultimately help improve the lives of the people and animals that stand to benefit from the research.

If an animal study is not designed to answer the scientific research questions being asked, then the animals and resources used to conduct that study are potentially wasted. Effective experimental design and statistical analysis are critical means of minimising the use of animals whilst achieving study outcomes. Every effort should therefore be made to improve research studies, using the best available guidelines to ensure that all details are recorded and results reported correctly, which will improve the quality of science and maximize the output from the use of the animals, into more translatable studies and maximize on 3Rs opportunities.

EFPIA organised a workshop with the pharma user community to enable an open discussion across industry on the concepts and importance of effective experimental design. The workshop was designed to increase awareness, find out what we are doing as an industry, and identify key factors and gaps to lead to take home messages and recommendations for organisations to consider in implementing effective experimental design processes.

Introduction

Designing animal studies can be complicated and there is a need to include different expertise. The workshop participants represented Industry research scientists, preclinical biostatisticians, members of ethics committee or animal welfare bodies and members of EFPIA's research and animal welfare group. The discussions included good practices and successes, gaps, challenges and need for improvements, change management, acknowledging the need to take advantage of experiences to improve systems.
There is the need for an open culture where established study designs and protocols are robustly challenged to ensure that they are optimal to achieve the objectives, including novel biostatistical methods. The scientific hypothesis for testing and confirmatory studies must first be clearly defined and then the experimental design follows.

An internal survey of industry members on study design prior to the workshop indicated that few companies have a policy in place relating to the principles of good experimental design. However, many have an internal process for experimental design and provided training, mostly to preclinical statisticians.

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A statement supported by the members of the research and animal welfare group of EFPIA was prepared (see appendix). In addition, the workshop was organized to create an open dialogue and share experience of effective experimental design processes.

Case Studies on Experimental Design

Presentations were given on the perspectives and activities of different organisations on how they consider and implement experimental design.

Setting the Scene - EQIPD – European Quality in Preclinical Development
Thomas Steckler, Janssen Pharmaceuticals

The Consortium of the IMI project EQIPD believes there is a need for simple, sustainable solutions that facilitate improvements in data quality without impacting innovation and freedom of research. The project aims to enable a smoother, faster and safer transition from preclinical to clinical testing and drug approval by establishing common guidelines to strengthen the robustness, rigor and validity of research data. This will ensure responsible animal use and quality preclinical data.
The project was launched in October 2017 and will run for 3 years, involving 29 institutions. This is the first IMI consortium completely dedicated to improving preclinical data quality and is a joint undertaking by Big Pharma, CROs, Academia and Scientific Associations.

The vision is for robust data and scientific rigor in animal studies which will impact on the 3Rs, enhance the pace of knowledge gain and shorten the time needed to make new drug treatments available to patients, whereby the objectives are:

- Within animal study design and data analysis, define the variables that influence the outcome of preclinical research conducted in industry and academia
- Define the components that will make up the EQIPD Quality Management System and formulate consensus quality recommendations for animal studies
- Validate the feasibility of the quality management system in prospective animal studies conducted by their partners
- Deliver an online educational platform providing certified education and training in the principles of quality management and rigor

There are various layers in the design and execution of an experiment with an interplay between the statistical protocol, research protocol and execution protocol. Protocols can vary along the discovery chain: from exploratory testing/screening to hypothesis testing/confirming.

Some specific activities underway in the project include focus on the historical analysis where the aim is to define variables of internal and external validity in experimental design, conduct and data analysis that are determinants of outcome in preclinical studies. Problems and concerns are raised over the reliability of animal research, and whether we can actually trust the results published in literature. Also the ethical concern of studies not designed to yield robust results or those not reported properly, potentially leading to a waste of animals.

The project aims to develop guiding principles and criteria to bring rigor to experimental design, conduct and analysis of preclinical studies (using animals) taking into account guiding principles on exploratory *versus*

Confirmatory Research: planning and use of Standard Operating Procedures (SOPs); statistical measures for meaningful data; randomization and blinding and use of full and comprehensive documentation.
An outcome of the project authorization would be setting the animal care and use requirements that a project must comply with.

Case study 1 - The Robust Study Design Initiative at GSK
Joanne Storey, GSK

This case study included how GSK as a company recognised the need for a focused and coordinated effort on robust study design for in vivo studies. Details were given on building the business case and implementation plans to date which included the challenges identified and the status of the culture change.

While recognising the need for a focused and coordinated effort on robust study design, GSK is implementing a robust study design initiative. Its aim is a consistent, coordinated approach to understand and apply the elements of robust study design.

There are numerous challenges identified including the need to overcome perceptions and established methods and bring about a change in the culture. Reproducibility is a broad concern to both the pharmaceutical industry and academia. However, with a robust study design the desired outcome would be to move to powered, randomized, and blinded *in vivo* study designs supported by clear documentation.

Case study 2 - Achieving change and ensuring "Good Statistical Practice"
Natasha Karp, AstraZeneca

In 2012, AstraZeneca adopted a global "Good Statistical Practice" standard. This required a formal review of all in-vivo experiments where 10 principles of the design and analysis were evaluated. It was possible to explore how this change was initiated, implemented and maintained within a large international pharmaceutical company.

The need for the development of the global standard followed the publication in 2007 of a paper indicating fundamental flaws in the use of animal tests in specific drug development. There was a recognized need for change, however, the reactions to change varied between resistance, reluctant compliance or commitment. At the same time there are often changes within an organisation making implementation more complex.

The Global Good Statistical Practice standards developed are based on 10 principles:
1. Appropriate design
2. Appropriate reference groups
3. Planned statistical analysis
4. Justification for animal numbers
5. Blocking
6. Randomisation to treatment groups
7. Appropriate processing order for treatment, sampling and termination
8. Appropriate order for sample processing and analysis
9. Blinding
10. Monitoring


Learnings are that to improve experimental design across an organisation leadership and management support (resources including financial support, strategy) are required. In addition; there is a strong need of senior leadership advocacy. The challenge is to initiate and then maintain systems that effectively and efficiently raise standards. A formal system has the potential to significantly improve the science and meet our ethical obligations.

The AstraZeneca and GSK company approaches illustrate there are different ways to support scientists to achieve good experimental design.

Case study 3 - Managing best practice for safety assessment study design in a Contract Research Organisation (CRO) environment
Andy Gibbs, Covance

In a CRO environment the work is with clients ranging from large pharma to very small biotechs, from all global pharmaceutical regions, and developing a wide range of therapeutic modalities. Drug development scientists from client companies have a wide spectrum of experience and expertise. Often initial study designs, suggested by clients, need to be modified to ensure good practice with regard to the 3Rs, to meet global regulatory requirements, but also to achieve the maximum scientific value from each study: design consideration and insight that comes from broad and deep experience.

The role of the drug development leader within the Early Phase Development Solutions group is to provide the scientific, drug development strategic input when putting together initial development plans or package of studies with clients and continue to provide support in moving forward.

The difficulty for CROs is working with a diverse range of clients, where some know what they need; some have limited experience relying heavily on the CRO and some come from territories which have different legislative requirements or animal use philosophy. However, all clients must comply with the requirements of drug competent authorities.

It is the responsibility of the CRO to work with their clients to ensure optimal study or programme designs from both an animal usage perspective and a scientific perspective. The advantage to the CRO is the vast experience gained by working with a variety of clients and the ability to use this to balance the client requests with good practice and ethical / legislative considerations.

Numerous case study examples were explained, involving different regulations, combining endpoints into one study leading to half the number of animals but increased the severity banding; dose range finding and group size. Proposals were changed to better streamline study expectations, which generally also led to less animals used.

Case study 4 – Benefit of longitudinal designs to increase statistical power and decrease the number of animal per group
Aymeric de Montfort, Sanofi

In pre-clinical research, being involved in the conception of experimental designs, statisticians set-up robust designs, focused on the biological questions, in collaboration with the scientists. As a major input, experiments


are designed with optimized sample size and sufficient statistical power. Using a real example of longitudinal experimental design, demonstrates how statisticians can help the scientist to design a powerful in-vivo experiment according to the Reduction principle.

The conception of an animal study involves team work between the biologists, statisticians and ethics committee. Longitudinal experimental design in this context involves an initial 'Exploratory' study, which looks at the project, cost, time, ethics, biological conclusions etc. The set-up of an exploratory study can help in the design of the subsequent 'Confirmatory' study to make it more robust and ultimately make best use of animals (reduction).

Break out sessions

1.1 Brainstorming breakout

Working in small breakout groups participants were asked specifically to identify good practices, gaps and challenges, taking into consideration the context for the sector:

- identifying similarities and relationship between the case-studies
- considered the situation in their own company or unit and how it may be similar or differ

Following fruitful discussions in each of the breakout groups, participants regrouped and each group fed back their key conclusions from their discussions to the full group.

1.2 Summary of Discussion on Good Practice, Gaps and Challenges

The discussion highlighted areas of good practice and also identified potential gaps and challenges (see Table 1). The factors summarized as 'good practice' were considered key to successful implementation.

High level sponsorship is vital to set the tone and drive cultural change in the organization, this is particularly challenging within companies where organizations are in a state of change (e.g. reorganization) and previously agreed approaches can be lost as the new organization evolves. Documenting requirements in corporate 'policies or standards' ensures that requirements once established are not lost. Having the right examples to illustrate to researchers why experimental design is important can be a challenge and cross-industry sharing of examples could help to address this. Study design needs to become a cross-functional responsibility with early input from all relevant parties, including biostatisticians (early means before the study/project application). An effective scientific and ethical review prior to study conduct, including assessment of both harms and benefits, should robustly challenge proposed studies and introduce rigor into the design process. This is because having appropriate experimental design helps maximise the potential benefits of the work. Challenges associated with review of outsourced work relate to whether the CRO has adequate context around the requested work to truly make a harm/benefit judgement; it is therefore important that sponsoring company provides enough information and context in relation to the study design to support the CRO review before outsourcing takes place. Continuous improvement can be further supported by ongoing retrospective assessment of whether scientific objectives have been achieved.

In a number of cases gaps were a direct counter to what was identified as good practice. A key gap identified was the requirement for biostatisticians. Availability of preclinical biostatistics resource within organizations is of ongoing concern as is the level of statistical training as part of biology education and the statistical 'know-how' within competent authorities. Some elements of efficacy data quality were highlighted as gaps; notable was the view that there is regulatory acceptance of different data quality efficacy data compared to safety assessment data.


Table 1: Identified good practices, gaps and challenges in implementing good experimental design

Good practices summary	Gaps summary (other than converse of good practice)	Challenges summary
- Vision and support from Senior Management - Cross-functional commitment, communication and review of study designs (both internal and external) including input and review from a Biostatistician - Governance mechanism to ensure compliance with experimental design principles - Robust data integrity processes - Retrospective review to assess whether objectives are achieved and to maximise learning for the benefit of any future studies	- Improve experimental design and statistical training as part of biology education - Lack of statistical knowledge and resource in competent authorities - Lack of clear accountability (scientist/ statistician/ethics or compliance group)	- Gaps between experimental principles and actual study conduct in some cases (e.g. blinding – there may be practical difficulties making this impossible to include) - Sponsor input into outsourced studies. Does CRO have full context of the study to ensure appropriate experimental design and conduct a harm benefit analysis - Having good examples to illustrate the risk of not ensuring appropriate experimental design - Randomisation methodology - Different regulatory expectations and lack of guidance - Senior management formal sponsorship - Time pressures - Constantly evolving organisations

2.1 Recommendations breakout

With a clearer understanding of good practice, gaps and challenges, the breakout groups reformed for a second session to discuss recommendations to take forward. Participants considered what would motivate companies or institutes to embrace a more formalised system to review the design of experiments. They considered what would be key to developing better experimental design within companies. The results of the interactive discussions led to the identification of a large number of tangible good practice recommendations to take forward:

2.2 Summary of Discussion

Unsurprisingly, recommendations (see Table 2) were generally aligned with the issues identified in the previous section. They can be divided into those which can be addressed within individual organizations (Statistician resource, study design and review, ongoing monitoring, data and reporting) and those where collaborative efforts could be beneficial. EFPIA member companies are encouraged to contribute to EQIPD and disseminate the learnings from this project across their companies. EFPIA can also play a role by preparing a solid and consistent presentation/guidance to provide members with leverage to support changes to policy. Consistent and easily available guidance on experimental design would be of value both to the EFPIA members and others within the Biomedical community, it is therefore proposed to call on the European Commission to work with stakeholders to ensure there is appropriate accessibility to recognised guidance on experimental design.


Table 2: Recommendations to be taken forward

Focus	Recommendation to be taken forward

Expertise	- Appoint person responsible for Statistics to input into study design, follow project and also analyse data
	- Education:
	  ○ Systemic engagement of statistics students and scientists to increase awareness/expertise of biostatistics
	  ○ Training in experimental design principles for biologists and ethics committee members
	  ○ Continuing education
	  ○ Incentives
	- Use of tools such as the NC3Rs Experimental Design Assistant (EDA)

Study Design and Review	- Review experimental design for validity as part of peer review. The PREPARE guidelines may be useful for this; - Apply same principles and standards across all studies and their design, in vitro and in vivo; - Apply same standards on experimental design to internal and external studies.
On-going monitoring	- Monitor implementation and progress and use the retrospective review of a project to influence good research practice - Raise awareness during company events or animal awareness days or through 3Rs awards - Internal sharing of examples - Defined governance process
Collaboration and sharing	- EFPIA to revisit the issue of experimental design and its implementation within the companies to follow-up and determine which recommendations have been taken forward and how experimental design has been implemented across industry - Company representatives are encouraged to nominate experts to join the scientific pool of the EQIPD programme to contribute further to the work; to take up the learnings and deliverables from the project and implement within their organisations where appropriate - Call on the Commission to set up a working group with Member States and stakeholders to develop guidance and promote accessibility to currently available experimental design resources (e.g. NC3Rs EDA) - EFPIA RAW prepares a presentation with rationale and case studies to provide members with leverage to support changes in practice within their own company: ○ Include tangible examples of risks (reputation, minimised chance of reproducibility and/or translation) and benefits (better, cheaper, more robust science, reduced animal use due to poor experimental design)


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	○ Examples of implementation of good practice ○ Develop pragmatic principles (common elements that need to be met) ○ Include case studies on randomisation and blinding
Other (not specifically related to experimental design)	
Data and Reporting	- More standard reporting of efficacy data for regulatory dossiers - More open approach to publishing efficacy data - Internal pre-registration of protocols (potential conflict with IP)

Appendix

Industry Statement on Experimental Design

The pharmaceutical industry strives to go beyond what is legally required and works to implement 3Rs to ensure high standards of animal welfare and high-quality science to ultimately improve the lives of the people and animals that stand to benefit from the research.

There are well reported issues with the reproducibility of animal studies with the experimental design and the reporting of studies being highlighted as major contributing factors. If an animal study is not designed to answer the scientific research questions being asked and publications do not contain the appropriate level of detail, then the animals and resources used to conduct that study are potentially wasted. Effective experimental design and statistical analysis are critical means of minimising the use of animals and achieving study outcomes.

Every effort should be made to improve research studies, using the best available guidelines to ensure that all details are recorded and results reported correctly, which will improve the quality of science and maximize the uptake of 3Rs opportunities.

EFPIA companies support the use of the following guidelines and resources when considering study design and reporting/publication of in vivo research:

- The Experimental Design Assistant (EDA). A free online tool designed to guide researchers through the design of their experiments, helping to ensure that they use the minimum number of animals consistent with their scientific objectives, methods to reduce subjective bias, and appropriate statistical analysis.

Details available from www.nc3rs.org.uk/experimental-design-assistant-eda

- Planning Research and Experimental Procedures on Animals: Recommendations for Excellence (PREPARE) is a newly published aide memoire to remind scientists of all the topics which may be relevant when planning experiments.

Details are available from https://norecopa.no/prepare

- Animal Research: Reporting of In Vivo Experiments (ARRIVE), which are widely accepted good practice guidelines to improve the quality and reliability of publications from research involving animals.


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Details are available from www.nc3rs.org.uk/arrive-guidelines


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