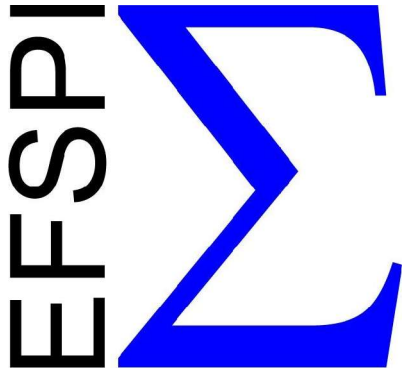# Visions on the role of Statisticians in the Pharmaceutical Industry

Merete Jørgensen
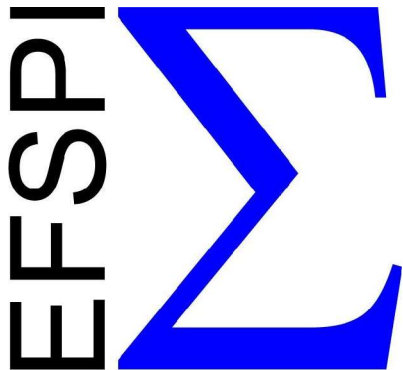
President EFSPI

VP Biostatistics, Novo Nordisk A/S
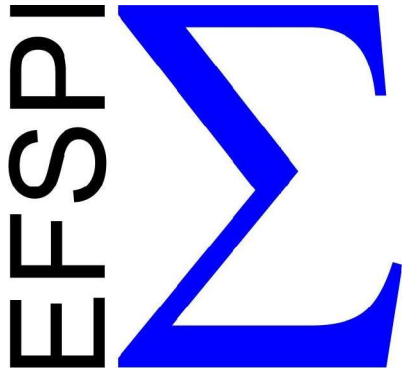
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Overview of presentation

- Vision & Mission
- A Historical view
- New Statistical Methodologies
- New types of Research Methodologies
- New types of Data
- New areas for Statisticians
- Barriers for the Vision to come through
- Suggestions to overcome these
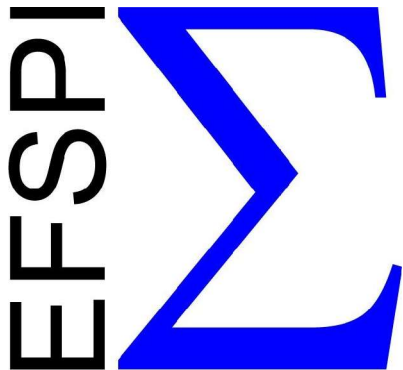- References

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Vision & Mission

Why do we need Statisticians in the Pharmaceutical Industry?

In order for the company to comply with GCP, or..?

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Vision & Mission
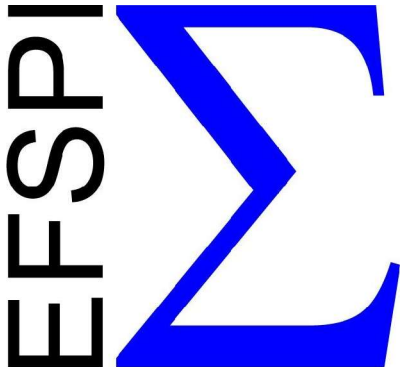
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To ensure our statistical competencies are utilised in the best way to create value in our industry
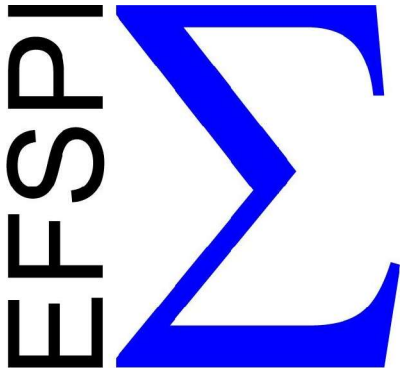
Vision:

To provide statistical competencies in an <u>entrepreneurial and proactive</u> way to all areas of the industry in which it will contribute to value creation

ref: Marquardt (1987)

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A Historical view

• -1970 : The majority of statisticians in the pharmaceutical industry was employed in the discovery/pre-clinical area.   ref: Grieve(2002)

• 1980's: Investigators carried out the clinical trials, from protocol to publication.

•1988: Guideline for the format and content of the clinical and statistical section of an application, gave guidance on the integrated clinical and statistical report as well as ISS and ISE documents.

•1990 Good Clinical Practice for Trials on Medicinal Products in the EC

•1994 CPMP Biostatistics Guideline

•1998 ICH E9 Statistical Principles for Clinical Trials

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A Historical view

- To get products on the market in US EU companies had to live up to the FDA demands

- Medical and Statistical functions built up in the pharmaceutical industry

- Requirements for statisticians from authorities to clinical trials

- Growth in number of statisticians almost solely to the clinical area
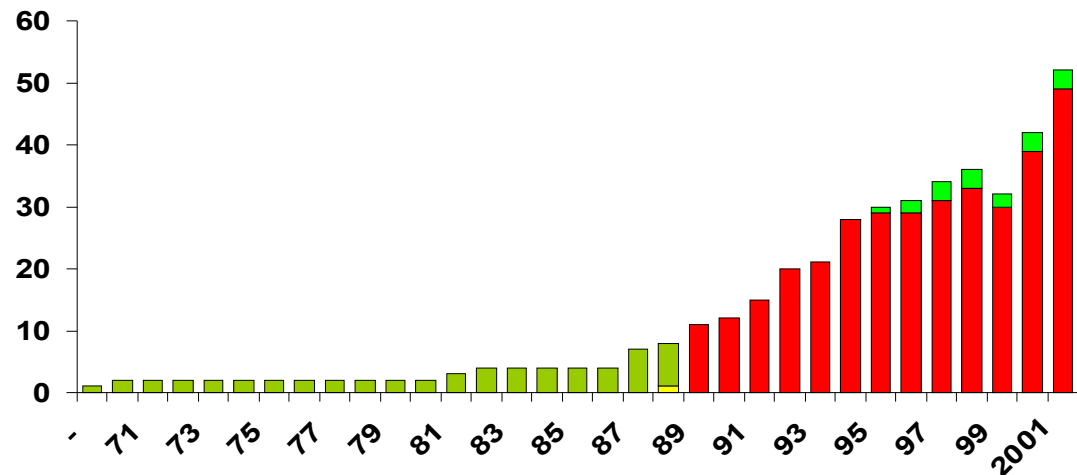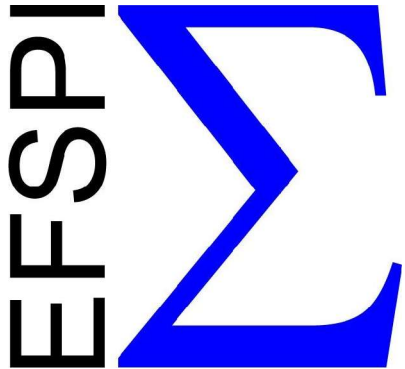
A Historical view

- Examples of 'New' methods applied from late 1980's

    - Non-linear regression models

    - Cox regression survival analyses

    - Repeated Measures, longitudinal analyses

    - Variance component models

    - Non-parametric curve estimation

    - Mixed Models

    - Frailty models

    - Graphical Models

    - Empirical Bayes methods

    - Bayesian methods

    - Iterative solutions to complex differential equations

    - Simulation techniques
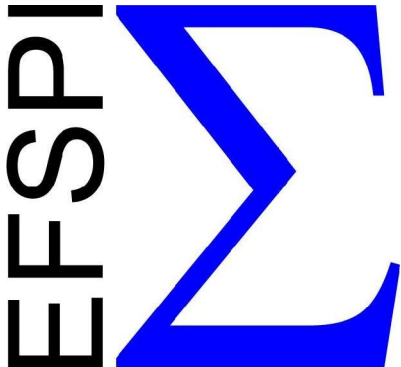
A Historical view

•Some methods known as theoretical models for a long time

•Very computer intensive methods if to be applied

•Drivers for their success:

  •Availability of stronger and cheaper computers

  •Development of statistical software packages

  •Competent statisticians who know the methods

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What will drive the development during the next 10 years to come?

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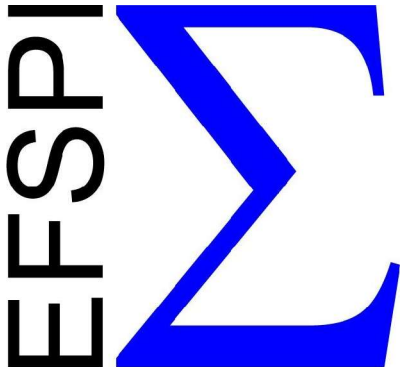
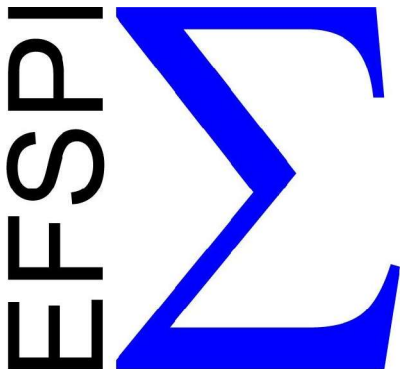# New Statistical Methodologies

Incremental statistical innovations
- known methods for new applications
- fine-tuning known methods to take new aspects into account

Will continue to be made!

Break through statistical innovations
- Methods that change the way we do drug development
- Methods for analysing types of data which we can not analyse today
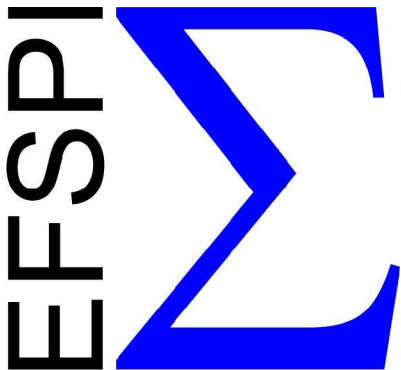
Will we see such innovations?

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New Statistical Methodologies

A provocative question:

- Will we continue to have to do phase III confirmatory trials?

- What does other industries do?
- Example the flight industry?
- They too have an efficacy and a safety issue?

New Statistical Methodologies

Trends

- Focus on exploratory trials, leading to more knowledge before phase III
- Focus on shortening time to market
- Market license for limited time periods, post marketing information

- Drugs with lifesaving potential is already there, ex. cancer treatment
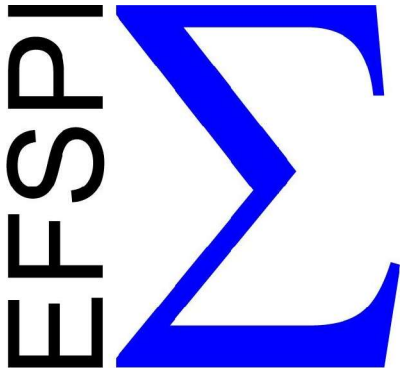
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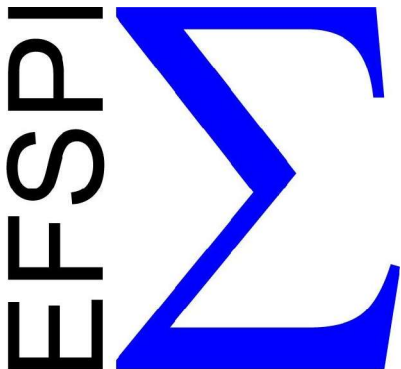
New Statistical Methodologies

An Example:

- Substitute for a randomised clinical trial

Requirement:

- Randomised, 3 year follow-up trial, post marketing

Approval:

- New Statistical Methodology
- Matched Cohort, based on propensity scores, Health care provider database
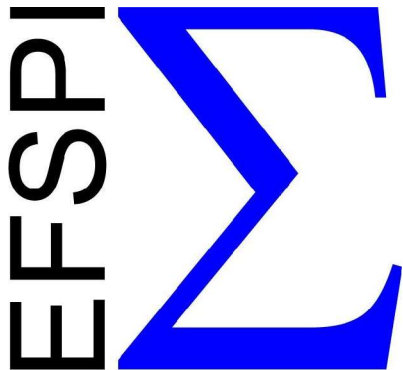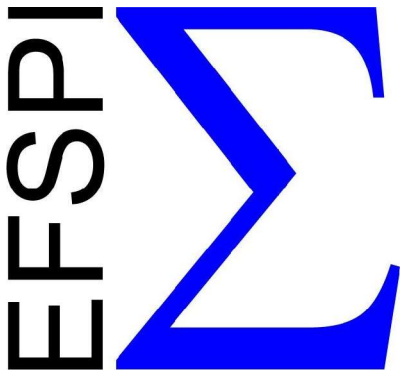
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New Statistical Methodologies

We need to:

- Get the statisticians more involved in the pre-clinical and early clinical investigations, where value is created in terms of knowledge

- If the information which the phase III trials are going to confirm, too often proves to be built on a too loose background, we will continue to have a demand for large confirmatory trials
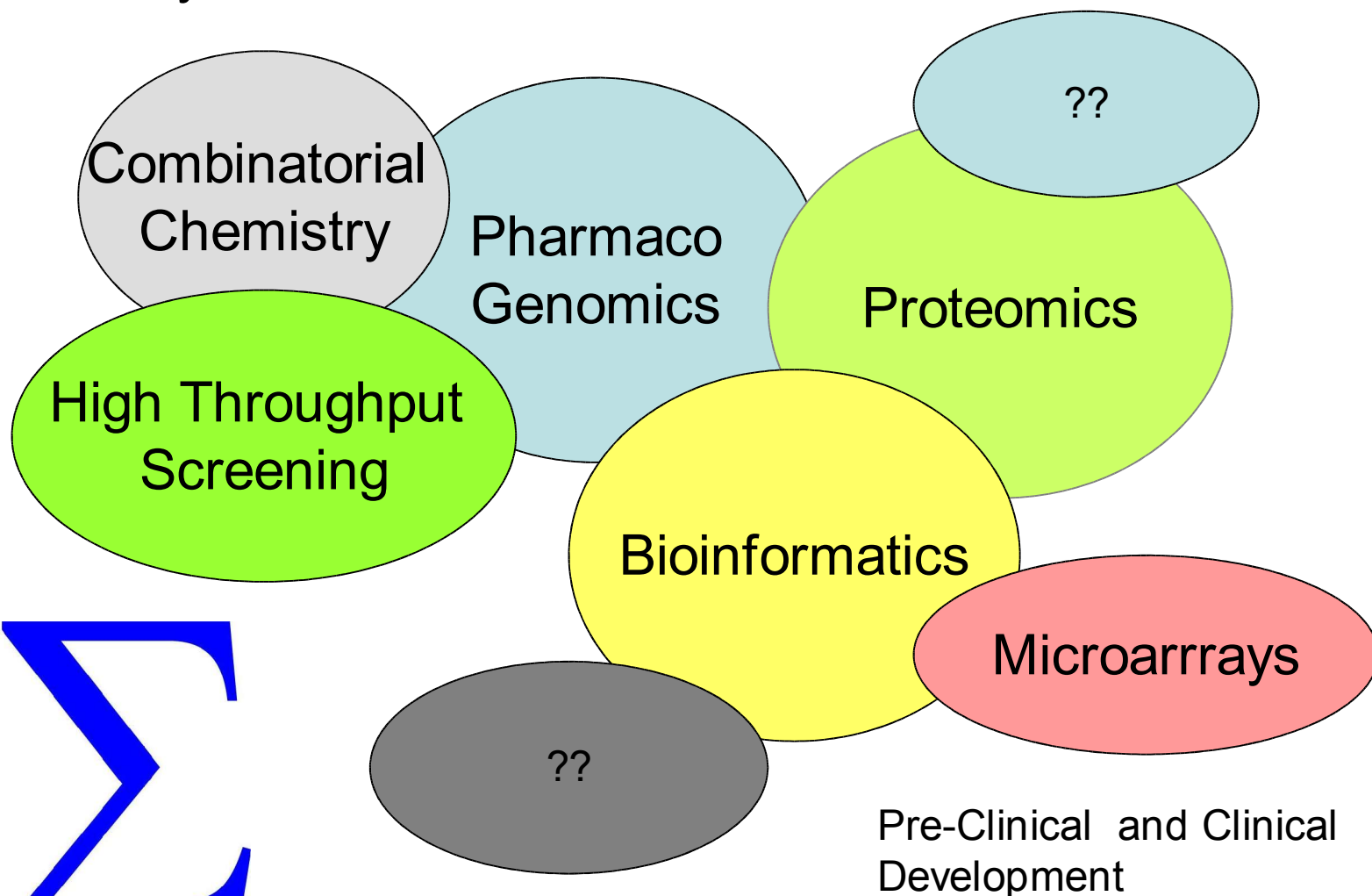
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New types of Research Methodologies

Discovery

Combinatorial Chemistry

Pharmaco Genomics

??

Proteomics

High Throughput Screening

Bioinformatics

Microarrrays

??

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Pre-Clinical and Clinical Development

New types of Research Methodologies

•New research methodologies will drive innovation of new statistical methodologies

•Examples

Bioinformatics/Microarrays

•Lots of data, few replications

•Both Universities and Pharma industries are active in the development of new methodologies

Pharmacogenomics:

Focus on individualised treatments challenge our thinking in large phase III confirmatory trials
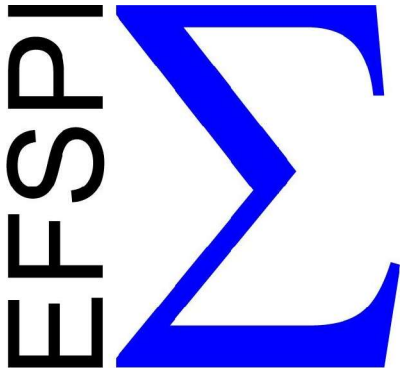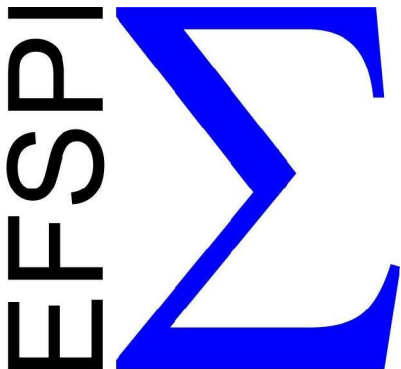
New types of Research Methodologies

•Will require a new philosophy, the current 'one endpoint' correction for multiplicity is challenged

•How will we as statisticians respond?

•We have to demonstrate that our capabilities and competencies can be used for a much broader range of research activities to create value of the research portfolio
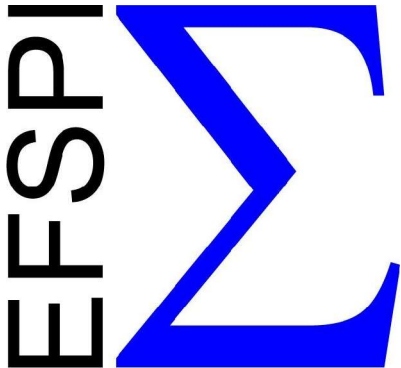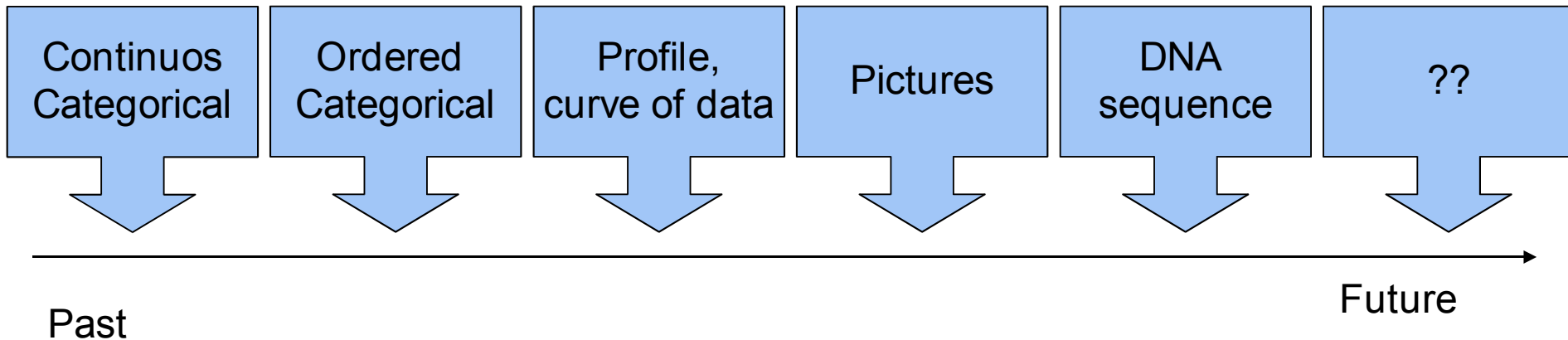
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New types of Data

| Continuos Categorical	Ordered Categorical	Profile, curve of data	Pictures	DNA sequence	??

Past → Future

New statistical methods are developed to deal with new types of problems, new types of data

in close collaborations between researchers and statisticians

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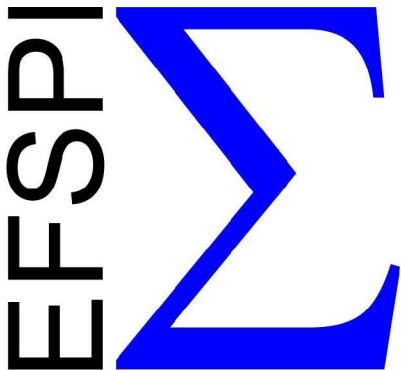
(New) areas for Statisticians

Examples:

Discovery:

Optimised sampling of molecules from gendatabases

Identification of hits in microarrays

Effects in cell cultures

Pre-clinical:

Toxicological tests

Mitogenicity

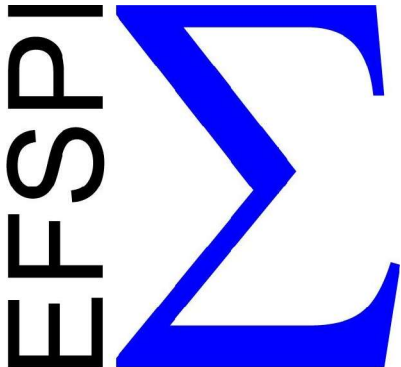PK/PD in animals, use of data <LLOQ?

CMC:

Optimal design of stability testing

Assay validation

Specification of Release limits

(New) areas for Statisticians

Examples cont.:

Production:

Optimisation

Quality control, improvement of methods

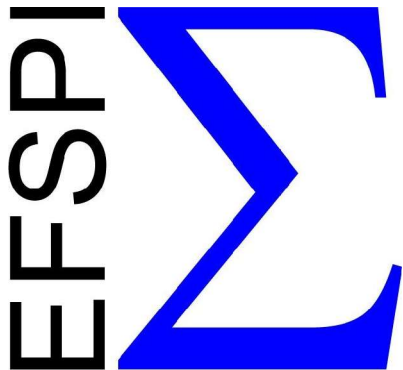**Health economics**

Portfolio management

Decision theory

NPV and success estimation

Clinical evaluation:

Epidemiological evaluations

......

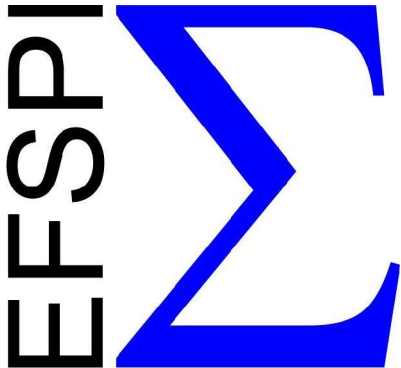Every step in the drug development process that requires data to substantiate a decision!

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Areas for Statisticians

Mission:
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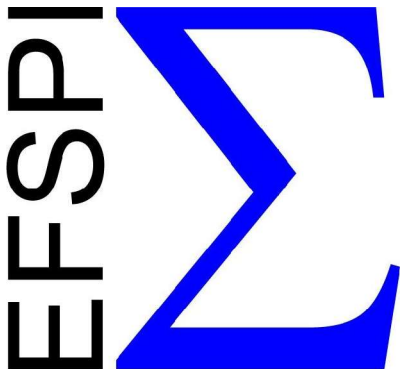
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Barriers for the Vision

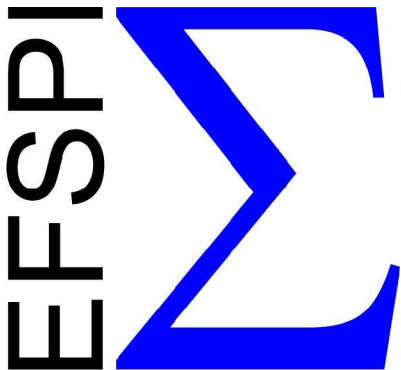**Stephen Senn (2002) in 'Lost opportunities for Statistics':**

'…many managers do not see statistics as something that adds value, perceiving it instead as something you do if you have to, which almost always means when the regulator forces you to.'

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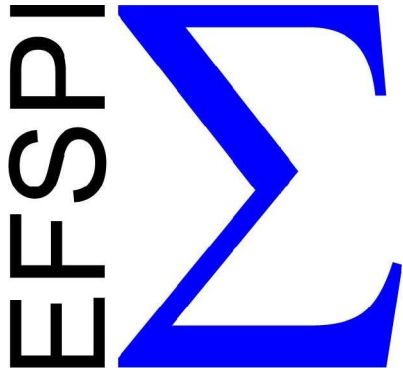
Barriers for the Vision

Our own excuses:

•We are too busy (doing clinical trial stuff)

•Management approve too few positions for statisticians

•Management focus on statisticians to be involved in projects close to market approval

•Researchers do not seek our advice, but want to do the analyses themselves

•Authorities only requires statisticians to be involved in clinical trials, not all the pre&non-clinical

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Barriers for the Vision

Grieve(2002):

•How are statisticians seen by others?

•Pharmaceutical Statistics seen as just clinical statistics

•Statisticians not statistics are important

•Finding the answer to the right question

•We do not always get called in early enough

•The status quo ('We have always done it this way')
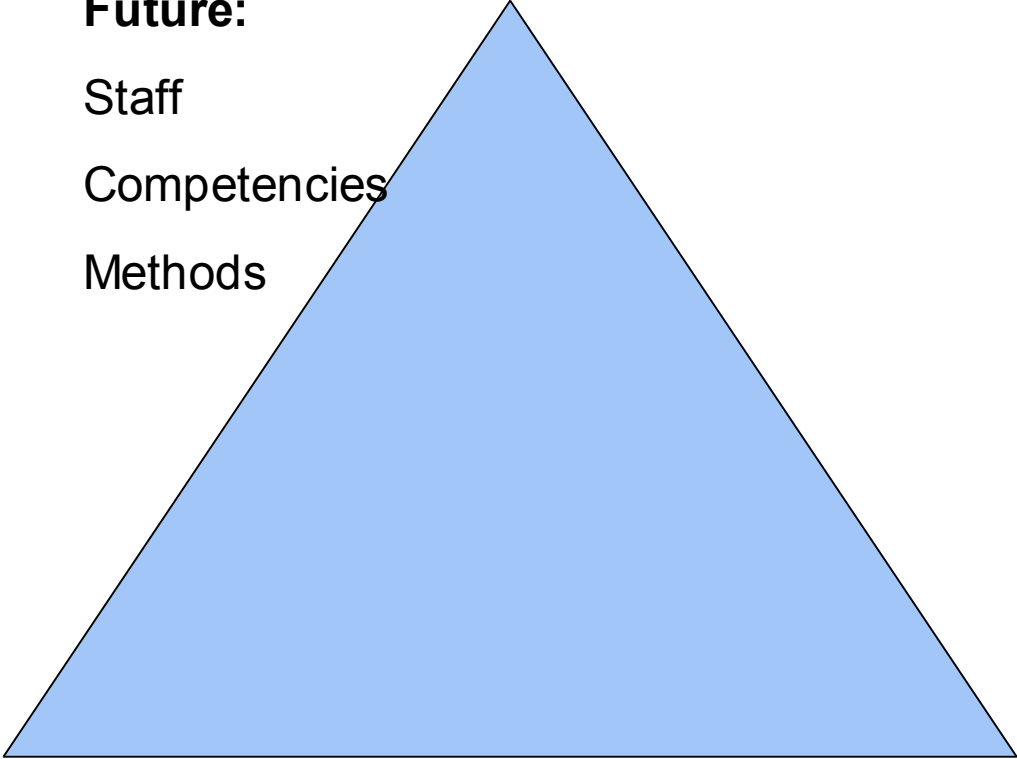
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Barriers for the Vision

•Competencies, do we have the right ones?

•Competencies, will we have sufficient in number?

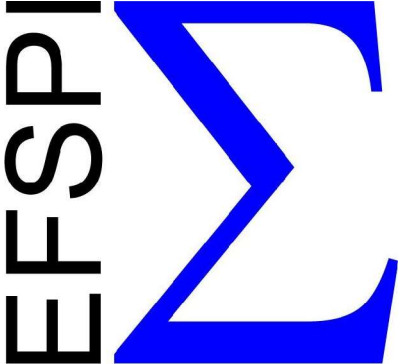•Methods needs to be developed

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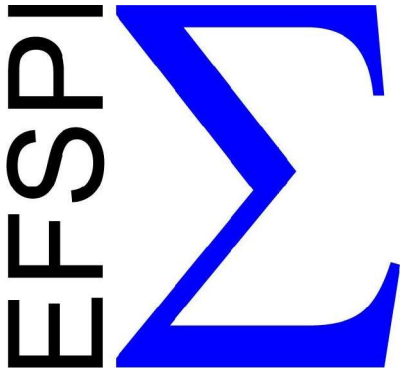
# Barriers for the Vision

Future:

Staff

Competencies

Methods

Internal:

Personal competencies
Workload
Managements attention
Clients view

External:

Authorities view

Guidelines and regulations

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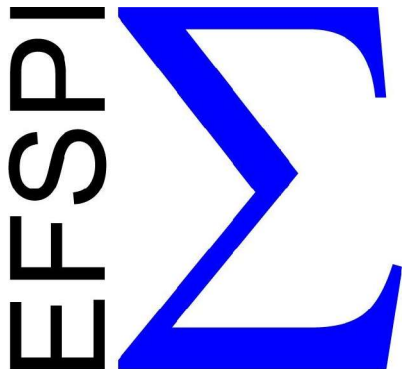
Suggestions to overcome the Barriers

Future:

Tomorrows needs for staff, competencies and methods:

Collaborative networks, we can all learn from one another even though we work for different companies

Collaborations with universities, PhD's, post-doc positions, exchange programs…

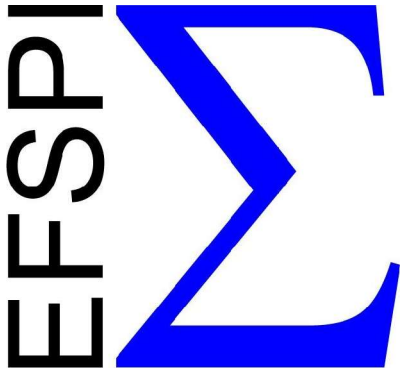Exposure to the pharmaceutical industry's challenges can drive innovation at universities

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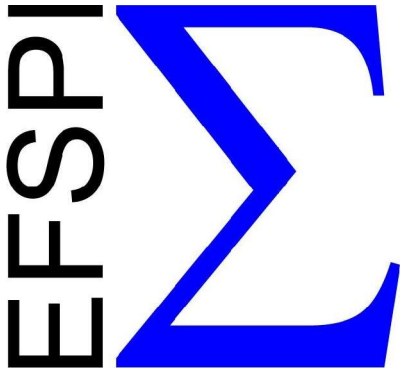
Suggestions to overcome the Barriers

External:
Authorities view
Guidelines and regulations

•Participate in networks to improve and influence guidelines

Suggestions to overcome the Barriers

Internal competencies:

•Statistical methods

•Therapy areas

•IT

•Research methods clinical and pre&non-clinical

•Authorities requirements

•Business understanding

•Presentation skills

•Self esteem

•Communication skills

Not everybody must have it all, but all must be present in the department

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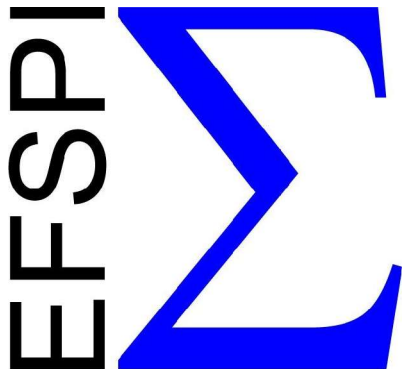
Suggestions to overcome the Barriers

The Statistics Strategy should be built on resources and Competencies

•What are we good at?

•Understand our internal clients needs

•Build on good collaborations

•Compile good examples

•Be visible

•Trust is the basis for good collaborations

•Be active and provide answers in a language managers can understand (time and money)
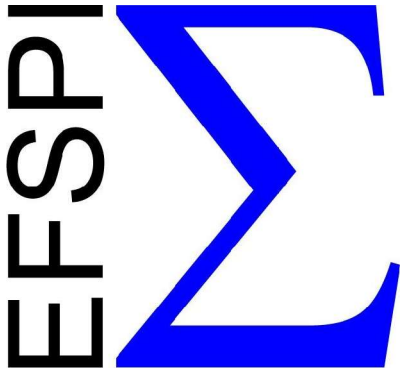
Suggestions to overcome the Barriers

Examples:

Marketing of Statistics:
Internal seminars on methods to be held together with good internal clients

Good stories:
Especially critical questions from authorities are good, but be careful not to point fingers at internal clients

Answer the right question:

Sample size is not only a number of patients needed, but a review of the **total time for a trial** considering:

possible designs, number of patients required, recruitment ratio, time under treatment
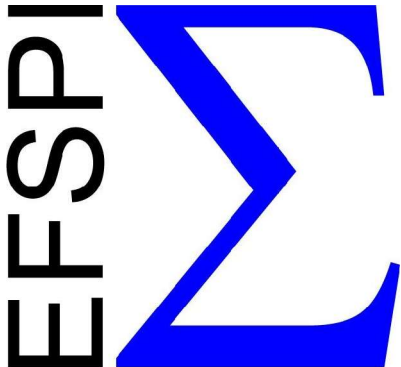
Improve the way we are seen by others

References

- Marquardt, DW (1987) The importance of Statistics. JASA, 82

- Grieve, A.P. (2002) Do statisticians count? A personal view. Pharmaceutical Statistics

- Senn, S. (2003) Lost opportunities for Statistics. Pharmaceutical Statistics

- Day, S (2002) Changing times in pharmaceutical statistics: 1980-2000 Pharmaceutical Statistics

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