# What to do prior to planning experiments?

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**Content: two topics to improve animal experimentation**

1. Identify previously performed studies
   - Lecture on Systematic Reviews and search tools
   - Practical on Comprehensive search strategies
2. Use of Gold Standard Publication Checklist (GSPC) when planning and reporting experiments
   - Introductory lecture
   - Practical using GSPC

# Identify previously performed studies

## What to do prior to planning experiments? Identify previously performed studies

Goal:

- Design animal experiment of highest relevance and quality

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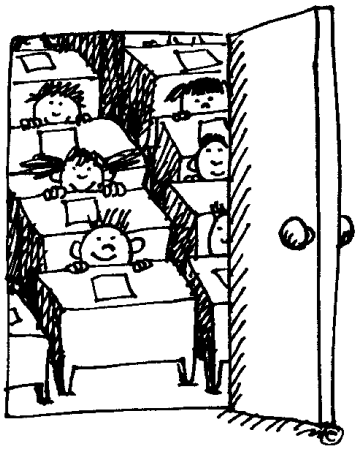
## To achieve highest relevance and quality

Thorough inventory and analysis of
previously performed animal studies

# Systematic Reviews



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3R Research Centre
Refine Reduce Replace


Rob Scholten, The Dutch Cochrane Centre
Amsterdam, The Netherlands

**FELASA Symposium,
Juni 2010 Helsinki, Finland**

## What is a Systematic Review and meta-analysis?

Systematic Review:

**Literature review focused on a single question which tries to identify, appraise, select and synthesize all high quality research evidence relevant to that question**

Meta-analysis:

**Combination of results of individual studies in statistical analysis**

## Systematic steps:

1. Define a specific research question
2. Search for all animal studies
3. Select studies by predefined criteria
4. Assess methodological quality
5. Extract data and meta-analyses
6. Data synthesis

## Why systematic reviews of animal studies?

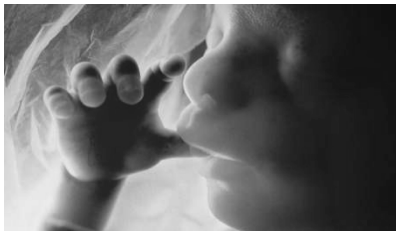
- To obtain an overview of available knowledge
- To help design clinical trials (patient safety)
- To improve translational transparency of animal studies
- To improve quality of primary studies

## Effect of pregnancy on vascular function of arteries

(data from Joris van Drongelen, UMC St Radboud)

**Many conflicting results in literature**

**Perform systematic review**

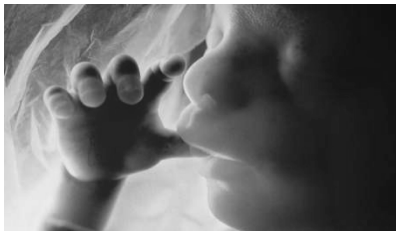


## Effect of pregnancy on vascular function of arteries

(data from Joris van Drongelen, UMC St Radboud)

| | Sprague Dawley rat | Wistar rat |
|---|---|---|
| ***Mechanic stimuli*** | | |
| **- Flow** | ↑ | ↑ |
| **- Myogenic reactivity** | ↓ | = |
| **- ECM elasticity** | ↑ | = |
| ***Pharmacological stimuli*** | | |
| **- $Gq_{EC}$ pathway** | ↑ | = |
| **- $Gq_{SMC}$ pathway** | ↓ | = |
| **- $Gs_{SMC}$ pathway** | ↑ | ? |
| **- NO-sensitivity** | = | = |

**Choice of an animal model**



## Why systematic reviews of animal studies?

- To obtain an overview of available knowledge
- To help design clinical trials (patient safety)
- To improve translational transparency of animal studies
- To improve quality of primary studies

**Example:**
**To improve translational transparency of animal studies**

Experience Malcolm Macleod (CAMARADES):

- 1026 drugs tested for stroke in animal models
- 374 drugs were effective in animal models
- Only 1 drug was effective in human
- Many confusing animal data are available

**WHY does efficacy in animals not correlate to efficacy in humans?**

**Translational transparency → perform SR**

**Internal validity:**

Results give reliable answer the research question

**External validity:**

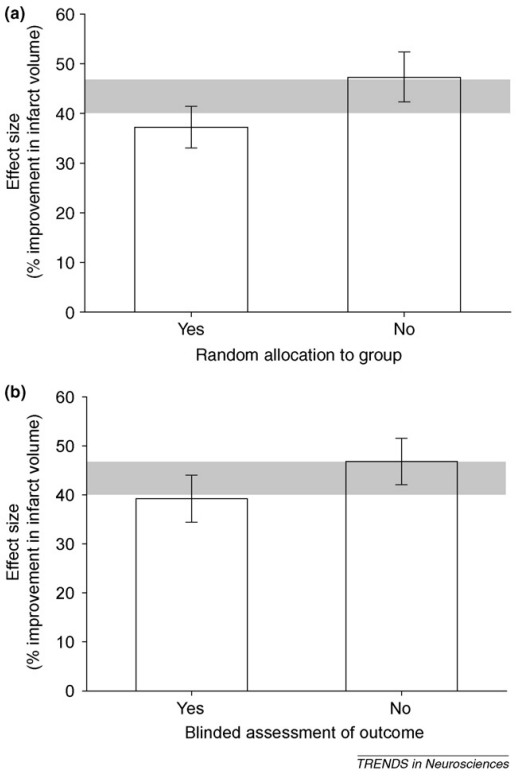
Results provide a correct basis for generalisations to the human condition (publication bias; Are the models we use good models? i.e. co-morbidity)

# To improve translational transparency of animal studies

## Internal validity

| | Randomisation | Blinded Outcome Assessment | Sample Size calculation |
|---|---|---|---|
| Stroke | 36% | 29% | 3% |

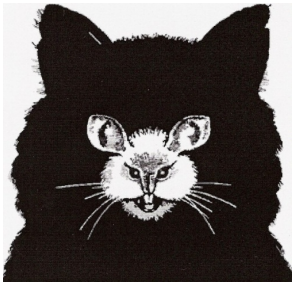
**Data from Malcolm Macleod (CAMARADES collaboration)**




**No randomization / no blinding**

**overestimation of effect size**

From: Sena et al. Trends in Neurosciences, 2010



**“If you take a closer look, you see more”**

2011
EIGHTH WORLD CONGRESS
ALTERNATIVES CONGRESS TRUST

## Montréal Declaration on the Synthesis of Evidence to Advance the 3Rs Principles in Science

### A call for a change in the culture of planning, executing, reporting, reviewing and translating animal research

*Adopted on the occasion of the Eighth World Congress on Alternatives and Animal Use in the Life Sciences: August 21-25, 2011, Montréal, Canada “The Three Rs: Together It’s Possible”*

www.ccac.wc8.ca

## 3R Research Centre, Nijmegen, The Netherlands

Focus:

**implementation of SR of animal studies**

- Developing methodology for SRs (tools)
- Executing SRs
- Education SRs
- International collaboration

## 3R Research Centre:

- Prof. Merel Ritskes-Hoitinga
- Dr. Marlies Leenaars (M.Leenaars@cdl.umcn.nl)
- Dr. Carlijn Hooijmans
- Dr. Rob de Vries
- Judith van Luijk MSc (PhD student)
- Brenda Bakker (BMS MSc student)

Collaboration in Nijmegen:

- NCEBP
- Medical library (Alice Tillema)


**9/10 February 2012, Nijmegen, The Netherlands**
**www.umcn.nl/3RRC**

*The Swiss Association of Cantonal Veterinarians have accredited the SR congress as 1.5 days of continuing education for the Swiss researchers (both days=1.5 days of continuing education; the 1st day=0.5 day of continuing education; the second days workshop=1 day of continuing education).*

## Systematic steps:

1. Define a specific research question
2. Search for all animal studies
3. Select studies by predefined criteria
4. Assess methodological quality
5. Extract data
6. Data synthesis

## Identify all animal studies

* Internet
* Tools to ease the process

## Tools to identify all animal studies (page 36-55 of the hand-out)

- Step-by-step guide to identify relevant animal studies
  (Leenaars et al., Laboratory Animals, 2011, in press)
- PubMed filter to find all animal studies
  (Hooijmans et al., Laboratory Animals, 2010)
- EMBASE filter to find all animal studies
  (De Vries et al., Laboratory Animals, 2011)

# Practical on Comprehensive search strategies

Leenaars et al, 2011
A step-by-step guide to systematically identify all relevant animal studies
(page 48 of the hand-out)

*Table 1*
Steps

1. Research question
2. Sources
3. Comprehensive search strategy
4. Search results
5. Relevant papers

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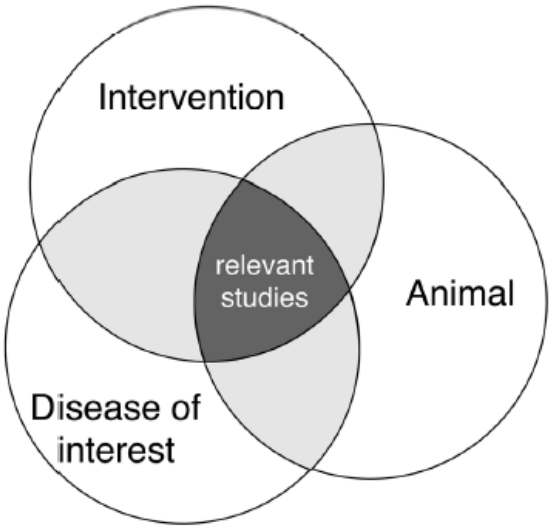
1. Research question

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1. Research question

What is the effect of probiotic supplementation in animal models for acute pancreatitis?

Search Components (SC)?

1. (acute) pancreatitis
2. probiotic(s)
3. animal (models)

## 2. Sources

- Bibliographic databases with thesaurus
  - E.g. PubMed [MeSH]
- Bibliographic databases with keywords
  - E.g. Web of Science, Scopus
- Google
- Etc.

## Quick search

Number of retrieved records depends on the selected search terms:

**4** (pancreas AND inflammation) AND probiotics AND animals

**3** pancreatitis AND probiotic AND animal models

**2** pancreatitis AND probiotic AND animals

**1** pancreatitis AND probiotics AND animals

# 3. Comprehensive search strategy:

| Search | PubMed Search terms | Results |
|---|---|---|
| #1 | **pancreatitis[MeSH Terms] OR** pancreatitis[tiab] **OR** pancreatitides[tiab] **OR** ANP [tiab] **OR** (pancreas[tiab] AND inflammation[tiab]) **OR** (pancreatic[tiab] AND inflammation[tiab]) | **58795** |
| #2 | **probiotics[MeSH Terms] OR** probiotics[tiab] **OR** probiotic[tiab] **OR** probiotica [tiab] **OR** synbiotic[tiab] **OR** synbiotics[tiab] **OR bifidobacterium[MeSH Terms] OR** bifidobacterium[tiab] **OR** bifidobacteria[tiab] **OR lactobacillus[MeSH Terms] OR** lactobacillus[tiab] **OR** lactobacilli[tiab] **OR** lactobacteria[tiab] **OR** lactobacterium [tiab] **OR lactococcus[MeSH Terms] OR** lactococcus[tiab] **OR** lactococci[tiab] **OR bacillus[MeSH Terms] OR** bacillus[tiab] **OR** bacilli[tiab] **OR saccharomyces[MeSH Terms**] **OR** saccharomyces[tiab] **OR** sporobacterin[Substance Name] **OR** sporobacterin[tiab] **OR** lactic acid bacteria[tiab] **OR** lactic acid bacterium[tiab] **OR** Nissle 1917[tiab] | **206335** |
| #3 | **#1 AND #2** | **188** |
| #4 | With PubMed **Animal Search Filter** | **47** |

# Your turn!

Leenaars et al, 2011
A step-by-step guide to systematically identify all relevant animal studies (page 51 of the hand-out)

Table 2 **Step A Search components?**

Topic:
**supplementation of omega-3 fatty acids in animal models for Alzheimer's Disease**

Search components:

1.omega(-)3 fatty acid(s)

2.animal (models)

3.Alzheimer('s Disease)

Leenaars et al, 2011
A step-by-step guide to systematically identify all relevant animal studies
(page 51 of the hand-out)

# Omega 3 fatty acids

*Table 2*

## Step B Comprehensive search strategy

- Identify standardized subject terms e.g. MeSH (page 50, paragraph 3.1B1)
- Identify free-text terms
- Combine standardized and free-text terms

## Comprehensive search strategy omega 3 fatty acids:

First find the MeSH term(s):

Fish Oils

**Fatty Acids, Omega-3**

Docosahexaenoic Acids
Eicosapentaenoic Acid

Also the synonyms per MeSH term
n-3 PUFA , n-3 Fatty Acids, Fatty Acids, n-3, n 3 Fatty Acids
n-3 Polyunsaturated Fatty Acid, n 3 Polyunsaturated Fatty Acid, etc.

**fish oils[MeSH Terms]** OR (fish[Tiab] AND oils[Tiab]) OR fish oils[Tiab] OR **"fatty acids, omega-3"[MeSH Terms]** OR (fatty[Tiab] AND acids[Tiab] AND omega-3[Tiab]) OR omega-3 fatty acids [Tiab] OR fatty acids omega 3[Tiab] OR (fatty[Tiab] AND acids[Tiab] AND omega-3[Tiab]) OR fatty acids omega 3[Tiab] OR **docosahexaenoic acids[MeSH Terms]** OR (docosahexaenoic[Tiab] AND acids[Tiab]) OR docosahexaenoic acids[Tiab] OR **eicosapentaenoic acid[MeSH Terms]** OR (eicosapentaenoic[Tiab] AND acid[Tiab]) OR eicosapentaenoic acid[Tiab] OR **alpha-linolenic acid [MeSH Terms]** OR (alpha-linolenic[Tiab] AND acid[Tiab]) OR alpha-linolenic acid[Tiab] OR (alpha[Tiab] AND linolenic[Tiab] AND acid[Tiab]) OR alpha linolenic acid[Tiab] OR **"dietary fats, unsaturated"[MeSH Terms]** OR (dietary[Tiab] AND fats[Tiab] AND unsaturated[Tiab]) OR unsaturated dietary fats[Tiab] OR (dietary[Tiab] AND fats[Tiab] AND unsaturated[Tiab]) OR omega 3 fatty acids [Tiab] OR polyunsaturated fatty acid[Tiab] OR n-3 PUFA[Tiab] OR PUFA[Tiab] OR n-3 fatty acids [Tiab] OR "n 3 polyunsaturated fatty acid"[Tiab] OR fatty acids n-3 [Tiab] OR DHA[Tiab] OR EPA[Tiab] OR ALA[Tiab]

#1 dementia[MeSH Terms] OR dementia[Tiab] OR "dementia, vascular"[MeSH Terms] OR alzheimer disease[MeSH Terms] OR alzheimer[Tiab] OR alzheimer's[Tiab] — 135699

#2 fish oils[MeSH Terms] OR (fish[Tiab] AND oils[Tiab]) OR fish oils[Tiab] OR "fatty acids, omega-3"[MeSH Terms] OR (fatty[Tiab] AND acids[Tiab] AND omega-3[Tiab]) OR omega-3 fatty acids[Tiab] OR fatty acids omega 3[Tiab] OR (fatty [Tiab] AND acids[Tiab] AND omega-3[Tiab]) OR fatty acids omega 3[Tiab] OR docosahexaenoic acids[MeSH Terms] OR (docosahexaenoic[Tiab] AND acids[Tiab]) OR docosahexaenoic acids[Tiab] OR eicosapentaenoic acid[MeSH Terms] OR (eicosapentaenoic[Tiab] AND acid[Tiab]) OR eicosapentaenoic acid[Tiab] OR alpha-linolenic acid[MeSH Terms] OR (alpha-linolenic[Tiab] AND acid[Tiab]) OR alpha-linolenic acid[Tiab] OR (alpha[Tiab] AND linolenic[Tiab] AND acid[Tiab]) OR alpha linolenic acid[Tiab] OR "dietary fats, unsaturated"[MeSH Terms] OR (dietary[Tiab] AND fats[Tiab] AND unsaturated[Tiab]) OR unsaturated dietary fats[Tiab] OR (dietary[Tiab] AND fats[Tiab] AND unsaturated[Tiab]) OR omega 3 fatty acids[Tiab] OR polyunsaturated fatty acid[Tiab] OR n-3 PUFA[Tiab] OR PUFA[Tiab] OR n-3 fatty acids [Tiab] OR "n 3 polyunsaturated fatty acid"[Tiab] OR fatty acids n-3 [Tiab] OR DHA[Tiab] OR EPA[Tiab] OR ALA[Tiab] — 66629

5036788

#3 animal experimentation"[MeSH Terms] OR "models, animal"[MeSH Terms] OR "invertebrates"[MeSH Terms] OR "Animals"[Mesh:noexp] OR "animal population groups"[MeSH Terms] OR "chordata"[MeSH Terms:noexp] OR "chordata, nonvertebrate"[MeSH Terms] OR "vertebrates"[MeSH Terms:noexp] OR "amphibians"[MeSH Terms] OR "birds"[MeSH Terms] OR "fishes"[MeSH Terms] OR "reptiles"[MeSH Terms] OR "mammals"[MeSH Terms:noexp] OR "primates"[MeSH Terms:noexp] OR "artiodactyla"[MeSH Terms] OR "carnivora"[MeSH Terms] OR "cetacea"[MeSH Terms] OR "chiroptera"[MeSH Terms] OR "elephants"[MeSH Terms] OR "hyraxes"[MeSH Terms] OR "insectivora"[MeSH Terms] OR "lagomorpha"[MeSH Terms] OR "marsupialia"[MeSH Terms] OR "monotremata"[MeSH Terms] OR "perissodactyla"[MeSH Terms] OR "rodentia"[MeSH Terms] OR "scandentia"[MeSH Terms] OR "sirenia"[MeSH Terms] OR "xenarthra"[MeSH Terms] OR "haplorhini"[MeSH Terms:noexp] OR "strepsirhini"[MeSH Terms] OR "platyrrhini"[MeSH Terms] OR "tarsii"[MeSH Terms] OR "catarrhini"[MeSH 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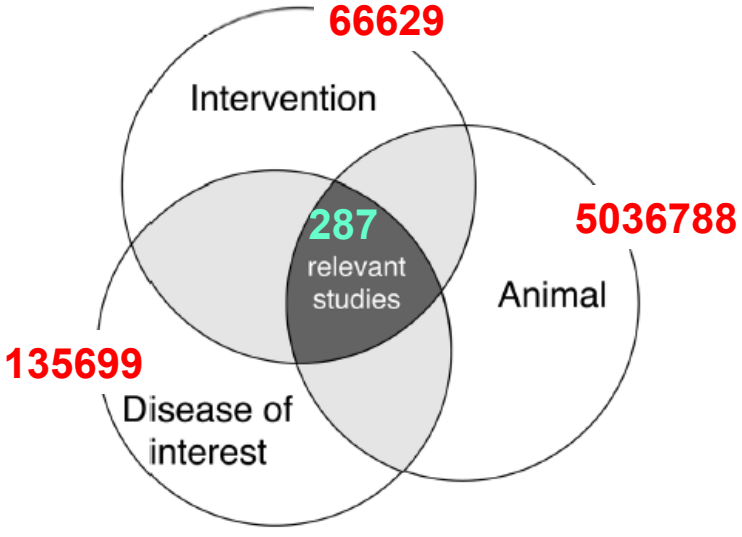
**#4** Search **#1 AND #2 AND #3** **287**



## Use of GSPC when planning and reporting experiments

- GSPC = Gold Standard Publication Checklist

Hand out (Hooijmans et al., 2010)

## You found interesting studies

- Interpret results
- Place into context
- Repeat experiment
- Confounding factors / possible bias

**you need details**

# 1) Developing a publication checklist

**Hooijmans et al 2010, ATLA**

**Publication checklist**

**Introduction:**
- Background information:
  - Description of the literature concerning the topic of the paper, including a short (global) description about how the results have been achieved / obtained.
  - Description of the gaps in the current knowledge concerning the topic,
  - The aim or objective of the current study.
- Research question or hypothesis
  - Specific and focused
  - Use as possible the PICO(t)
    - Patient Group or Animal species
    - Intervention (or exposure)
    - Comparison / Control Group
    - Outcome measure
      If applicable:
    - Time (duration of intervention)
- Clinical relevance or other relevancy of research
  - Reasons why a specific animal model has been chosen and
  - Specific characteristics of animal-model

**Methods:**
- Experimental design (if possible)
  - For example:
    - Completely randomized design
    - Block design
    - Factorial designs
    - Repeated measures design
    - Sequential designs
- Experimental groups and controls
  - Quarantine and acclimatisation period after transportation to animal facility of transportation
  - Species
  - Designation of strain (exact genetic code)
  - Origin and source of animals
  - Genetic background (outbred, inbred, F1 hybrid, mutant, transgenic, congenic, consomic etc)
  - 
  - Define the experimental unit (individual animal/ animals in one cage)
  - Number of animals per group (and possibly power and sample size calculations)
  - Sex
  - Age (at the beginning and the end of the experiment)
  - Weight (at the start of the experiment)
  - Microbiological status
    - Conventional specified pathogen free (SPF) / Gnotobiotic, germ free
    - Measures to protect microbiological status (for example; Open-system, Closed system (SPF) ,Individually ventilated cage racks, Isolation unit).
  - Housing
    - Animal room
      - Temperature ± range (regulated or not)
      - Relative humidity ± range (regulated or not)
      - ventilation
        - Over- or underpressure
        - Air changes per hour
      - Lighting
        - Natural or artificial
        - Number of hours light per 24 hours,
        - Light intensity
        - Time when light is switched on
        - Transitional decrease in light intensity
      - Noise (Music etc)
    - Cage
      - Type and size
      - Number of animals per cage (and if individual housed, why?)
      - Bedding (ref; if not: type, quality????, pre-treatment)
      - Presence and kind of cage-enrichment
      - Frequency of cage change???????
    - Frequency of handling
  - Nutrition
    - Type (natural-ingredient diets, chemically defined diets or purified diets)
    - Composition or batchnumber (If possible use a reference)
    - Feeding regimes (ad libitum, meal feeding, restricted, etc.)

    If not ad libitum:
    - Amount of food given
    - Frequency and time of feeding
  - Water
    - Type
    - Pre-treatment (concentration of acidification or chlorination)
    - Water schedule
      - Quantity (ad libitum?)
      - Frequency of water supply (in case of restriction)
    - Frequency of change
  - Method of allocation to treatment group: i.e: Randomly assigning animals to a specific group
  - Describe how the disease or intervention is defined in the animal
  - Description of the reasons to exclude animals from the experiment
  - Describe the control groups in the experiment, and explain why these specific control groups are important for answering the research question.
- Description of compliance to national regulatory principles.
- Description of the ethical and qualitative assessment by an independent organization within the institute (give the name, like DEC for example)
- The intervention
  - Time schedule
    - Day and time of intervention within experiment
    - Time between intervention and sampling or processing
  - Kind of intervention
  - Description of operation techniques or other techniques and materials used
  - Dose and/or frequency of intervention (when applicable)
  - Number of animals per intervention
  - Administration route (enteral (oral or via the anus)/ parenteral/ trans-dermal)
  - Drugs and dose tested (product name, manufactures, concentration)
  - Other products used (product name, manufactures, concentration)
  - Method and time of sampling (blood, urine etc)
  - Anaesthesia (duration, kind of drug and method)
  - Analgesia (kind of drug and method)
  - Euthanasia (kind of drug and method)
  - Description of general well being of the animal during and at the end of the intervention.
- Outcome
  - Describe parameters of interest, and the method of determination.
    - Include also important physiological parameters and reference values to define well being of animal.
  - Age and specific time within the experiment when parameters will be determined.
  - Description whether or how the staff was blinded to the treatment modality.
- Description of the statistics used.

**Results:**
- Numbers and reasons of premature deaths during the experiments (short description of autopsy findings).
- Excluded animals (number and reason why they were excluded).
- Short description/ explanation of included animals with peculiarities.
- Power analysis after adjustment for diseased and excluded animals (to determine the reliability of the study).
- Description of the most important relevant physiological parameters during intervention (like temperature, bodyweight, heart rate etc).

**Discussion:**
- Discuss the (indirect) clinical and overall scientific relevance of the outcome
- Define whether or not follow up studies are necessary.



# Publication checklist and ARRIVE guidelines

| GSPC | ARRIVE |
|---|---|
| • May 2010 | • June 2010 |
| • Checklist for planning, design, execution <u>and</u> reporting of animal experiment | • Guidelines for reporting |
| • Description of items in more detail (housing, nutrition, water)<br>➢ diminishing the likelihood of interpretation errors | • Global description of items |
| • Operationalized and specified | • Only names the items |
| • <u>Checklist,</u> and is therefore well-structured and easy to use | • Guidelines |

Letters to the editor: Hooijmans et al. 2010 in Br. J. of Pharmacology and Laboratory Animals

## Goal

- Awareness of importance of reporting details in papers

## Instruction

- What do you need:
  - Provided GSPC checklist
  - Provided paper: Ritskes-Hoitinga et al. 1998

## Instruction

- Read:
  - Abstract
  - Relevant parts of Materials and methods
  - Relevant Tables

- Fill out checklist item 2-65 of provided checklist

- Tuesday: discuss checklist