

Preclinical Systematic Reviews: heritage and avenues ahead

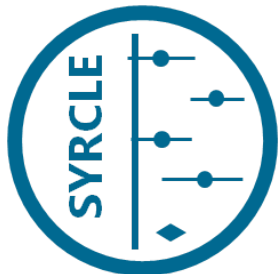
Merel Ritskes-Hoitinga

Professor in Evidence-Based Laboratory Animal Science

SYRCLE , Department for Health Evidence

Visiting professor AU

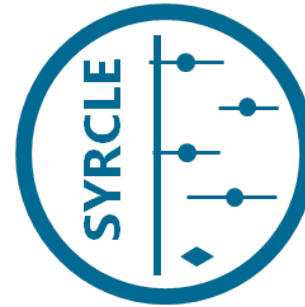
AUGUST conference April 2017



www.syrcle.nl

Radboudumc

Who are we at SYRCLE?



SYstematic
Review
Centre for
Laboratory animal
Experimentation

Judith van Luijk

Marlies Leenaars

Cathalijn Leenaars

Rob de Vries

Kim Weaver

Merel Ritskes

Carlijn Hooijmans



My mission started in 1986

Atherosclerosis in the rat

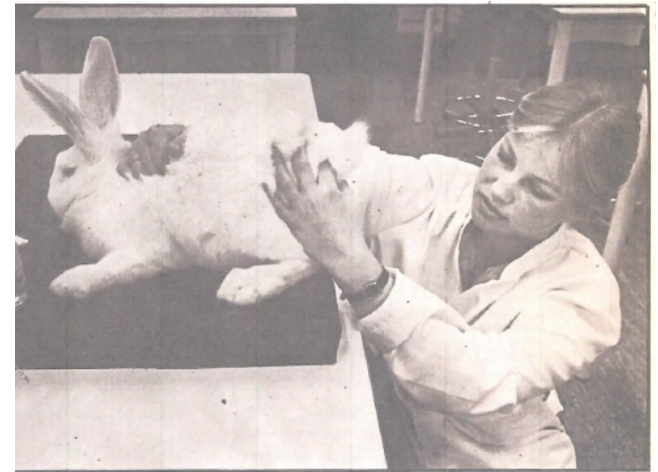
Literature review at Veterinary University Utrecht

Artery 1988

Improve quality science ánd

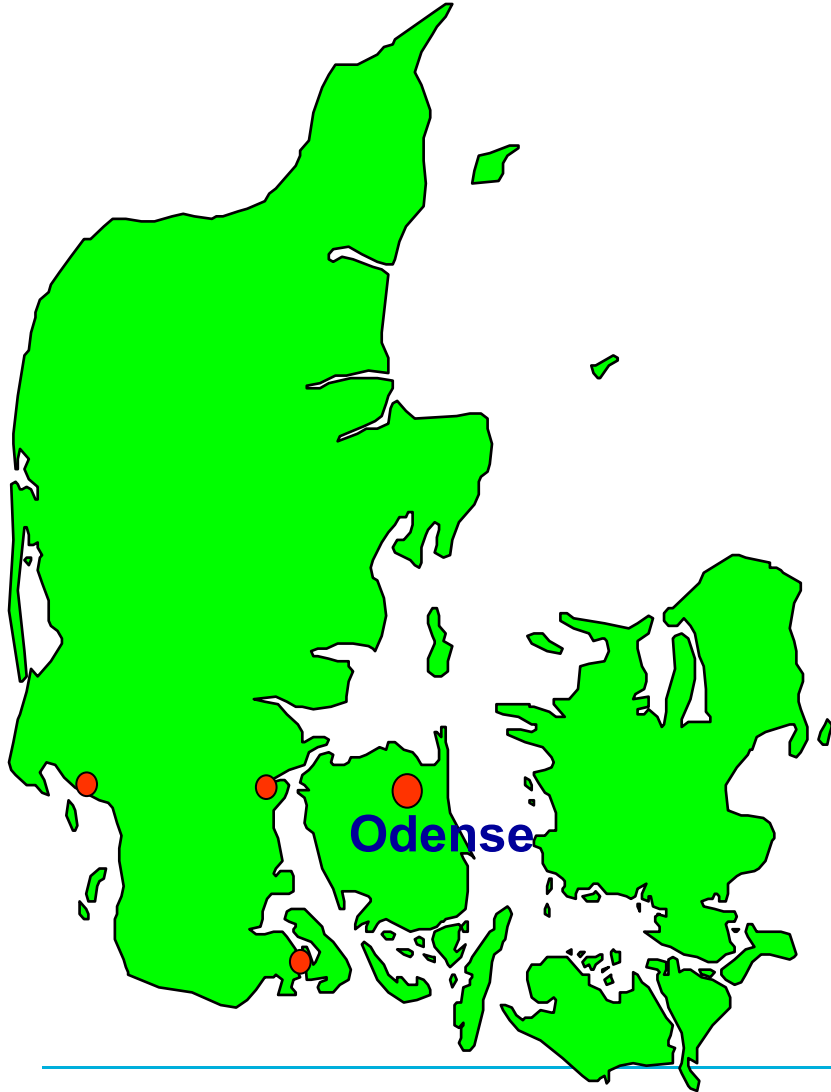
Improve animal welfare ánd

Improve translation



U-blad 1988

1996-2005 Biomedical Laboratory, SDU



2005-2016



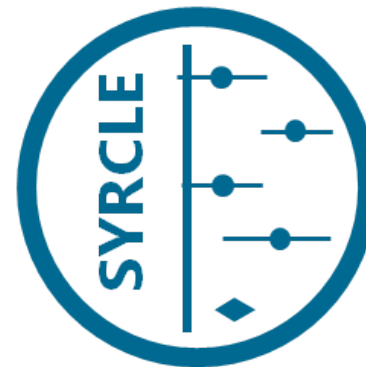
Head CDL and professor in Laboratory Animal Science

Initial focus on 3Rs Replacement Reduction Refinement

Since 2008 shift in focus towards Systematic Reviews



2006 - 2012



SYRCLE
Systematic
Revue
Centre for
Laboratory animal
Experimentation

2012 - now

Shift in focus from 3R towards systematic reviews (SR) of animal studies

PhD Judith van Luijk



Radboudumc

Public accountability lecture 2016



Worldwide goal

$\frac{1}{2}N$ 2Q 4P

saving 50 million animals

Setting a goal ½ N 2Q 4 P

- Economy uses national goals, medical science rarely does
- Usefulness of goals:
 - Transparency
 - Making choices
 - Evaluation



**THE COCHRANE
COLLABORATION®**



Cochrane

Efficacy

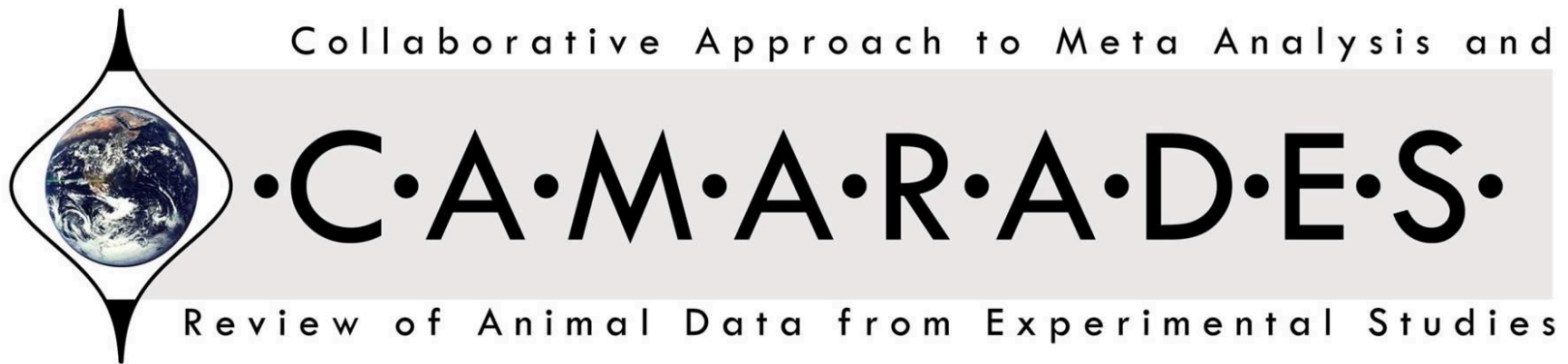
Janneke Horn 2001

Side effects

Pandora Pound 2004

COST action B24

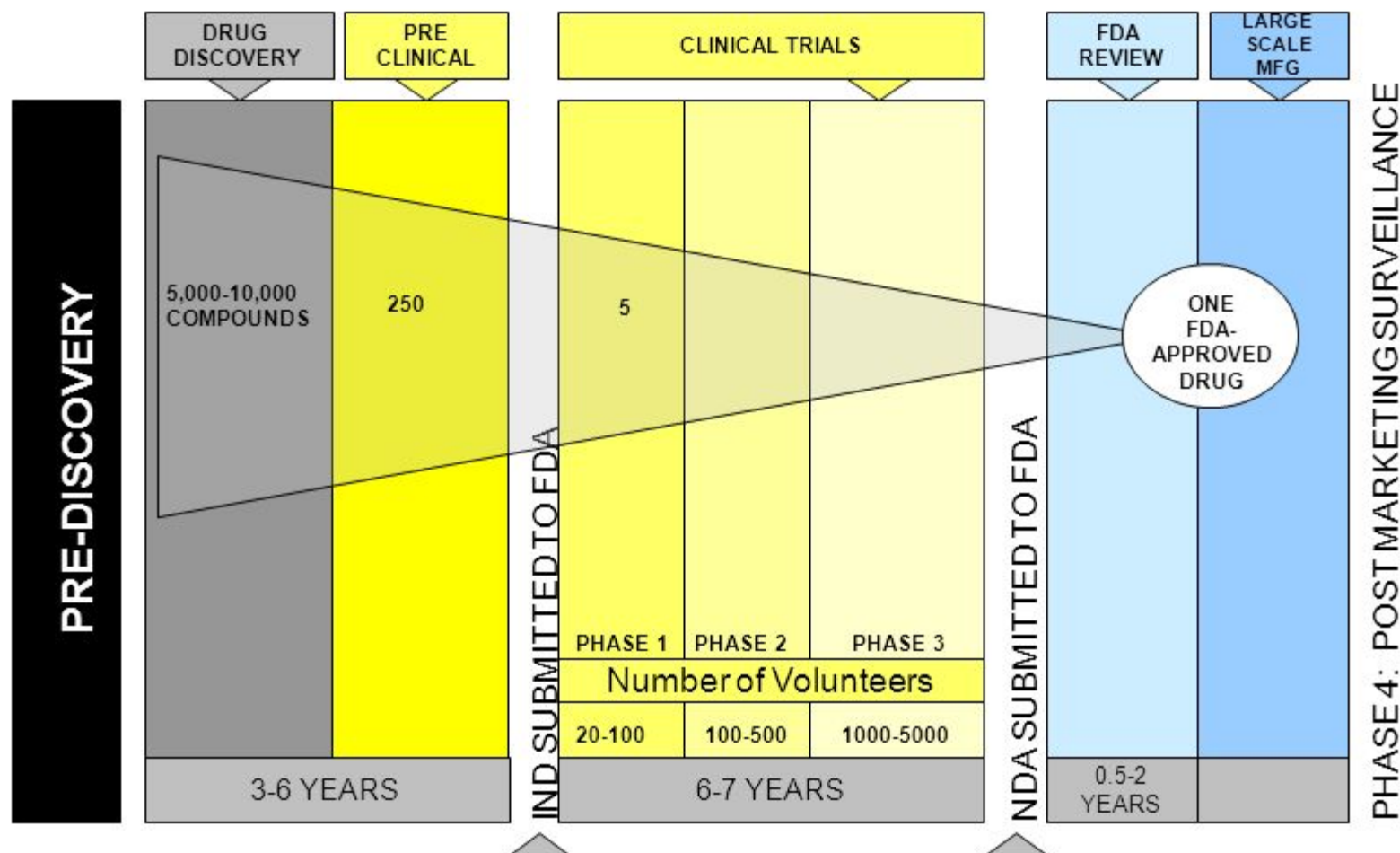
Laboratory Animal Science and Welfare



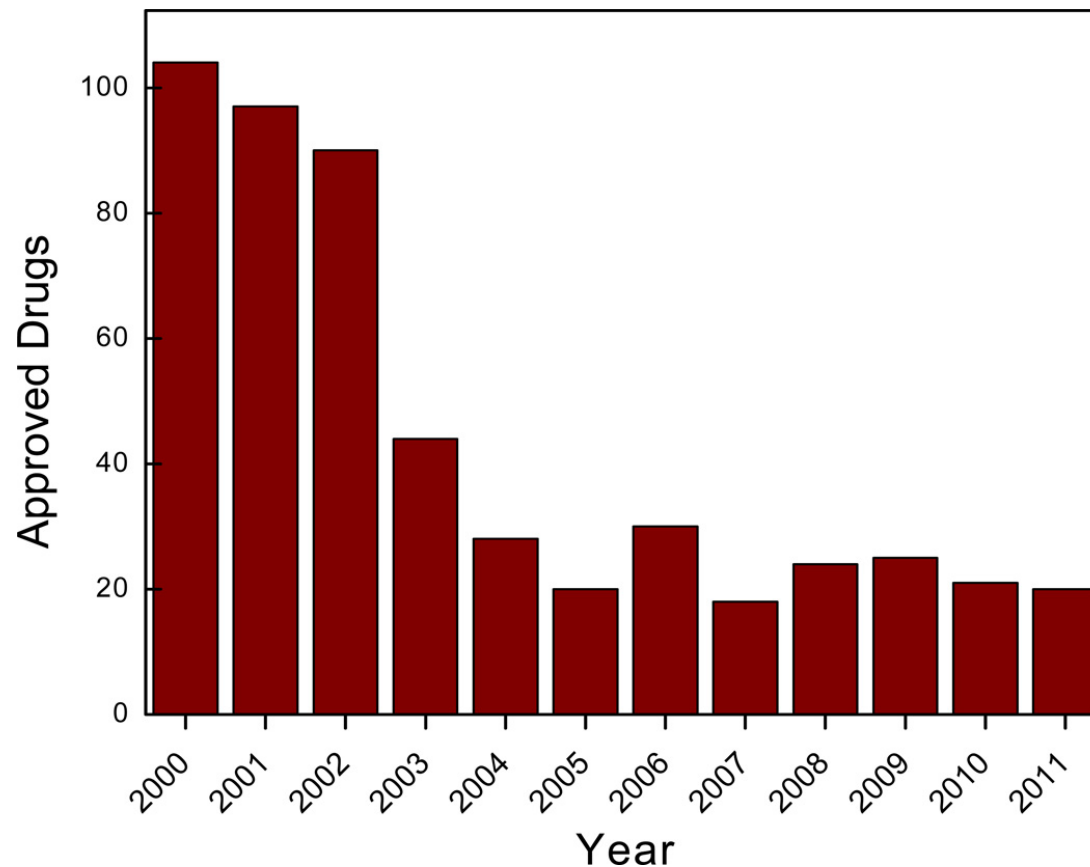
What about translation?

- Success rate of translation of animal studies to humans is very low
- What are the possible reasons?

Research and Development Process



Nr of FDA approved drugs is declining



SRs create transparency

<https://vimeo.com/142124487>



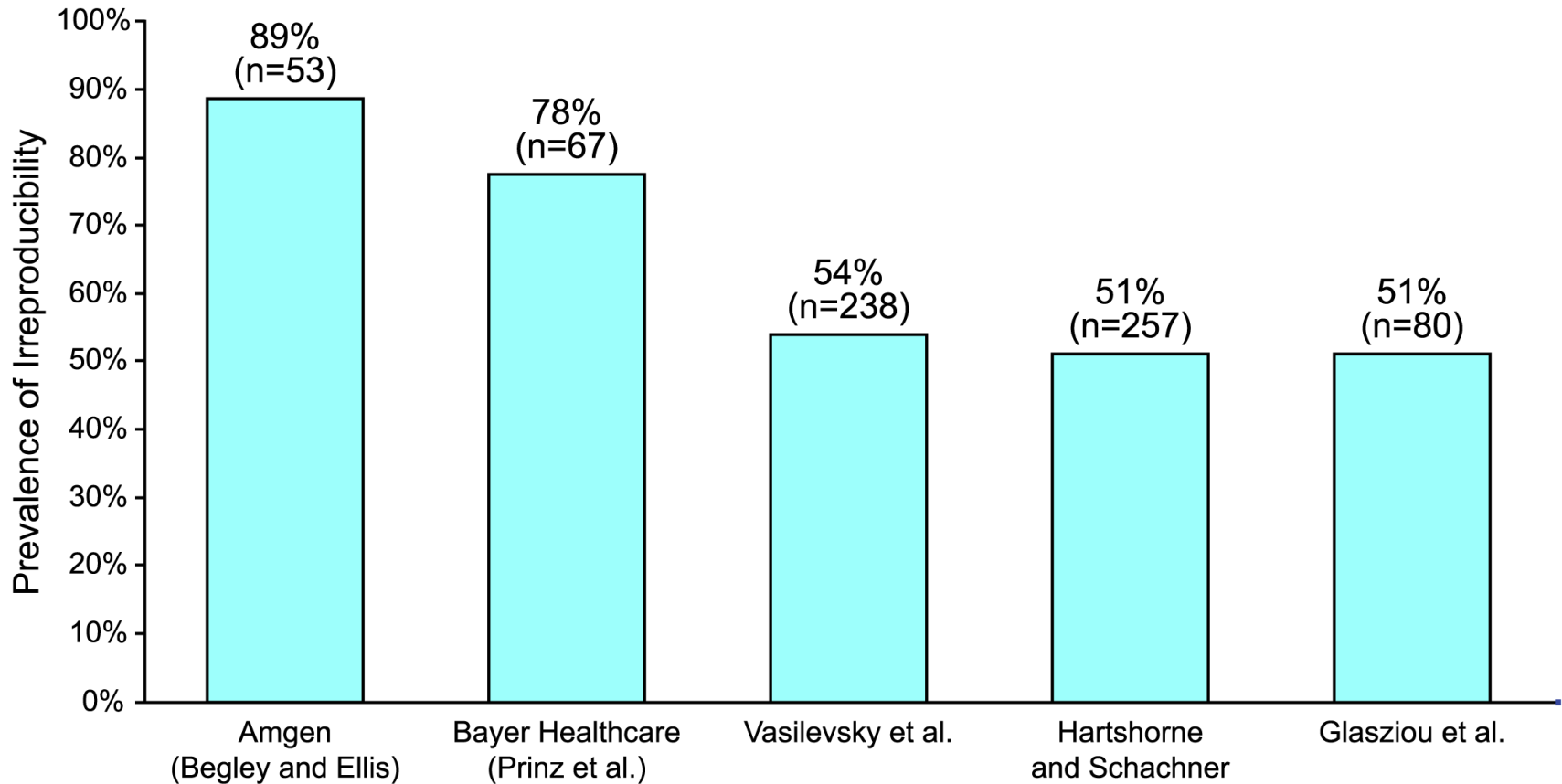
Ministerie van Economische Zaken

Assessment of study quality

Quality of reporting is *inadequate!!*

ARRIVE guidelines for reporting

Non-reproducibility



Costs

**non-reproducibility of
preclinical studies in the US
\$ 28.000.000.000,-
per year**

Translation Stroke and MS

0.4%

CAMARADES

What does SYRCLE do?

Vision (what do we want to achieve):

- Syrcle strives to optimize (preclinical) animal studies in a sustainable manner, in order to reach more succesful translation

Mission (why do we exist):

- Optimizing animal experimentation in a sustainable manner through high quality research and education in the field of laboratory animal science, animal models and systematic reviews and meta-analysis

Main SYRCLE activities

- Methodological research
- Training & Coaching
- Tool and guideline development
- E-learning
- SR conduct
- Strong networks





Dutch Parliament motions on SRs



2012: SRs also the norm for animal studies

SRs compulsory education in obligatory courses in LAS



Examples SR

SRs lead to

- A more evidence-based choice of animal models

van Drongelen, Am J Physiol Heart Circ Physiol 2012

De Vries RB, Tissue Engineering Part B 2012

Sloff M, PloSOne 2014

Zeeff SB, Inflammatory Bowel Dis 2016

} Better translation large animal models

- More translational transparency

Hooijmans CR, PloSOne 2012

Vesterinen HM, Mult Scler 2010

Howells DW, Int J Stroke 2012

- Making quality transparant

PROPATRIA clinical trial

- Probiotics treatment acute pancreatitis
- Mortality in treatment group was higher
- Clinical study was stopped



Media:

***“problems clinical study,
despite animal studies ...”***



Sacrifice ritual??

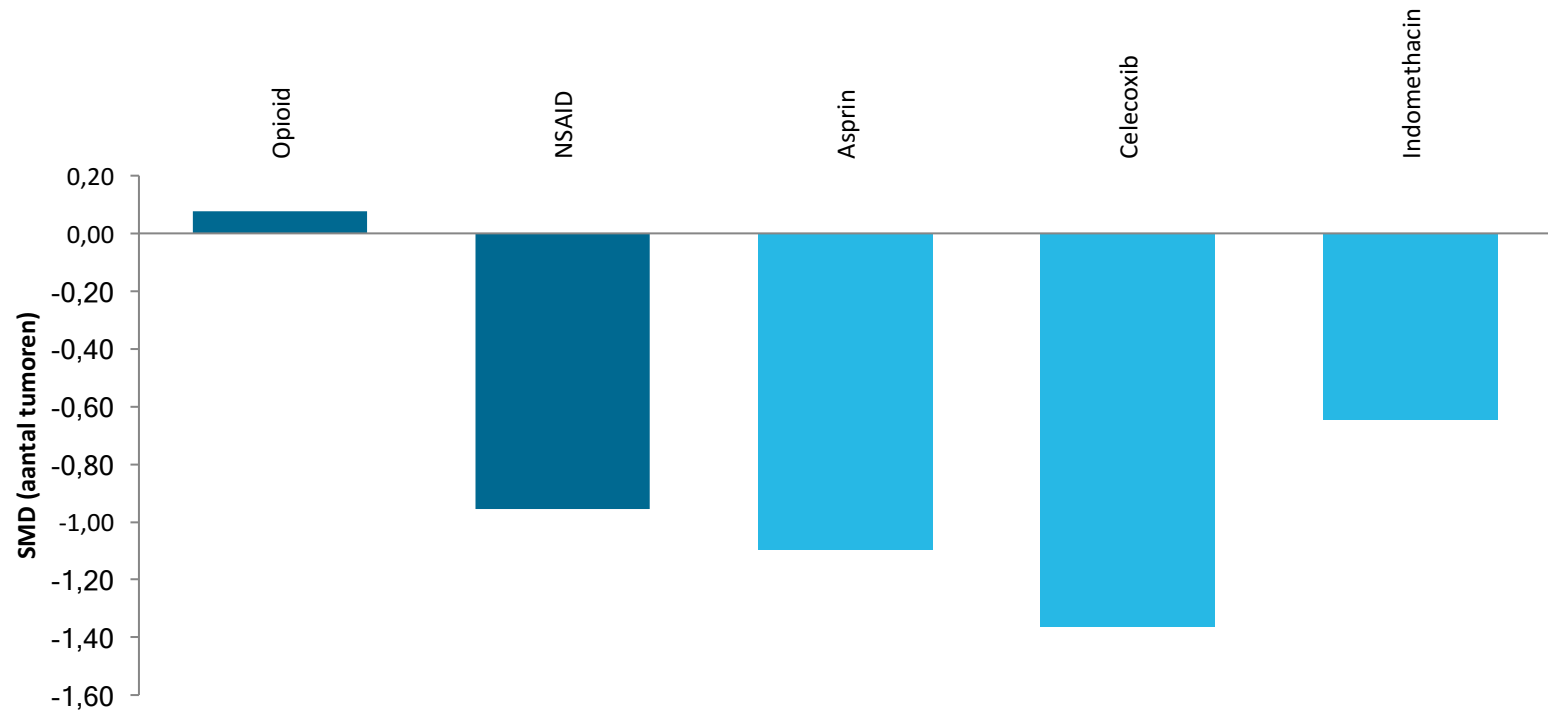
Translation

PROPATRIA trial lessons

- From rat to human
- Many differences in experimental design
 - Type of probiotics
 - Timing of treatment
 - Location of treatment
 - Disease induction
- Which role does the animal study play for the clinic?
- How does the MEC evaluate animal study results?
- Animal studies ran ***simultaneously*** with clinical studies: why do them then?

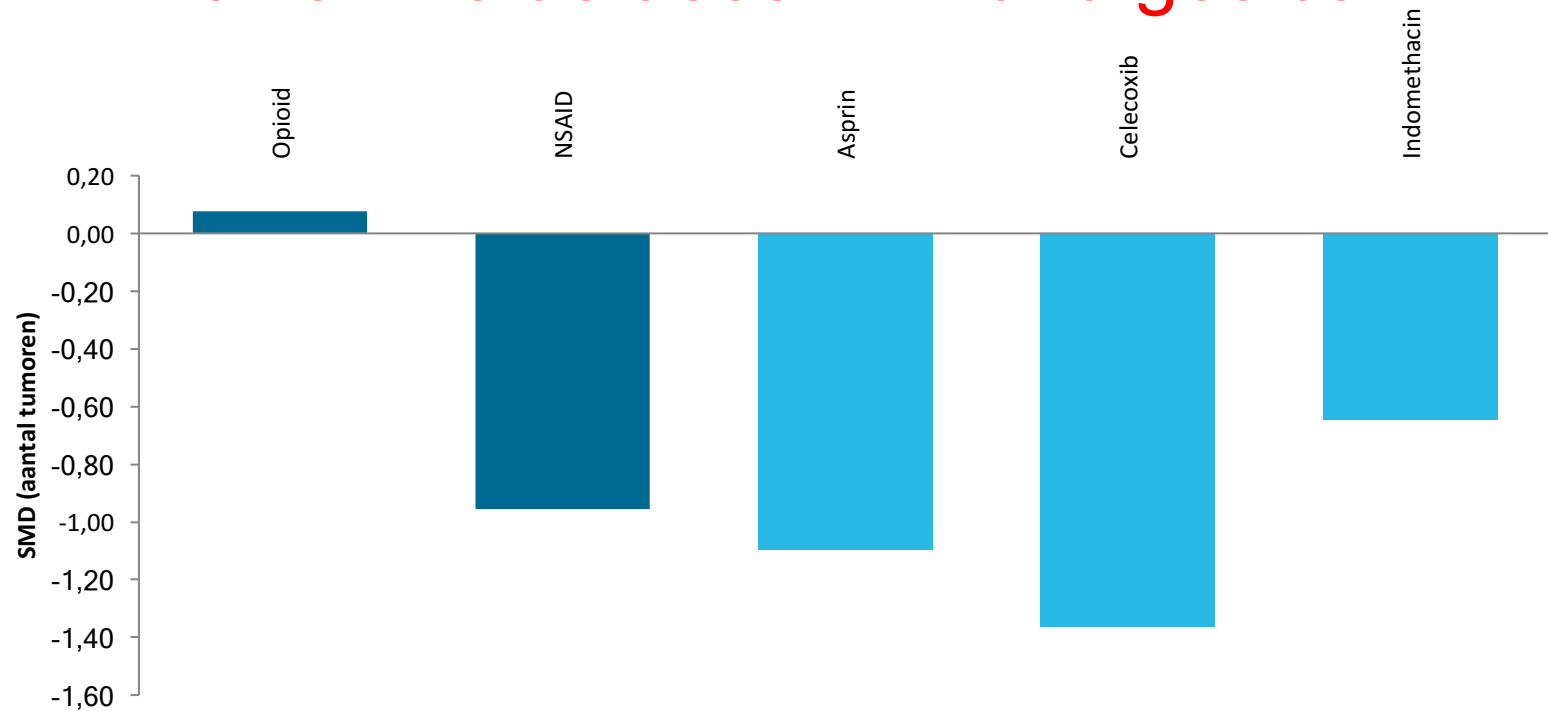


Clinic: do analgesics lead to more metastases?



Clinic: do analgesics lead to more metastases?

Fewer metastases with analgesics



Aspirin protective for colon cancer in humans

Quality Intestinal anastomosis models

- 350 publications
- 73304 animals used
- Unnecessary repetition e.g. adverse effect of chemotherapy on healing
- 83 % no mention of sterility in surgery
- 91% no mention of postoperative analgesia

Towards better translation

Research project



- Guidelines towards more effective translation on RA and CF

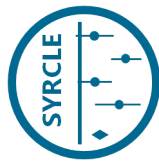
What are succes
factors?

Patiënt
participation



NWO project

- SRs to improve translational success
- Integrated approach exploring the entire research chain
- Optimising animal experiments
- Translational strategies guidelines
- Patient's perspective and participation throughout



Improving translational success: SRs

SRs of animal studies:

- Component of translational strategies
- Provide overviews of the available models
- Choosing the optimal animal model
- Choosing the optimal experimental design



Types of CF animal models:

- Genetic (662 publications)
- Infection (84 publications)
- Pharmacological (54 publications)
- Administration of patient materials (18 publications)
- Xenografts (17 publications)
- Diet (5 publications)
- Other (4 publications)



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?



Experiences

- Patient participation in clinical research is mutually rewarding
 - Patients appreciate knowing that you are working on their disorder
 - Patients enjoy sharing their experiential knowledge
 - Quality of protocols and output improve
 - Great reminder of why we do what we do
- Reumazorg Nederland RZN gives training for patients to participate in research

Valorisation panel



***“Systematic reviews of
animal studies are a good
model for translation
from animal to human”***

Dutch Ministry

Requests reduction animal studies - 8 April 2016

Letter Martijn van Dam to National Committee on advice for policy on animal experimentation (Ncad)

Van Dam expresses the ambition that the Netherlands will be world leader in animal-free innovations in 2025

<https://www.ncadierproevenbeleid.nl/documenten/brief/16/5/17/brief-verzoek-afbouwschema-dierproeven>

SR = animal free innovation

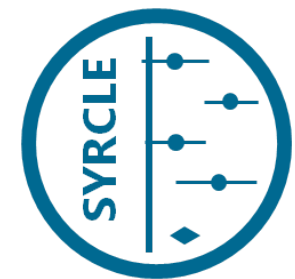
Future

Only do animal studies after thorough evaluation of

- research question
- SR on gaps in knowledge
- SR on choice of model
- SR on chances for translation



- Website www.syrcl.nl
 - *Free newsletters*
 - *E-learning*
 - *Workshops*
 - *Coaching*
- Contact: Merel.Ritskes-Hoitinga@radboudumc.nl



Thank you!