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Good laboratory practice in preclinical efficacy studies: to be or not to be?

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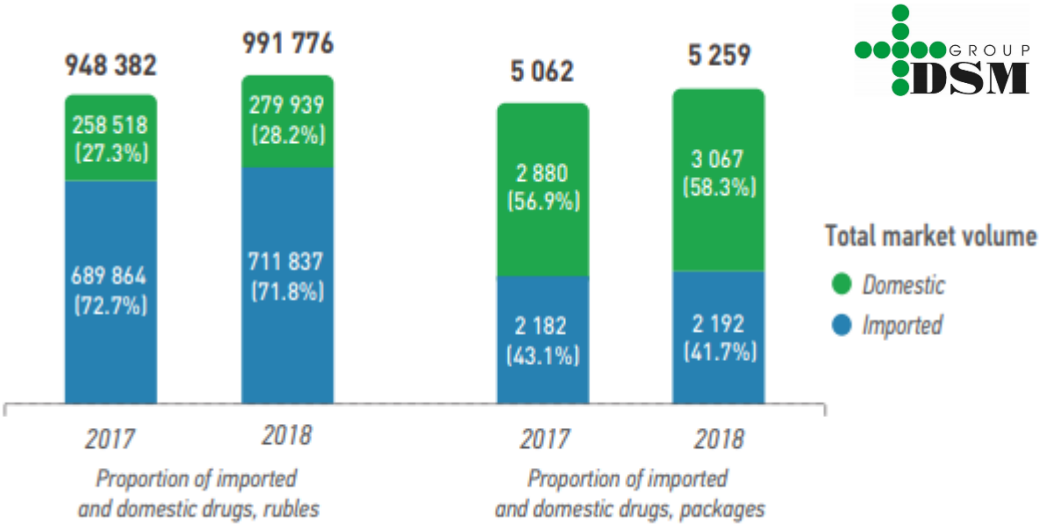
Saint Petersburg - 2019

Analytical background
Russian pharmaceutical market

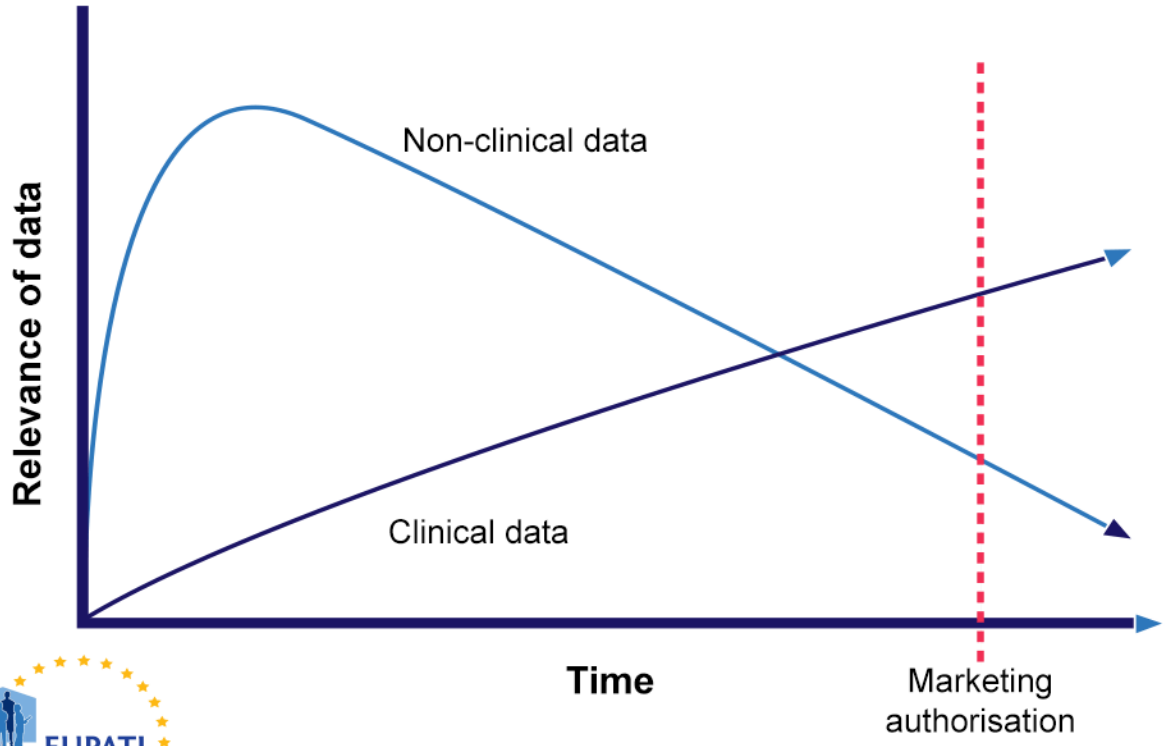
- 429 medical patents were registered (2017);
- Growth in the share of Russian drugs in drug consumption. 59% of the drugs sold on the market were of Russian origin (2018);



Proportion of Sales of Imported and Domestic Drugs on Commercial Retail Market

- The Ministry of Health (Minzdrav) issued a 746 permits for a clinical trial (2019). This indicator increased by ***14,2%*** compared with 2018;
- Six drugs were registered that replace imported ones and are used for the treatment of cancer, cardiovascular diseases and HIV infection (2018); Four of them were reproduced for the first time;
- Since the beginning of 2019, two drugs for the treatment of orphan diseases have been registered. Two drugs to treat rare or “orphan” diseases were approved from January 2019.

Relevance of non-clinical studies in medicines development

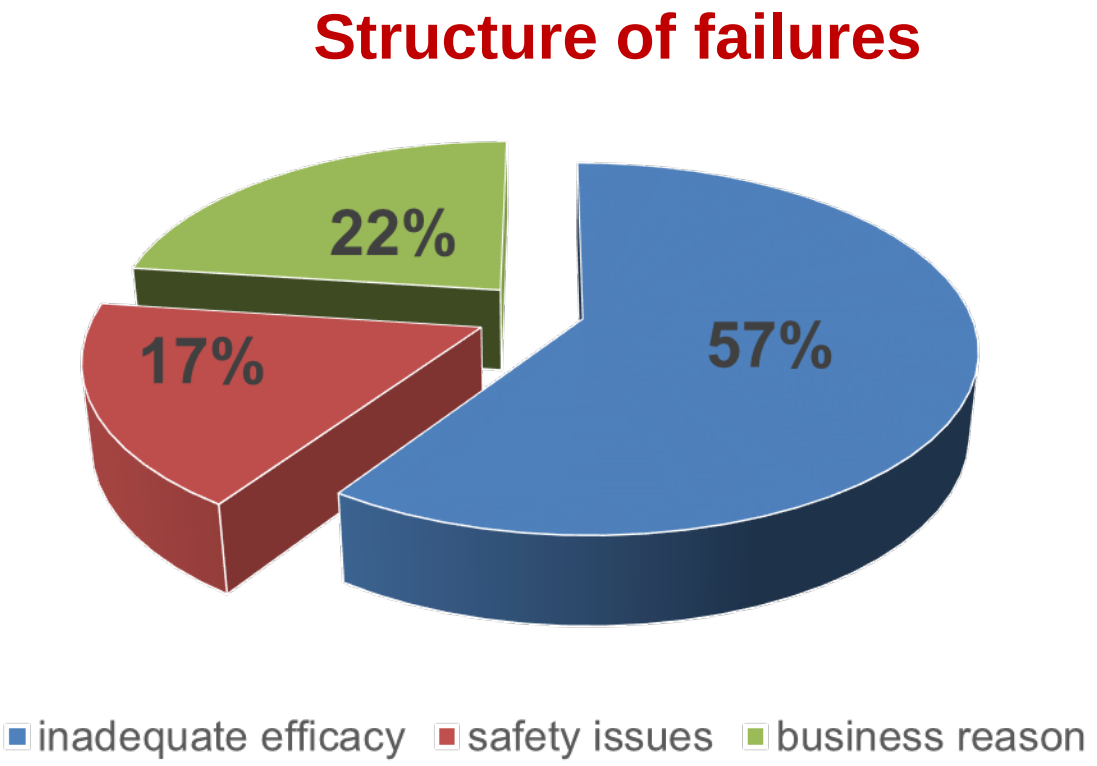


EUPATI
European Patients' Academy on Therapeutic Innovation
www.eupati.eu

Adapted from Nieto-Guiterrez, M. (2011) *Non-clinical assessment requirements.* London: European Medicines Agency.

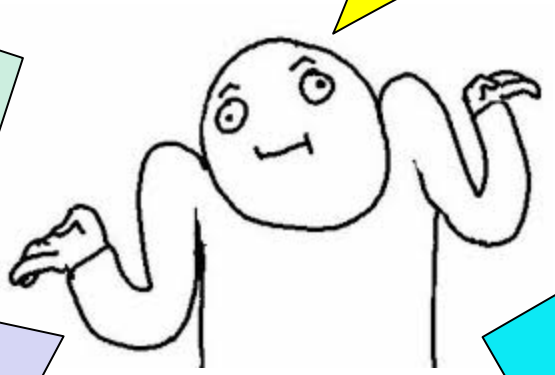
«From animals to people»
Problems of data translation:

Many investigational drugs fail in late-stage clinical development [*Thomas J Hwang, 2018*];



Difference between humans and animals

Flawed preclinical research (reliability, reproducibility, representation)



Insufficient knowledge of condition (disease)

. . .

Brief comparative characteristics of preclinical studies:

Evidence for the safety

GLP

- The absence of the hypothesis
- Studies are performed using standard protocol
- A large amount of routine work
- Are regulated by the GLP standard
- **Performers of preclinical studies. Characteristic:**

- Strict following of the instruction
- Discipline
  Attentiveness
  Accuracy

Evidence for the efficacy

non-GLP

- Developing and testing hypotheses
- A study protocol is developed individually (regulatory documents, literature data should be taken into account)
- Disease models need to be developed
- **Performers of preclinical studies. Characteristic:**

- Creativity and research capabilities
- Broad outlook and erudition
- Flexibility in deciding

The specific features of efficacy studies:

- Cross-disciplinary collaboration during the early in the planning stage of a preclinical studies

- Choice of relevant animal models:

  - Biological similarity of humans and animals
  - Similar development mechanism (pathogenesis) of disease

- Study design:

  - Selection of experimental conditions
  - Inclusion (exclusion) criteria
  - Choosing primary endpoints
  - Definition of efficacy criteria

- Use of study object of different stages of drug discovery and development. Efficacy studies do not stop after the drug has passed into clinical development

- Use of a wide range of techniques (non-invasive imaging methods, telemetry monitoring, etc.). Biomedical research is becoming increasingly expensive and complex

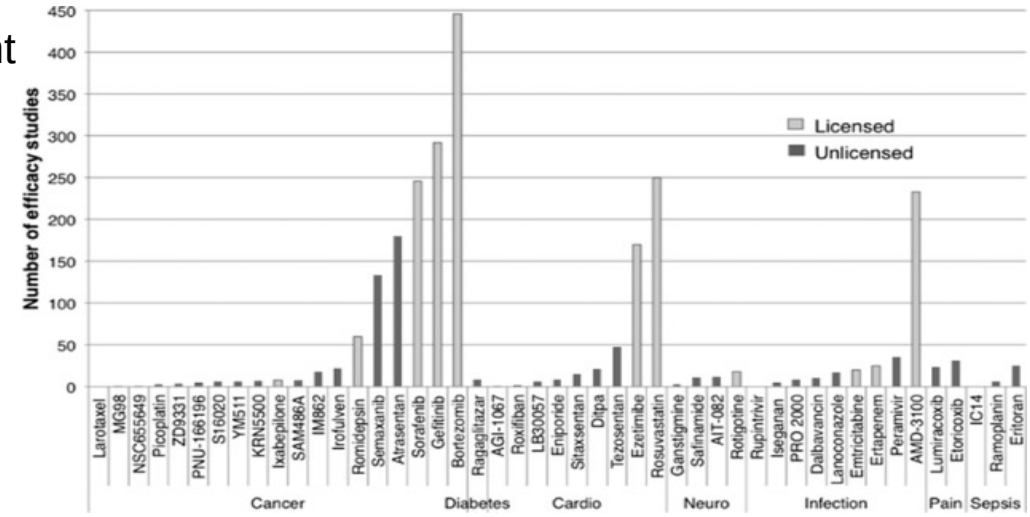
- Flexibility in the amount of data

The specific features of efficacy studies. Problems[1].

- Many preclinical investigations are withheld from publication. Efficacy studies are frequently published *after* clinical testing - unavailability of preclinical data for new developments.

- The volume of published efficacy studies is related to how far the agent advanced in clinical development

- Low transparency



Federico, C A et al., 2014

- Negative or neutral results are practically not represented - ethical problems

- There is no analysis of the reasons for obtaining "non-positive" results (Exclusion of systematic errors) Publishing the results of such studies – limiting factor for development)

The specific features of efficacy studies. Problems[2].

- Poor internal validity (systematic errors)

  - design of a studies,
  - performance
  - analysis of data

- Low reproducibility and poor external validity. More than 70% of researchers have tried and failed to reproduce another scientist's experiments, and more than half have failed to reproduce their own experiments *[Baker M, 2016]*:

  - selective reporting
  - low transparency
  - bad documenting

Analysis and Reporting of Research Using Animals on live rats, mice and non-human primates carried out in UK and US publicly funded research
[Kilkenny et al., 2009]

The review of published animal research (271, с 2003-2005гг):

Randomization – 12%, of which 9% is a detailed description
Blinding – 14%
The hypothesis or objective of the study, and the number and characteristics of the animals used (i.e., species/strain, sex, and age/weight) – 59%
The number of animals used anywhere in the methods or the results sections– 4%
Sample size justification– 0%
Statistical methods are fully described them and presented the results with a measure of precision or variability – 70%

NC 3Rs National Centre for the Replacement Refinement & Reduction of Animals in Research

ARRIVE
(Animal Research:
Reporting In Vivo Experiments)

The purpose of the guide:
increase reproducibility, transparency,increasing predictive value

ARRIVE

Checklist of 20 items:

Title

1. Accurate & concise description

Abstract

2. Background, objectives, methods, key findings and conclusions

Introduction

3. Background

4. Objectives

Methods

5. Ethical statement

6. Study design (blinding/randomisation)

7. Experimental procedures (How? When? Where? Why?)

8. Experimental animals (species, sex, weight)

9. Housing and husbandry

10. Sample size

11. Allocation experimental groups

12. Experimental outcomes

13. Statistical methods

Results

14. Baseline Data

15. Numbers Analysed

16. Outcomes & estimation

17. Adverse events

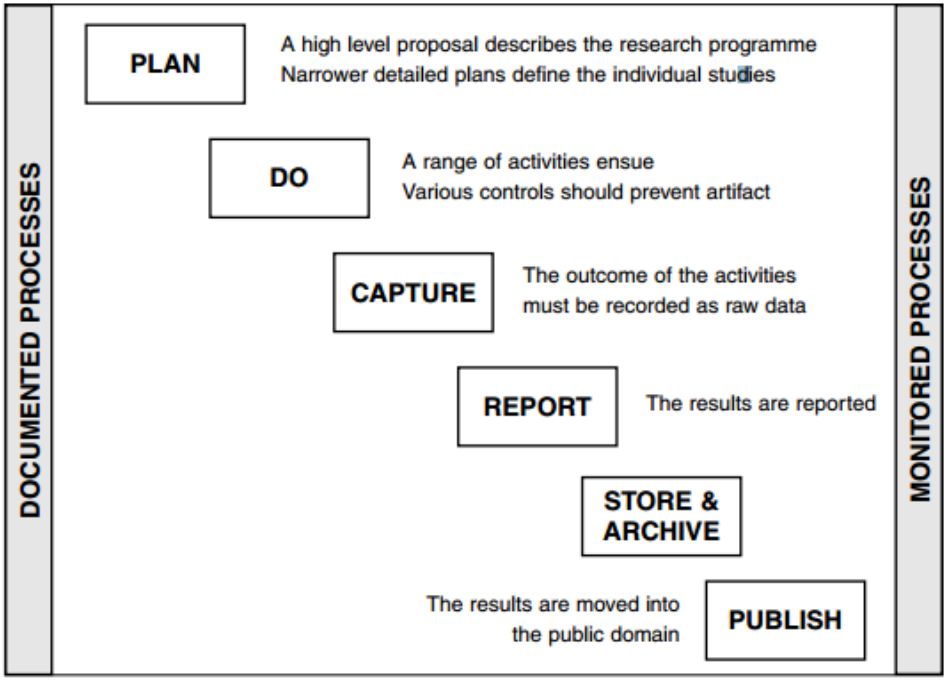
Discussion

18. Interpretation & implications

19. Generalisability and translation

20. Funding

Quality practices in basic biomedical research:



Principles of evidence-based medicine - the key to improving quality?

- Experimental research in new drugs should be built on the same principles as clinical research – randomization, blinding, multicenter nature, statistical justification etc.;

- Large scientific organizations conduct randomized, blind, statistically-based research;

A multiple independent laboratories collaboratively conduct a research experiment using a shared protocol (2019: 12 research):

- *C*onsortium for Preclinic*A*l Ass*ES*sment of C*AR*dioprotective Therapies (**CAESAR**);

- Multicenter consortium of academic institutions designed to assess the efficacy of immunotherapeutic methods for the treatment of autoimmune diabetes in NOD T1D mice;

- Preclinical randomized controlled multicenter study of CD49d-antibody efficacy in two different mouse models of stroke

- As of 2019: 12 studies.

Analysis of this approach:

Similarities between studies:
- Sources of funding (mainly government)
- participating countries (9 studies - all centers in the USA; 3 - international with the participation of centers from the USA, Germany, France, Canada, Finland, Hungary, Italy, Great Britain and Spain)
- animal species (93% lab rodents)
- average sample size was 13

Main results:
- inconsistency with results obtained in previous single-center studies:
- In four studies, the results confirmed previous results obtained at one centre; in six studies, no effect was found; in two - a mixed effect.

Conclusions:

Pros:
- Reducing bias
- accurate assessment of intervention effects
- the possibility of involving centers for administration, data processing
- high completeness of reporting

Cons:
- Lack of clear reporting standards/recommendations
- Difficulties in validating ethical standards (different approval rules in the centres)
- difficulties in joint protocol development (different funding of centres)
- complexity of the organization

Victoria T. Hunniford et al., 2019

Good laboratory practices

- Good Laboratory Practice (GLP) is a quality system that is concerned with organizational process and conditions under which non clinical health and environment studies are planned, performed, monitored, recorded, reported and archived for risk assessment process (OECD, 1997);

- GLP requirements are primarily implemented to ensure data quality and integrity and are not directly related to scientific aspects. It is an assurance for the quality system, that the test data are generated under the controlled conditions;

- a tool that also improves research and data quality by applying stringent documentation requirements, allowing any activity to be redesigned back to its start;

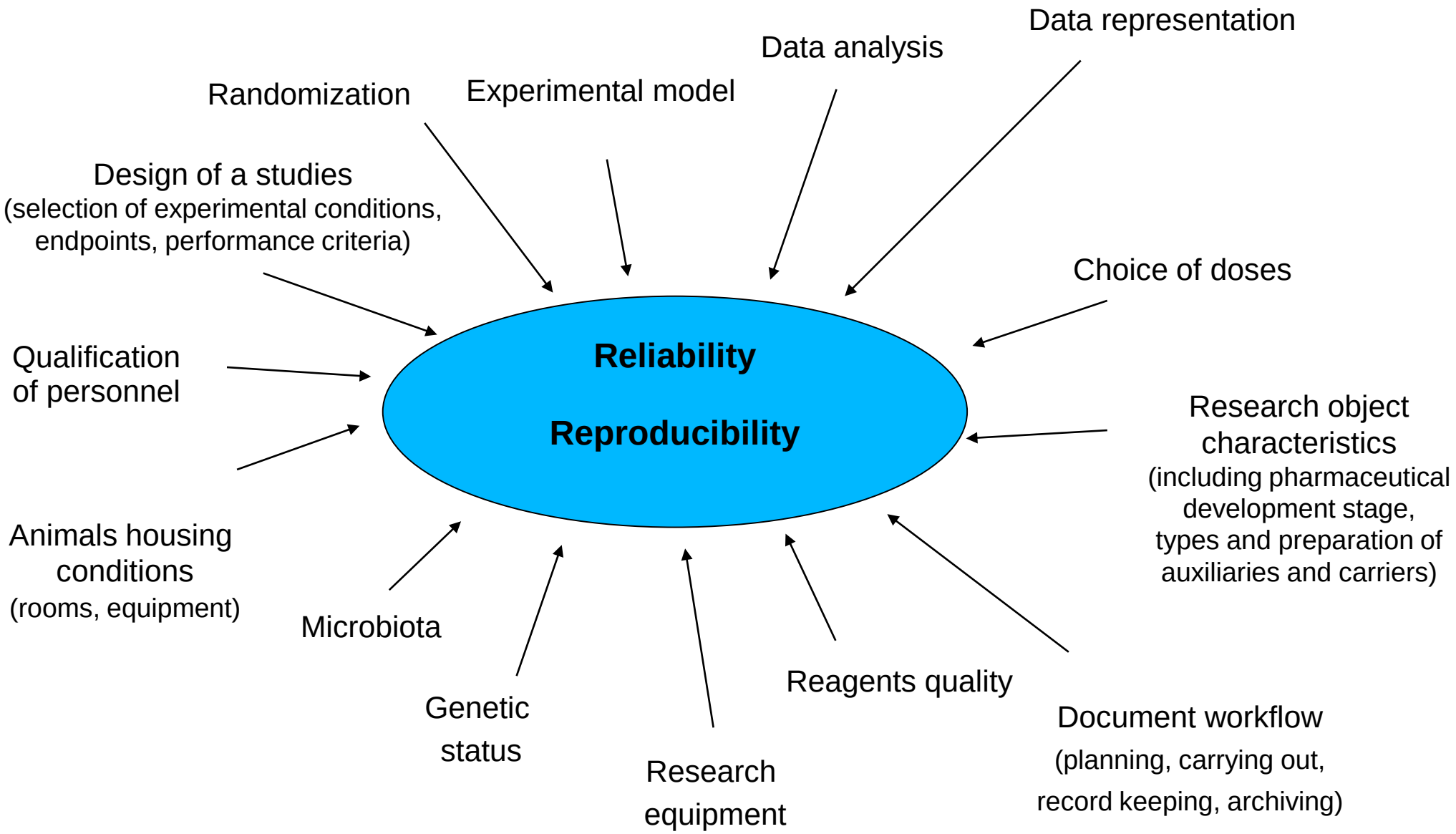
Application of GLP in different field of scientific research:

- inclusion of GLP in animal research will increase the potential of basic translational science [*Wells, 2015; McCarty et al., 2012*] through increased transparency, detailed documentation, clear allocation of responsibilities [*Buonsante et al., 2014*];

- some authors note the importance of applying GLP to ensure an adequate level of scientific significance *[Verhagen et al., 2003];*

- long-term data storage, standardization of current experimental protocols, record archiving – clue to reproducibility *[Nussbeck et al., 2014].*

Factors affecting the quality of preclinical efficacy studies



Advantages and disadvantages of GLP application in efficiency research

Advantages	Disadvantages
Increased standardization and reproducibility of results	Study duration and cost Increased
-	Complication of scientific process
-	It is impossible to find optimal research methods (early phases of drug development)
-	Shift in focus to document management, risk of excessive bureaucratic work
-	Personnel problems

It is important that efficacy studies should be carried out with high quality standards to ensure the reliability of the obtained data;

The application of GLP rules can improve the quality of efficiency research through standardization;

The full application of GLP rules in efficacy studies is impossible and impractical;

To use GLP rules in preclinical efficacy studies, their concept needs to be adapted.