FederaDag 2017

Too valuable to waste:

Experiments on humans and animals

New Insights and Challenges

Friday, June 16th 2017

Organized by

the Dutch Federation of Medical Scientific Societies

Federatie Medisch Wetenschappelijke Verenigingen

in co-operation with

ZonMw (The Netherlands Organisation for Health Research & Development)

Nederlandse organisatie voor gezondheidsonderzoek en zorginnovatie

At

NWO (Dutch Organisation for Applied Science)

Nederlandse Organisatie voor Wetenschappelijk Onderzoek

Laan van Nieuw Oost Indië 300, The Hague (NL)

Federa promotes a sound research environment

COREON promotes a sound regulatory environment

Outline

Human clinical trials and animal experiments for the advancement of medicine need a sound regulation, experimental design and reporting. That is needed to get valid and comparative results and to avoid waste of efforts. This field is rapidly changing in light of advances in personal and precision medicine.
Clinical trial researchers and animal experiments researchers do not often meet together, while their challenges are similar and interrelated.
The FederaDag 2017 will offer opportunities to meet and interact with experts in both fields.

The FederaDag 2017 has four subjects:

- Regulatory challenges
- Advances in experimental design
- Reporting by design
- Tomorrow's testing on trial

- biomedical research with new insights, new opportunities
- meant for scientist, doctors, patients and policy makers
- in one day insight in actual research and effects for society
- scientists address themes and invite the best of the field
- at the forefront of biomedical science

FederaDag 2017 is organized by

Federa promotes a sound research environment

Federatie van Medisch Wetenschappelijke Verenigingen
Foundation Federation of Dutch Medical Scientific Societies

The **Federa** (Foundation Federation of Dutch Medical Scientific Societies) aims to represent scientific biomedical societies by promoting interdisciplinary communication through an annual thematic conference, guarding general interests of scientists, like career perspective, and self-regulation (COREON). The Federa bundles 27 scientific biomedical societies with all together 8,000 members and coordinates about 20 organizations in COREON.

COREON promotes a sound regulatory environment

Streamlining regulation and promoting self-regulation for the responsible use of data and materials from human subjects has become a major activity by Federa/Coreon e.g. by means of developing Codes of Conduct, together with a legal expert. This is a necessity in an era of abundant and overlapping regulation of biomedical science, especially when EU-guidelines aim at harmonization. The Commission Regulation Research (*COmmissie REgelgeving ONderzoek;* COREON*)* develops **codes of Conduct** for biomedical research in Dutch and English, which can be found online at www.federa.org/codes-conduct:

- The Code of Conduct for the *Use of Data in Health Research* (1995) and revised in (2004).
- *Human tissue and Medical Research*: Code of Conduct for Responsible Use (2001). Revised in 2011.

These documents are also crucial in the education and training of young professionals.

ZonMw

ZonMw stands for innovation: we enable others to develop new (scientific) knowledge. And we do everything we can to ensure that this new knowledge is used in policy and health care practice. ZonMw is an independent self-governing organisation. Our 2016–2020 policy plan addresses the greatest challenges facing health care, and describes how research and innovation contribute towards new solutions. This goes further than simply developing new therapies. ZonMw also directs its efforts towards:

- the constant renewal of science itself,
- providing opportunities for and stimulating the dynamics between basic, translational and applied research,
- developing scientific talent.

Research results need to have an impact on science and on society, so we design our granting programmes in collaboration with the parties for whom the information is intended; which makes it much more likely that new knowledge is actually used in practice. Nevertheless, roles remain distinct. ZonMw is responsible for knowledge development, dissemination and promoting implementation; the job of actually implementing this knowledge is taken on principally by other parties.

ZonMw's principal commissioners are the Dutch Ministry of Public Health, Welfare and Sport (VWS) and the Netherlands Organisation for Scientific Research (NWO). ZonMw also increasingly works on behalf of other parties, such as local authorities, health funds, health care insurers, private companies, and professional associations.

We work closely with the Netherlands Organisation for Scientific Research (NWO). ZonMw is responsible for health care research, and the NWO for other scientific research areas. ZonMw has defined six policy priorities:

- large, long-term sustainable programme clusters
- international collaboration
- independent research and talent development
- The Dutch National Research Agenda
- programmes directed towards practice, participation, and knowledge agendas
- strengthening the impact of research

Program FederaDag 2017

09:00 - 09:30 *Registration and coffee*

09.30 - 09.35 Welcome by John Jacobs

Chair *Merel Ritskes-Hoitinga*

Regulatory challenges

09.35 - 10.00 Challenges in implementation of EU directive Animal Research
Susanna Louhimies, European Commission, Brussels (BE)

10.00 - 10.25 Challenges in implementation in the Netherlands
Martje Fentener van Vlissingen, Dutch Society for Laboratory Animal Science, Erasmus MC, Rotterdam

Advances in experimental design

10.25 - 10.50 Validity of human clinical trials
Jennifer de Beyer, Equator, Oxford (UK)

10:50 – 11:10 *Coffee break*

Chair *Jean Philippe de Jong*

11.10 - 11.35 Validity of animal studies for medicine
Harald Schmidt, Maastricht University

Reporting by design

11.35 - 12.00 Registered Reports: Using peer-reviewed preregistration to improve transparency in scientific reporting. Christopher Chambers, Cardiff University (UK)

12.00 - 12.25 Experimental design, analysis and reporting of animal studies
Nathalie Percie du Sert, NC3Rs, London (UK)

12.25 - 12.45 *Lunch*

Poster session

12.45 - 13.35 Poster session chaired by *Evert van Leeuwen & Gerard Swaen.*

Tomorrow's testing on trial

Chair: *Erica van Oort*

13.35 - 14.00 Population diversity in clinical trials
Olaf Dekkers, LUMC, Leiden

14.00 - 14.25 Individual patient data analysis in meta-analysis
Maroeska Rovers, Radboudumc, Nijmegen

14.25 – 14.45 *Tea break*

Award, booklet & closing

Chair: *John Jacobs*

14.45 – 15:15 Federa Award to Janneke Horn, AMC by John Jacobs
Lecture Federa Award by Martien Limburg, former promotor of Janneke Horn

15.15 - 15.30 Presentation cahier “Proeven met mensen”
www.biomaatschappij.nl/product/proeven-met-mensen
Wiel Hoekstra Biowetenschap & Maatschappij.

15.30 - 15.40 Poster prize & closing of the day

15.40 *Drinks*

Lecturers and abstracts

Federa laureate lecture by Janneke Horn, AMC, Amsterdam

The Federa is delighted to announce that Janneke Horn, MD, PhD receives the Federa Award 2017. Horn published the first systematic review on animal experiments in 2001. The reason for her to perform this was the failure of Nimodipine in human clinical trial of patients with brain haemorrhages that was based on positive results in animal experiments. After the failed trial, Horn performed a systematic review on all animal experiments. Her meta-analysis of all results on Nimodipine in animal research also showed it was ineffective, and thus no clinical trial should have been performed.

Horn had courage and perseverance to introduce this clinical method into preclinical animal experiments. This method has received extensive follow up in the field and by organizations like SYRCLE and CAMARADES (also on the neurological field). At the FederaDag 2016, both Federa and ZonMw stress that systematic reviews should have the first priority in animal research to avoid waste of valuable scientific research, experimental animals and avoid exposing patients in clinical trials to ineffective and/or even damaging treatments.

Stroke. 2001 Oct;32(10):2433-8.Nimodipine in animal model experiments of focal cerebral ischemia: a systematic review. Horn J, de Haan RJ, Vermeulen M, Luiten PG, Limburg M. www.ncbi.nlm.nih.gov/pubmed/11588338

Other lectures

Challenges in implementation of EU directive Animal Research

Susanna Louhimies, European Commission, Brussels (BE)

Susanna Louhimies works for the European Commission in the Directorate-General for Environment, in the Chemicals Unit. She is the Policy Officer dealing with the protection and welfare of animals used for scientific purposes. She was involved in the Implementing the Three Rs Through Policy by developing and implementation of the EU Directive 2010/63/EU. She is also responsible for the review of the Directive due by the end of 2017.

Challenges in implementation in the Netherlands

Martje Fentener van Vlissingen, Erasmus MC, Rotterdam

Martje Fentener van Vlissingen is is Director of the Erasmus Animal Experimental Center (EDC). Fentener van Vlissingen is European Veterinary Specialist in Laboratory Animal Medicine (ECALAM). she chairs the Dutch Society for Laboratory Animal Science and has contributed in the contexts of FELASA (The European Federation for Laboratory Animal Science and ECLAM in the shaping and implementation of the Directive 2010/63/EU internationallly and nationally.

The Directive was implemented in Dutch law by adapting the current law (1976, revised 1996. This has resulted in long and tedious processes and a structure that is really hard to comprehend or even apply, and rather inefficient. The talk will relate to the gains and the challenges, also with regard to the international context.

Validity of human clinical trials

Jennifer de Beyer, Equator, Oxford (UK)

Dr Jennifer de Beyer is a specialist in science writing, dissemination and publication. After training in laboratory research and working in academic editing, she joined the EQUATOR Network's UK Centre at the Centre for Statistics in Medicine, University of Oxford. Here she develops online resources and delivers training on using reporting guidelines for clear, transparent health research reporting. More information at www.csm.ox.ac.uk/team/jennifer-de-beyer

For a clinical trial to deliver its potential value, it must concern well-designed and well-conducted research on good research questions. It must be disseminated clearly and completely. Its results must be easily found and easily compared with similar trials. The current global and EU focus on research integrity and transparency includes initiatives to optimise the value of every part of this trial pipeline. The EQUATOR Network supports both good research design and clear, complete dissemination of health research through the use of reporting guidelines. These guidelines help researchers to include every important detail in a research protocol or publication, ensuring they can be understood, reproduced, and used to inform clinical practice and future research.

Validity of animal studies for medicine

Harald H.H.W. Schmidt, Maastricht University, Maastricht University

With a double degree in Medicine and Pharmacy Harald Schmidt has a passion for innovative drug discovery and therapy. As an ERC Advanced Investigator, he performs high risk/high potential benefit research on free radical medicine in areas of major medical need, such as stroke, atherosclerosis and diabetes. As chair of the COST action OpenMultiMed he is a leader in the Big Data evolution for Medicine. His multi-national leadership experience in Academia and Industry has led to excellent scientific achievements (Hirsch-index 81) with high socio-economic impact such as patents and biotech spin-offs. He is a reputed drug expert, successful entrepreneur, dedicated teacher and team leader.

In the past 30 years, the success rate of drug discovery has been steadily declining. There are two major reasons for that. The first is our current definition of disease, which is based on organs and symptoms rather than a molecular understanding of their causative mechanism. This leads to targeting surrogate markers rather than curing disease. In consequence, the numbers of patients needed to treat is high and pivotal clinical trials often fail to reach significance. The second cause is a frequent lack of efficacy of the newly developed drug. Connected to this is the failure of translating basic research into clinical relevant applications. In recent years, several studies have shown that approximately 60% of the published biomedical literature is not reproducible. Clearly, if this represents the body of evidence for subsequent drug discovery, any drug development is bound to fail.

In this talk, two cases of target validation for the indication of ischemic stroke will be presented exemplifying these problems. Pharmaceutical industry has essentially completely withdrawn from the indication stroke, despite the fact that this is the second cause of death and the first of disability. In a slightly sarcastic review this was titled 1,028 experimental stroke therapies, of which none translated into the clinic. Own data will be shown and discussed for the targets NOX2 and PSD-95 to document that even a substantial body of evidence from the basic science literature published in so-called high impact journals can be simply wrong. Major reasons for this are a positive publication bias and a lack of statistical power and study quality. However, one should not end on a negative note but point towards a way forward. In order to increase study quality, target validation should be limited to so-called preclinical randomised confirmatory trials (pRCT). Any other study should be termed an exploratory trial and not end with any conclusion on a target or a mechanism being involved in a given disease phenotype. The second initiative aims to facilitate meta-analyses of preclinical data by the foundation of pre-clinicaltrials.org, an open access database to deposit unpublished negative or positive target validation data for later meta-analysis. Together these approaches should both foster collaborations amongst scientists and increase data quality and their clinical translation.

Registered Reports: Using peer-reviewed preregistration to improve transparency in scientific reporting

Christopher Chambers, Cardiff University (UK)

My principal research interests include the use of brain stimulation (TMS, TES) and brain imaging techniques (fMRI, MRS, MEG) to understand cognitive control, attention and awareness in the human brain. I am especially interested in translational applications of cognitive neuroscience in the domain of obesity and behaviour change. My group is also working on the simultaneous combination of TMS and MRI, as well as technical advances in TMS methods to improve the precision and reliability of cortical stimulation. For more see psych.cf.ac.uk/contactsandpeople/chambersc1.php

Abstract: In 2013 the journal Cortex became the first outlet to offer Registered Reports, a format of pre-registered empirical publication in which peer review happens prior to data collection and analysis (cos.io/rr). The philosophy of Registered Reports is that in order to neutralise publication bias and various forms of reporting bias (such as p-hacking and post hypothesising), the publishability of a scientific study should be decided by the importance of the research question and rigour of the methodology, and never based on the results of hypothesis testing. In this talk I will provide an introduction to Registered Reports and update on its progress, including future uptake in clinical trials. Together with allied initiatives, Registered Reports are helping to reshape the incentive structure of science to place transparency and reproducibility on par with conventional indicators of scientific quality. key background: www.nature.com/articles/s41562-016-0021

Experimental design, analysis and reporting of animal studies

Nathalie Percie du Sert, NC3Rs, London (UK)

Nathalie Percie du Sert is a programme manager at the National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs), which she joined in 2010. She is responsible for the programme of work on experimental design and reporting of animal studies. This includes the development of the Experimental Design Assistant, an online tool to guide researchers through the design of in vivo experiments and dissemination of the ARRIVE guidelines to improve the design and reporting of animal research.

She holds a PhD from St George's University of London and worked as a post-doctoral researcher in the field of nausea and emesis at the University of California, San Francisco and at the Chinese University of Hong Kong, where she developed expertise in in vivo research and systematic reviews and meta-analysis of animal models.

This presentation will cover NC3Rs resources to improve the experimental design, analysis and reporting of animal studies such as the ARRIVE guidelines and the Experimental Design Assistant.

The reproducibility of biomedical research using animals has come under scrutiny in recent years, and quality standards in the design, analysis and reporting of in vivo research have been flagged as concerns. The NC3Rs has been working in this area over the last ten years and led the development of two key resources to support researchers and improve the design, analysis and reporting of in vivo experiments. The ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines consist in a 20 item checklist, which summarise the minimum information necessary to describe a study in a comprehensive and transparent manner. The guidelines cover the main aspects of a scientific publication and make recommendations on the reporting of the study design, experimental procedures, animal characteristics, housing and husbandry, and statistical analysis. The Experimental Design Assistant (EDA; eda.nc3rs.org.uk) is a web application with a supporting website, which helps researchers design animal experiments, by increasing the transparency of the experimental plan, and providing feedback to improve it.

Features of the EDA include:

- Computer-aided design tool to develop a diagram representing the experimental plan
- Critical feedback on the experimental plan – using computer-based logical reasoning
- Statistical analysis suggestions
- Sample size calculation
- Randomisation sequence generation
- Support for allocation concealment and blinding
- Web-based resources to improve knowledge of experimental design and analysis

The objective of these resources is to maximise the output of research using animals. Wide dissemination and uptake are essential to ensure the science emerging from animal research is fully exploited.

Population diversity in clinical trials

Olaf Dekkers, LUMC, Leiden

Olaf Dekkers is postdoctoral researcher at the departments of Clinical Epidemiology and Endocrinology. He is adjunct professor at the department of Clinical Epidemiology at Aarhus University (Denmark). He studied medicine philosophy and graduated (MA) on the 'truth definition according to Frege'. He was trained in epidemiology (MSc) at the London School of Hygiene and Tropical Medicine. Research topics are epidemiology of endocrine diseases, meta-analysis and methodology of research. He works in close collaboration with the Institute of Social and Preventive Medicine in Bern (Switzerland) and with the department of Clinical Epidemiology in Aarhus (Denmark). He is methodological chair of the guideline committee of the European Society of Endocrinology.

Clinical trials try to determine treatment effects in populations with similar clinical characteristics; however, relevant clinical differences between included patients may still exist. The question whether trial results can be generalized to all patients, or whether certain characteristics are associated with a better treatment response is the driving motive for subgroup analysis. The interesting question is whether personalized medicine is the methodological answer to the often problematic practice of subgroup analysis.

Individual patient data analysis in meta-analysis

Maroeska Rovers, Radboudumc, Nijmegen

Maroeska Rovers is professor of evidence-based surgery at the Radboudumc, where she was trained as a clinical-epidemiologist. Since her PhD she has been working on individual patient meta-analyses, and the further methodological development of this method. She is co-convenor of the IPD meta-analysis methods group and an editor of the Diagnostic Test Accuracy review group of the international Cochrane collaboration. Together with Hans Reitsma from the Julius Center she received a TOP grant to evaluate and improve prevailing approaches, and to develop novel methods where needed, for investigating and interpreting subgroup effects in treatment response when multiple IPD sets are available.

Evidence is accumulating that the response to treatments (beneficial and side effects) can differ between subgroups of patients. Treatment decisions based on a valid and clinically relevant subgroup effect will enhance benefits or avoid harms for patients, and prevent unnecessary use of health resources. The quest for identifying subgroups is therefore understandable and will only be fuelled by the fast rate in which biomarkers, high resolution imaging techniques, and genetic markers provide new insight why the response in treatment may vary between individuals.

Meta-analyses of individual participant of multiple trials on the same (type of) treatment are considered the gold standard approach for investigating whether an intervention is more or less effective between subgroups of individuals. The validity of IPD meta-analysis is also acknowledged by the various initiatives for sharing research, including the European Commission, AllTrials campaign, European Medicines Agency, Institute of Medicine, and several grant agencies like ZonMw.

Furthermore, the estimated 'waste in clinical research' of 85% of research funds (about 100 billion dollars per year) due to flawed design, non-publication and poor reporting, only refers to activities prior to the point of publication. Much waste clearly occurs after publication: from poor access, poor dissemination, and poor uptake of the findings of research. The development of data-sharing and subsequent IPD meta-analyses is important to reduce this post publication waste.

External session chairs

Jean Philippe de Jong, KNAW

Is a Senior Policy Officer on research & knowledge at the Royal Netherlands Academy of Arts and Sciences (Koninklijke Nederlandse Akademie van Wetenschappen; KNAW). The KNAW is an advisory body to the Dutch Government. De Jong was involved in the KNAW report focusing on the usefulness and necessity of replication studies and the preconditions for these studies. Replication studies are indicated by the irreproducibility of many scientific results. This report focuses on replication studies as a way of testing and improving defective reproducibility, and less on the occurrence of inadequate reproducibility (for example, by improving study designs). These things are thus complementary. The KNAW report will be presented in September 2017.

Poster presentations

Posters on Regulatory challenges

WMA declaration of Taipei for biobanks enables Opt-out method for residual material in medical research.

Peter Riegman (p.riegman@erasmusmc.nl**).**

Pathology dept., Erasmus MC, Rotterdam, The Netherlands.

The opt-out system for residual materials in medical research has been widely adopted in the Netherlands since the FEDERA publication of the Code of Conduct in 2002. COREON has been very supportive of this method which also lead to a revision in 2011. The acceptance of this method in the rest of Europe and globally however has been far from ideal until now. On every occasion there is a major change in European legislation this method needs to be defended. Even now in the aftermath of the new Privacy rules it is hard to keep the options open. This is certainly true looking at the developments in the declaration of Helsinki that only accepts informed consent and widens its boundaries from trials towards residuals every time an updated is presented. This was also true for the draft versions of the World Medical Association (WMA) Declaration of Taipei on ethical considerations in Health Databases and Biobanks. Through strong counter arguments the declaration now accepts other consent methods then signed informed consent as long as the country is democratic.
Arguments submitted:
In countries where signed informed consent is the norm, it is common practice that in case of secondary use of biomaterials a waiver is given after a request from the IRB or Medical Ethical Committee. Under the waiver all the requested materials can be used despite the fact the donor could not make a choice. In case there is an opt-out system active, the objections have been collected and saved from the patients over the years, the objections can be applied when secondary use of biomaterials is requested, even after decades.
The waiver is actually violating the integrity of the person in its freedom of choice, whereas an opt-out system supports that particular point. This violation is needed because the first amendment in democratic countries requires the best health care for its inhabitants and the requested medical research is considered to be more important and in the interest of the population. More important than the freedom of choice.
In fact, also in countries where health care is accessible to all and where there is hardly any difference between rich or poor, a more liberal standpoint is possible due to higher trust between patients, medical staff and government. In fact the draft text would strongly inhibit these better developed countries in their more positive medical research development.
It is clear that the final version is the way forward and a sign of trust. The draft text of the declaration where signed informed consent was the norm, would even strongly oppose to positives developments, where actually medical research should become a well-accepted integrated part of the diagnostic process and altruism is something we discussed in the past. If we really want to see the best in the “four P” developments this is a must.

The future of animal science: will the Netherlands be the world-leading country in animal free innovations by 2025?

Steffi Bressers (rha.animalresearch@gmail.com**), Hester van den Elzen, Cathrin Gräwe, Daphne van den Oetelaar, Pieter Postma, Sybren Schoustra.**

Participant think tank ‘Animal Research: science policy and ethics’; Radboud Honours Academy, Nijmegen. All authors contributed equally.

The complexity of animal experiments is well-known to researchers and those involved, and can lead to challenges regarding the regulation and implementation of animal experiments and alternatives for these experiments. Another challenge is the goal of the Dutch government to be the world leading country in animal free innovations by 2025.
The question remains whether this goal is achievable or even desirable. In order to obtain an understanding of the views on these issues from people in the scientific field of animal research or alternatives, an international survey (N=440) was conducted. In this survey, several roadblocks to the implementation of this 2025-goal were explored. Respondents were asked to rank the importance of these roadblocks, and to give their opinion regarding the 2025-goal.
Generally the respondents were not in favour of the 2025-goal: only 40% would support it and 70% did think the goal was not desirable and achievable in their field. The survey suggested that the most important obstacle for using alternatives to animal models was the lack of reliability of alternative methods. Moreover, over 50% of the respondents stated that they would leave their country or move their research if the research they are currently performing on animals would no longer be allowed, while 25% of the respondents stated that they would consider to leave their country.
Animal research faces the regulatory challenges to simultaneously improve the welfare of animals and keep the standard of science in the Netherlands at an excellent level. This problem asks for clear communication between regulators and the scientific community regarding the implementation of the 2025-goal.

Ethical Issues in the Use of Animal Models for Tissue Engineering: Reflections on Legal Aspects, Moral Theory, 3Rs Strategies, and Harm-Benefit Analysis.

Gabriel R. Liguori[1,2] (gabriel.liguori@usp.br**), Bertus F. Jeronimus[3,4] , Tácia T. de Aquinas[1,2], Luiz Felipe P. Moreira[2] , Martin C. Harmsen[1].** 1. Cardiovascular Regenerative Medicine Research Group (CAVAREM), Department of Pathology and Medical Biology, University of Groningen, University Medical Center Groningen, NL. 2. Laboratory of Cardiovascular Surgery and Circulation Pathophysiology (LIM-11), Heart Institute (InCor), Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Brazil. 3. University of Groningen, Department of Developmental Psychology, NL. 4. University of Groningen, University Medical Center Groningen, Department of Psychiatry, Interdisciplinary Center Psychopathology and Emotion regulation (ICPE), NL.

Animal experimentation requires a solid and rational moral foundation. Objective and emphatic decision making and protocol evaluation by researchers and ethics committees remains a difficult and sensitive matter. We discuss four tools that facilitate to consider the minimally acceptable standard for animal experiments, in particular in Tissue Engineering and Regenerative Medicine. Firstly, the boundaries provided by law and public opinion in America and Europe. Secondly, the contemporary moral theory to introduce the Neo-Rawlsian contractarian theory to objectively evaluate the ethics of animal experiments. Thirdly, reduction, replacement, and refinement strategies, which should be accounted for in moral decision making and protocol evaluation of animal experiments. Fourthly, an algorithmic and graphic harm-benefit analysis tool based on the most relevant aspects of animal models in tissue-engineering. Finally, we conclude with a consideration of future avenues to improve animal experiments.

Providing easy accessible 3Rs information: Humane Endpoints website, Interspecies Database and FCS-free Database.

Saskia Kliphuis (s.kliphuis@uu.nl**) and Jan van der Valk**
3Rs-Centre Utrecht Life Sciences, Dept. Animals in Science & Society, Faculty of Veterinary Medicine, Utrecht University, the Netherlands.

The 3Rs-Centre Utrecht Life Sciences (ULS) has initiated the 3Rs Database Programme, which aims to make information on Replacement, Reduction and Refinement (3Rs) of animal experiments freely available. Consequently, the 3Rs Database Programme contributes to the implementation of the 3Rs in research. The programme has adopted the Interspecies Database and the Humane Endpoints website. In 2017, the FCS-free database will be added to the programme.
The Interspecies Database (www.interspeciesinfo.com) provides insight into physiological, anatomical and biochemical parameters of different animal species and humans. With the database, researchers can design their experiments smarter with respect to the choice of an animal model. This could lead to a *reduction* in the number of experimental animals.
The Humane Endpoints website (www.humane-endpoints.info) provides information and training modules on how to recognize and apply humane endpoints in laboratory animals. This helps to prevent unnecessary pain and distress in the animals. Therefore, the website contributes to *refinement* of animal experiments.
In addition, a database on fetal calf serum (FCS)-free media will be launched in 2017. FCS is a common component of animal cell culture media. FCS is harvested from bovine fetuses taken from pregnant cows during slaughter. The use of culture media containing FCS raises both moral and scientific concerns. The FCS-free Database (fcs-free.org) will allow researchers to exchange information on the quality of growth media that do not contain FCS. This website will contribute to *replacement* of animal use in research. For more information on the 3Rs Database Programme, check www.uu.nl/en/3rsdatabases%20or contact the 3Rs-Centre ULS on 3RsCentreULS@uu.nl.

3Rs-Centre Utrecht Life Sciences: Replace, Reduce and Refine animal experiments.

Saskia Kliphuis (s.kliphuis@uu.nl**) and Jan van der Valk**
3Rs-Centre Utrecht Life Sciences, Dept. Animals in Science & Society, Faculty of Veterinary Medicine, Utrecht University, the Netherlands.

Mission statement. The mission statement of the 3Rs- Centre Utrecht Life Sciences (ULS) is to stimulate the development, acceptance and implementation of methods which can Replace, Reduce and Refine (the 3Rs) animal experiments.
Activities. The 3Rs-Centre ULS facilitates 3Rs-research by advising and communicating about 3Rs-methods. The centre publishes a monthly newsletter and participates in laboratory animal education. Furthermore, it has initiated and is responsible for the 3Rs-database programme which makes 3Rs-information freely available to researchers (and others) through information resources online. The centre is also involved in the activities of the local Animal Welfare Body and relevant activities in a national and international context.
The centre includes the only chair of “Alternatives to Animal testing” in the Netherlands.
3Rs in animal experimentation. The 3Rs (Replacement, Reduction and Refinement) were described for the first time by the British biologists Russell and Burch in 1959. Researchers are obliged to take these 3Rs into account at the start of, during and at the end of the experiment, by using approaches which do not involve the use of animals (Replacement), fewer animals (Reduction), or which entail less painful procedures and improve animal welfare (Refinement).
3Rs Database Programme. The 3Rs-Centre ULS has initiated the 3Rs Database Programme. This programme makes 3Rs information freely available and aims to contribute to the implementation of the 3Rs in animal research. For more information, read our second abstract and visit the poster on the FederaDag 2017.
Position. The 3Rs-Centre ULS is administered by the Department of Animals in Science and Society of the Faculty of Veterinary Medicine, Utrecht University. This department focuses on issues pertaining to animal welfare in our society. The centre is affiliated with Utrecht Life Sciences (ULS, www.utrechtlifesciences.nl). For more information, check www.uu.nl/en/organisation/3rs-centre-uls or contact the 3Rs-Centre ULS on 3RsCentreULS@uu.nl.

Posters on Advances in experimental design

From animal model to translational strategy: A systematic literature review of animal models for cystic fibrosis.

CHC Leenaars (Cathalijn.Leenaars@radboudumc.nl), **RBM de Vries, FR Stafleu, C Punt, W Beumer, FLB Meijboom & M Ritskes-Hoitinga.**

Introduction. Inter-species differences, inadequate research methodology and other factors may contribute to the worryingly low translational value of current animal studies. So-called translational strategies, comprising an integrated approach covering the entire research chain including the patient's perspective, may improve translational success. An important component of translational strategies are systematic reviews (SRs) of animal studies. They may help choosing the optimal experimental design for preclinical studies.
Research question. We are currently performing such a systematic literature review describing the animal models for cystic fibrosis (CF).For CF, a multitude of animal models is available to the researcher. Preceding narrative reviews have focussed on e.g. genetic mouse models or on specific disease aspects. A complete and structured overview of all available animal models, which can help researchers to choose an appropriate model for their specific research question, is so far lacking. Our SR is meant to answer the question "What are the currently available animal models for CF?" and will also shed light on the sub-question "What has been measured as a surrogate for CF?".
Methods. We developed a search string for Pubmed and Embase based on terms used for cystic fibrosis and standard animal filters. For the purpose of our review, we define "animal model for CF" as animals in which a spontaneous or induced pathological process can be investigated, in which the process, according to the authors, is intended to represent CF in humans in one or more respects. We excluded studies not addressing CF; studies not in animals (e.g. studies in cells or unicellular organisms and studies describing ex-vivo measurements of tissue dissected from healthy animals), abstracts (without a full description of materials and methods) and reviews not containing new data. Studies in which a pharmacological agent is administered to healthy animals to study ADME (Absorbtion, Distribution, Metabolism, Excretion) or safety have also been excluded.
The full protocol for this SR has been posted online (Leenaars et al., 2015. Available on www.syrcle.nl).
Preliminary results. Literature searches were performed on28-Dec-2015; from Pubmed 7976 references were retrieved, from Embase 9403. After duplicate removal, 12310 references were imported into EROS (Early Review Management System) for screening of the title and abstract. 9700 references were excluded based on screening of the titles and abstracts. 1153 were excluded based on screening of the full text. The included 844 references have preliminary been distributed over the following groups of models: Genetic (662 publications), Infection (84 publications), Pharmacological (54 publications), Administration of patient materials (other than pathogens; 18 publications), Xenografts (17 publications), Diet (5 publications) and Other (4 publications).
Data-extraction is currently in progress. In the final review, the retrieved models will be tabulated. Models will be clustered by induction method, species and strain.
This project is funded by the Netherlands Organisation for Scientific Research (NWO_313-99-310)

From animal model to translational strategy: A systematic review of experimental design in the preclinical and clinical studies of methotrexate for Rheumatoid Arthritis (RA).

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Introduction. Inter-species differences, inadequate research methodology, experimental design and other factors may contribute to the low translational value of current animal studies. Besides by the biological inter-species differences, differences in results may also be explained by differences in experimental design between animal and human studies. Systematic review (SRs) of animal studies may shed light on the comparability of experimental designs for preclinical and clinical studies. We are performing an SR studying experimental designs for methotrexate (MTX) efficacy studies in Rheumatoid Arthritis (RA).
Research Questions

1.) Are the experimental designs of the pre-clinical animal studies comparable with those of the clinical trials?
2.) Are the improvements (in swelling, pain, fatigue, bone- and cartilage damage) found in RA animal models comparable with the improvements found in patients?

Methods. A search for all relevant references has been performed in Pubmed and Embase, using a search strategy to identify animal and human experimental studies on RA with MTX. We excluded studies of other disorders and other drugs, observational studies, safety and ADME (Absorbtion, Distribution, Metabolism, Excretion) studies, in vitro and in silico studies, abstracts providing little experimental detail and reviews without primary data. The full protocol for this SR has been posted online (Leenaars et al., 2016. Available on www.syrcle.nl).
Preliminary results. Our search resulted, after duplicate removal, in 8217 references of which the titles and abstracts were screened for inclusion. 6698 references were excluded at this stage, and the full text of the remaining 1429 was screened. After exclusion of 734 papers based on the full text, data are currently being extracted from the remaining 695 papers. Approximately 25% of the included papers is on animal studies, the remainder is on human studies.

We will compare the design of the animal and human studies and perform assessments of the risk of bias in both. We will perform meta-analyses to investigate the effects of study design on outcome effect size.
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Exploring frailty and relevant events in Alzheimer's Disease drug trial.

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Introduction. Frailty has been widely reported in observational studies as an important predictor for adverse health outcomes, including disability and mortality [1-3]. Among individuals with Alzheimer's Disease (AD), frailty has been associated with worse risk of cognitive decline [4]. However, the relevance of frailty in AD drug trials has not been reported, especially in relation with events commonly encountered in trials, i.e. study withdrawals and adverse events (AE). In this study, we examined whether frailty is linked with these relevant events, using data from a European multicentre AD drug trial.
Methods: Data of 469 participants with mild to moderate AD in the NILVAD-frailty substudy [5] were used for analyses. A Frailty Index (FI) with a range of 0 (fittest) to 1 (frailest) was derived based on a previously defined approach [6] from 26 deficits across seven domains (i.e. daily functioning, cognition, morbidity, physical performance, social network, polypharmacy, and body mass index) assessed at baseline and at study end (78±1 week follow up). All-cause withdrawal status and recorded adverse events were evaluated during the study. Baseline characteristics were evaluated among all participants, participants who withdrew and who did not withdraw from the study. Differences in means, medians and proportions were evaluated using independent samples t-test, chi-square test and Mann-Whitney U test, respectively. Spearman's correlation coefficient was examined between baseline FI and number of recorded adverse events.
Results: Baseline characteristics of the participants are described in Table 1. At both time points 408 participants had available FI, with positive-skewed distribution at baseline (median=0.17), which became significantly higher (median=0.29, p value<0.001) and normalized in distribution at follow up. No difference of baseline FI was found between men and women. Participants who withdrew from the study were older and had higher FI at baseline (Table 1, p value=0.001 and 0.012 respectively). No association was found between baseline FI and number of recorded AE (Spearman's correlation coefficent= -0.03, p value=0.548).
Discussion and conclusions: Our findings suggest that the frailty status of participants in AD drug trials will significantly increase over one and a half year of study duration. Being older and/or frailer apparently determines attrition during the 78 weeks period of AD drug study. Although in observational studies frailty has been confirmed as a better predictor of death and self-management abilities compared to age [2, 7, 8], this does not implicate that measuring either frailty or age would be sufficient, as both are intertwined with each other [9]. Frailty assessments could therefore complement a general characteristic such as age to better anticipate dropouts in future AD drug trials. Nonetheless, in such multi-national study, further analyses are needed to evaluate whether country differences also affect withdrawal status and number of recorded adverse events.

Table 1. Baseline characteristics of all NILVAD-Frailty substudy participants and of participants grouped by withdrawal status

Variables	All participants (N=469)	Withdrawn (n=52)	Not withdrawn (n=417)	Significance (*p* values)
Age, mean (SD)	73.2 (8.2)	76.7 (8.3)	72.7 (8.1)	0.001†
Women, n (%)	289 (61.6)	30 (57.7)	259 (62.1)	0.548‡
MMSE, median (IQR)	21 (18 – 23.5)	20 (17.3 – 22.8)	21 (18 – 24)	0.187*
FI, median (IQR)	0.18 (0.11 – 0.26)	0.23 (0.14 – 0.31)	0.17 (0.10 – 0.26)	0.012*

Note: Differences among withdrawal status were evaluated with † independent samples t-test; ‡ chi-square test; and * Mann-Whitney U test

SD = Standard Deviation; FI = Frailty Index; IQR = Interquartile range.

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Posters on Reporting by design

Responsible Epidemiologic Research Practice.

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Background Or its abbreviation: RERP. That is the title of a research guideline that has been developed by a working group of the Dutch Society for Epidemiology (VvE). Several publications about the need to prevent Questionable Research Practices (QRPs) triggered this work. Among these were a series in the Lancet on research waste1 and a subsequent series in the Journal of Clinical Epidemiology.2 devoted to this topic. The reputation and trust in epidemiologic research in The Netherlands is still high and the VvE wishes to keep it that way. The aim of the RERP guideline is to reduce research waste and to increase the value and reliability of epidemiologic research in The Netherlands by means of increasing transparency and accountability.
Methods The guideline deals with how epidemiologic research, and perhaps research in other disciplines as well, should be conducted archived and disclosed. It does not deal with the more technical aspects, such as required sample size, choice of study design, etc. The guideline describes each step in the process of conducting an epidemiologic study, from the first idea to the ultimate publication and beyond. Next it provides recommendations for each of these steps on how they should be described, archived and disclosed.
Preceeding the 2016 annual epidemiology Conference in Wageningen a preconference was organized to discuss the draft guideline and to assess support. Support was clearly present and the provided recommendations were incorporated into the draft guideline. On March 19, 2017 the VvE Board has reviewed and endorsed RERP. It was also sent to all 1100 Society members with the question to provide comments. Received comments were all in support, with some additional remarks that have been taken on board.
Results RERP has been endorsed by the board of the VvE and is now available on the Society's website. epidemiologie.nl/onderzoek/richtlijn-rerp.html

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Scientific Citations Favor Positive Results: A Systematic Review and Meta-analysis

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Objective: Citation bias, the selective citation of previous literature based on its outcome, can distort the evolution of knowledge and has been studied in different fields. In this systematic review we bring together all evidence and quantify the pooled impact for the first time.
Method: An extensive search strategy was developed and applied to the Web of Science Core Collection and Medline.
Results: We identified 52 studies across disciplines, mostly biomedical. Random effects meta-analyses showed that statistically significant studies are cited almost twice as often as non-significant ones, and, similarly, that studies supporting a specific hypothesis are cited more than twice as often as non-supportive ones.
Discussion: Positive studies are on average cited two times as often as negative studies. It seems likely that this imbalance threatens the valid evolution of knowledge.

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