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Bayesian approaches to analysing studies and summarizing evidences

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Conventional Statistical Rules

- A study **must** have an adequate size

Conventional Statistical Rules

- *A study **must** have an adequate size*
- Required Size, based on:
  - Significance level (usually 5%)
  - Power (usually 80-90%)
  - **Minimal clinically worthwhile difference**

Sample Size
in cancer clinical trials

In trials in early disease, cumulative mortality from 10% to 70%: **500-5000** pts

In trials in advanced disease, cumulative mortality from 50% to 90%: 3**00-1000** pts

Conventional Statistical Rules

- *A study **must** have an adequate size*
- *Required Size: Usually Hundreds/Thousands of patients*
- In many rare cancer conditions: **NOT POSSIBLE**

Conventional Statistical Rules

- A study **must** have an adequate size

Unjustified Implication

- If an adequate size cannot be attained, (RARE CANCERS) no methodological ties

Small size → **Poor quality**

Poor Quality?

- (Study protocol)
- (Classified as Phase II trials)
- No Randomised controls
- Opaque selection of cases
- Primary endpoint: Objective response
- No statistical plan

First point to stress

The organization of a trial of **small** size requires **more** care in

- Protocol preparation
- **Study design/methodology**
- **Statistical design**
- Addressing Clinical Organizational issues

…than a standard size trial

Methodological issues

- *Statistical Power*

- Study Design
- Bias in evaluating outcome (double blind)
- Endpoint

VALIDITY!

Study Design

- Phase II trials?

Phases = Aims, not Design

Study Design

- *Phase II trials?*
- Uncontrolled trial/Historical Controls
  - Well Kown Biases
  - Sufficient if outstanding benefit
  - Necessary if control group unethical

Careful and transparent methodology

Need of guidelines/research

Study Design

- *Phase II trials?*
- *Uncontrolled trial/Historical controls*
- Randomised Controls

WHY NOT?

RCT's in rare cancers

- Loss of power (50% less patients in exp treatment)

Available patients : 100

Response Rate in controls: 40%

RCT (50 x2): 80% power for delta= 30%

Uncontrolled tr. 80% power for delta= 21%

RCT's in rare cancers

- Loss of power /Precision

(50% less patients in exp treatment)

Available patients : 100

RCT (50 x2): Difference +/- 15%

Uncontrolled tr. Difference +/- 11%

(Histor. Controls)

Trials in Rare Cancers

If, despite International cooperation/Prolonged accrual/Surrogate endpoints,

- it is possible to assemble (in a reasonable time) only **a limited number of patients**,

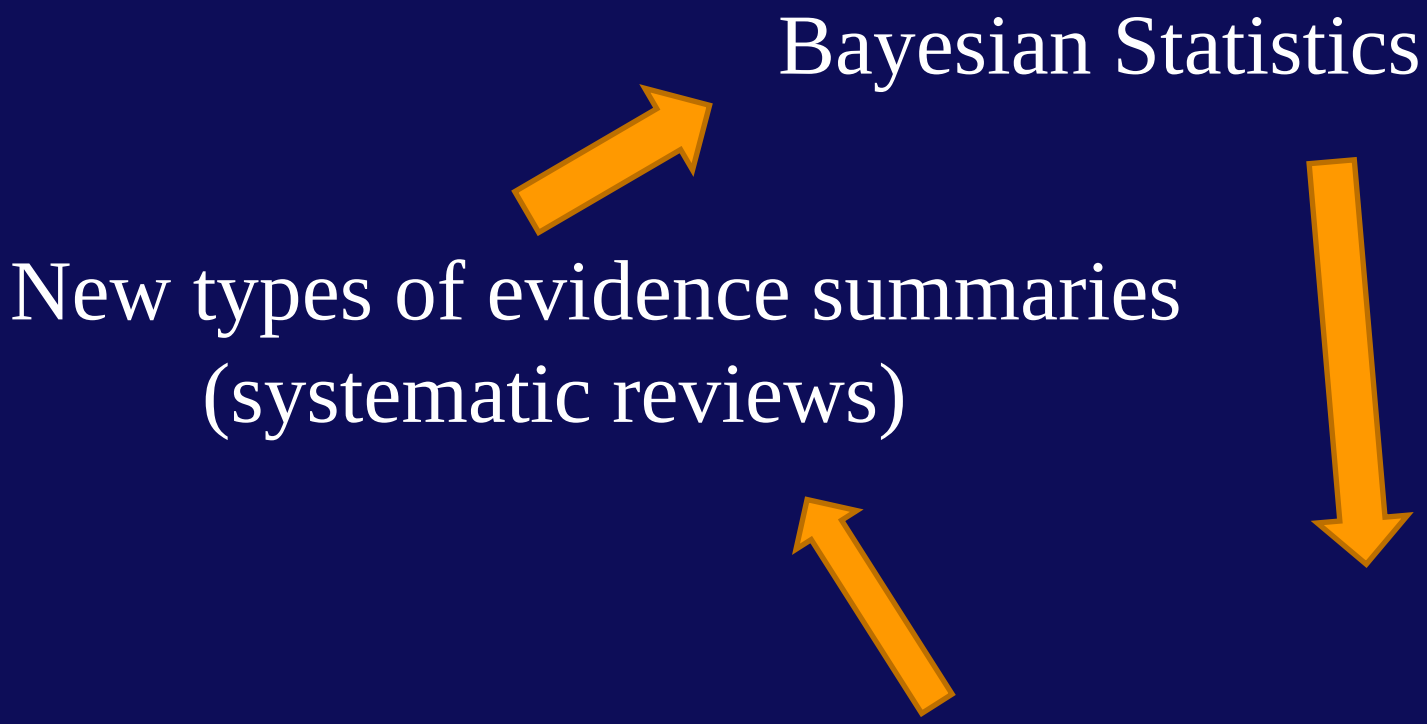
(and the efficacy of a new treatment is not outstanding), …

What can be done?

Recent developments (<10 yrs)

- Bayesian Statistics
- New types of systematic reviews
- Adaptive trials

What can be done?



What can be done?

Bayesian Statistics

New types of evidence summaries
(systematic reviews)

Adaptive trials

Differences between Conventional (Frequentist) and Bayesian Statistics

- Meaning of probability
- Use of prior evidence

Conventional P

Probability **of the observed difference** (if the experimental therapy does not work)

Bayesian Probability

Probability **that the experimental therapy works/doesn't work** (given observed difference and prior knowledge)

Differences between Conventional and Bayesian Approaches

- *Meaning of probability*
- **Use of prior evidence**

Conventional P

Probability of the observed difference (**if the experimental therapy does not work**)

Bayesian Probability

Probability that the experimental therapy works/doesn't work (given observed difference and **prior knowledge**)

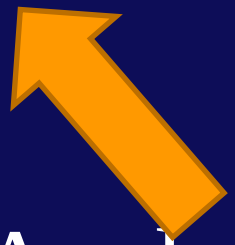
Foundations of statistics commonly used in medicine

- *Dominant theory is true (=standard therapy is better) until sufficient evidence becomes available **against** it*
- *To this purpose, only evidence collected within one or more trials aimed at falsifying it can be used*
- **No use of**
  - **External evidence**
  - **Evidence in favor of…**

Squamous gastric cancer

Planning a trial of

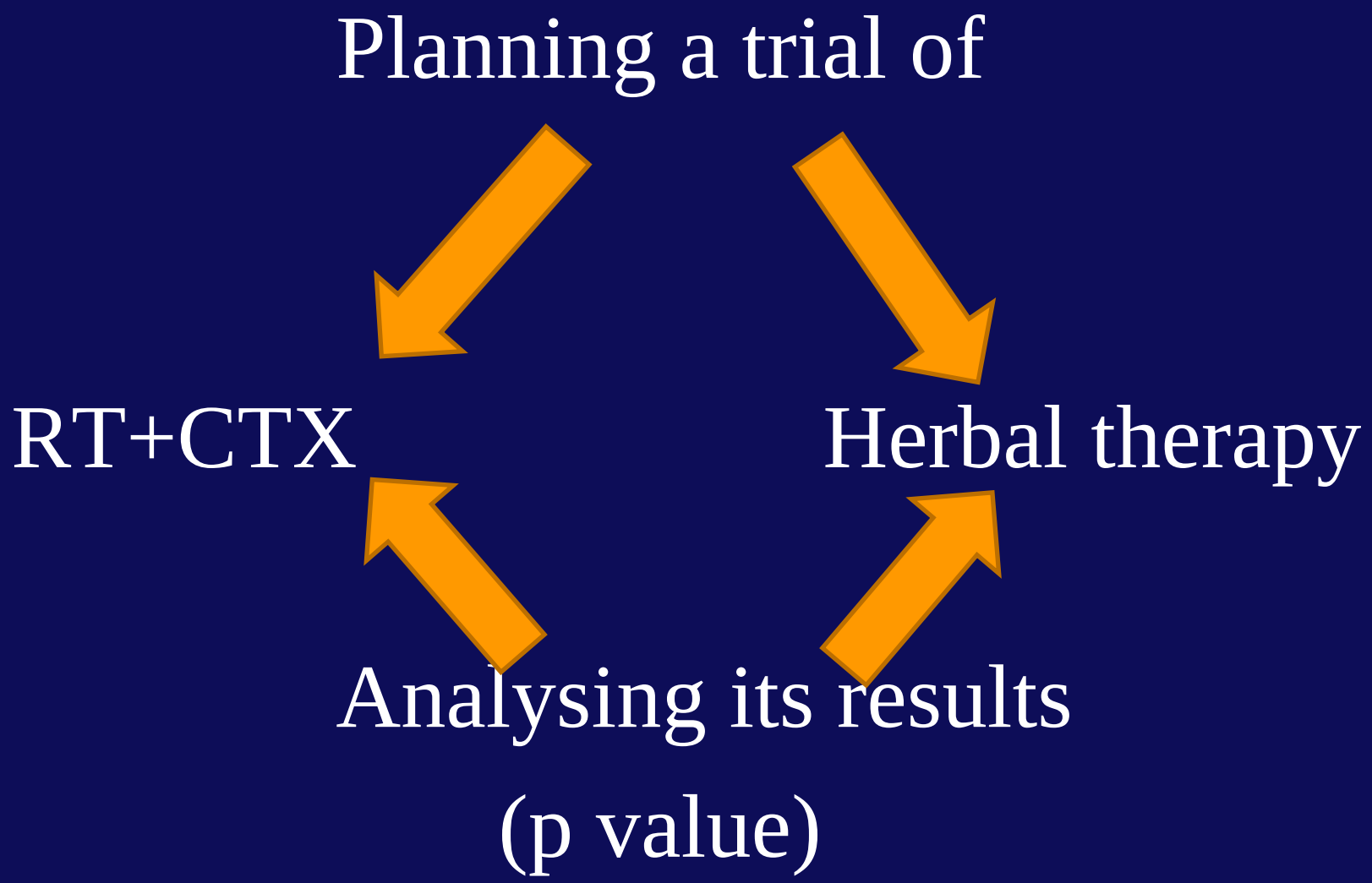
RT+CTX



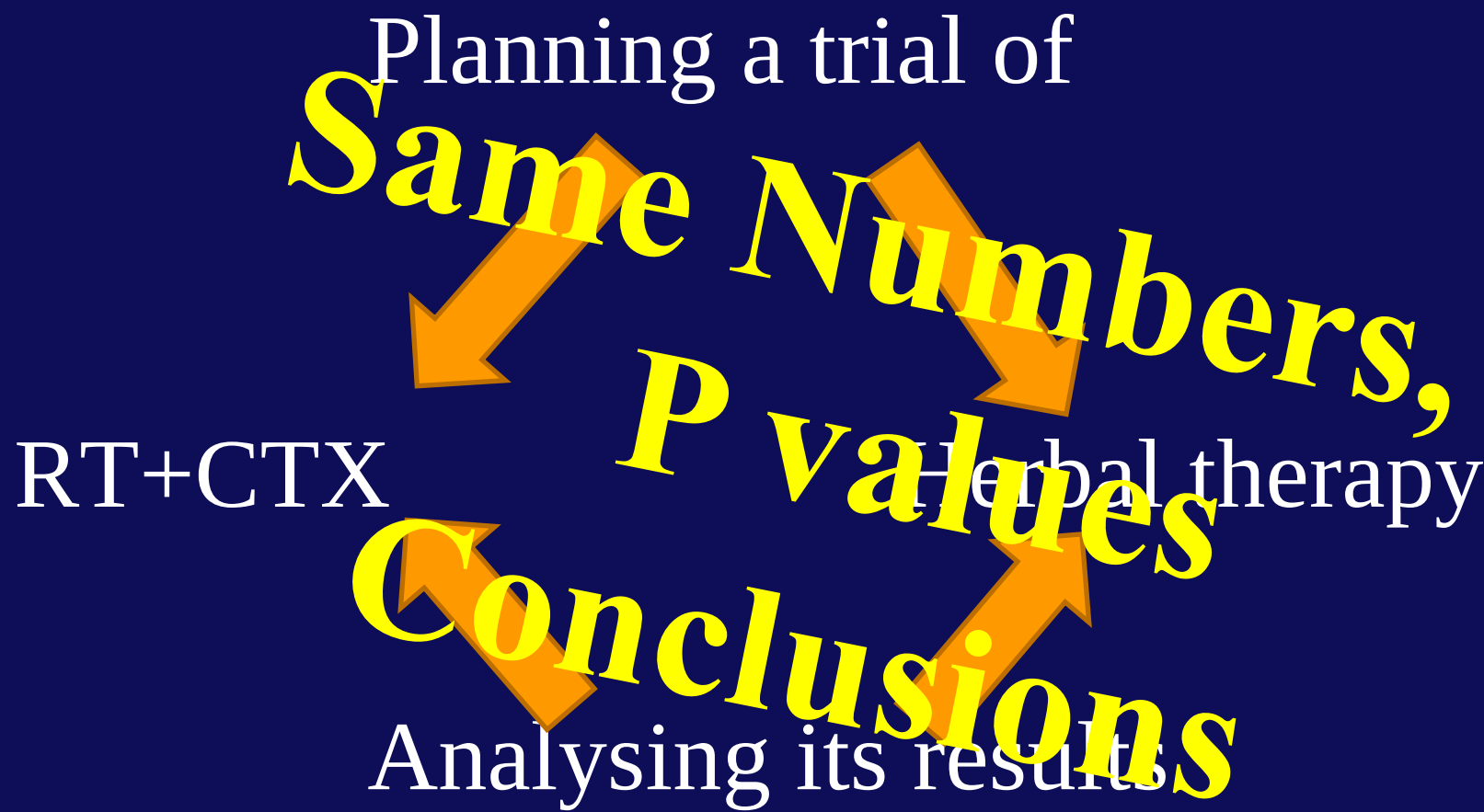
Analysing its results

(p value)

Squamous gastric cancer



Squamous gastric cancer



Conventional (frequentist) statistical reasoning

Experimental evidence

Conventional (frequentist) statistical reasoning

Experimental evidence

Bayesian statistical reasoning

Experimental evidence + Previous Knowledge

Example

		Mortality
Tumor X	**Nil vs A**	**15% vs 10%**
N=2000		**P = 0.0001**

H0 Rejected: A is effective in X

Example

		Mortality
Tumor X	*Nil vs A*	*15% vs 10%*
N=2000		*P = 0.0001*
Tumor Y	**Nil vs A**	**15% vs 7.5%**
N= 240		**P=0.066**

H0 not rejected: A not shown effective in y

Prior Information:
X and Y are BRAF+

		Mortality
Tumor X	*Nil vs A*	*15% vs 10%*
N=2000		*P = 0.0001*
Tumor Y	Nil vs A	15% vs 7.5%
N= 240		**P=0.066**

Prior Information:

X and Y are BRAF+

A = Anti BRAF

Mortality

Tumor X *Nil vs A* *15% vs 10%*

N=2000 *P = 0.0001*

Tumor Y Nil vs A 15% vs 7.5%

N= 240 **P=0.066**

INTERPRETATION?

Interpretation of the two trials

CONVENTIONAL

Tumor X: P = 0.0001

Tumor Y : P= 0.066

Efficacy of treatment A

proven in X

undemonstrated in Y

Interpretation of the two trials

CONVENTIONAL

Efficacy of treatment A is proven in X, undemonstrated in Y

BAYESIAN

(Posterior) Probability that treatment A **significantly (HR<0.8)** lowers mortality

in tumor X: 90%

in tumor Y: 90%

Disadvantages of Bayesian Statistics

- It is (felt as)
  - Subjective
  - Arbitrary
  - Amenable to manipulations (*pharma companies?)*

Advantages of Bayesian Statistics

- Reflects human reasoning (“common sense”)
- It is focused on estimates of effect
- Provides a conceptual framework for medical decision making
- **IT IS TRANSPARENT**

Prior evidence in Bayesian statistics

- **Needed in order to compute posterior probability**

Prior evidence in Bayesian statistics

- *Needed in order to compute posterior probability*
- **It must be transformed into a probability distribution (mean, median, standard deviation, percentiles, etc)**

Prior evidence in Bayesian statistics

- *Needed in order to compute posterior probability*
- *It must be transformed into a probability distribution*
- **Based on**
  - Objective information
  - Subjective beliefs
  - Both

Prior evidence in Bayesian statistics

Note: The difference between Bayesian and conventional statistics decreases with increasing strength of the empirical evidence

Rare Tumors!

Prior evidence in Bayesian statistics

No special way to elicit/obtain prior information

No special way to summarize information

- Meta-analytic techniques

Frequentist - Bayesian

Sources of prior evidence

- *Randomised Trials*
- Biological & Preclinical Studies
- Case-reports
- Uncontrolled studies
- Studies with surrogate endpoints
- Studies on other similar cancers
- Studies on the same cancer in different stages
- Others?

Meta-analyses in frequent tumors

- ***Randomised Trials***
- Biological & Preclinical Studies
- Case-reports
- Uncontrolled studies
- Studies with surrogate endpoints
- Studies on other similar cancers
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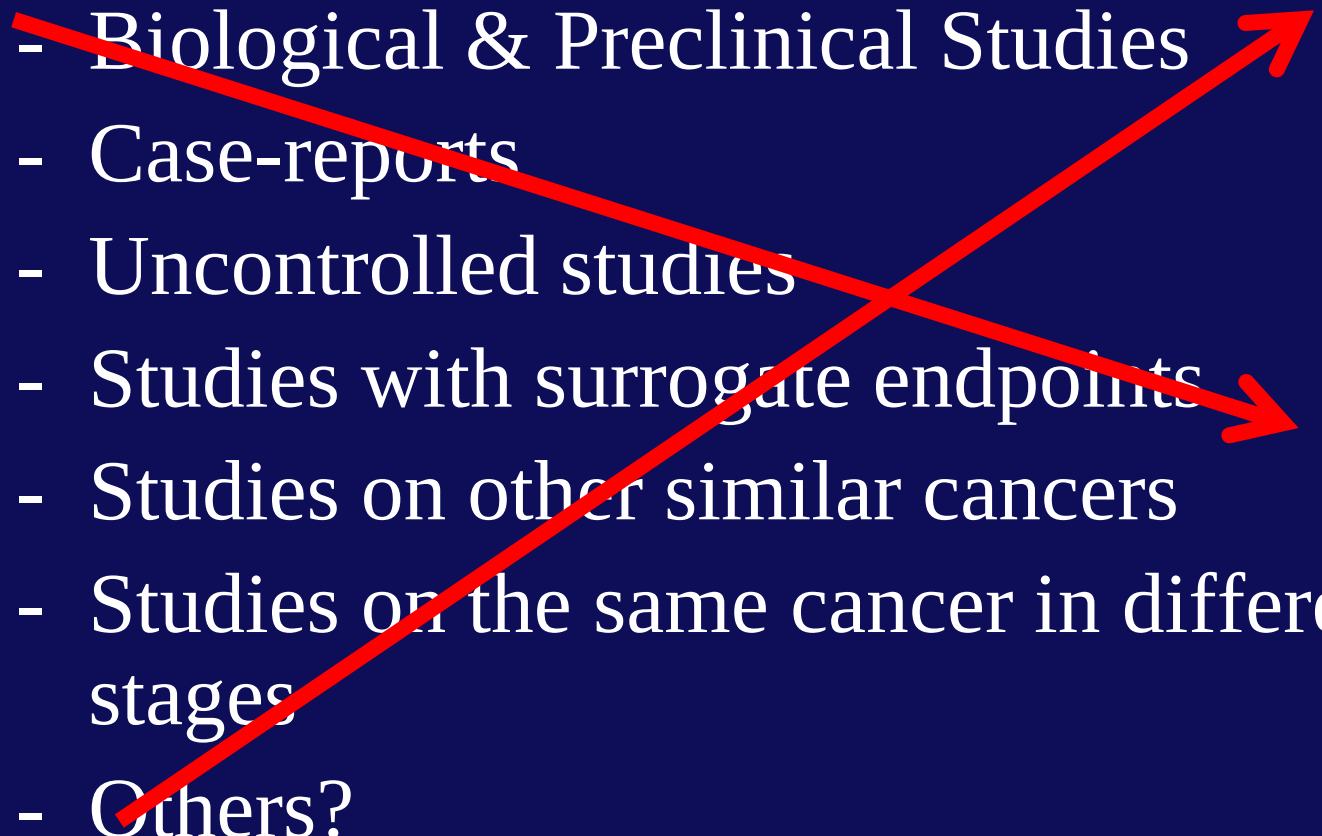
- Others?



Meta-analyses in frequent tumors

- ***Randomised Trials***

Weighted exclusively based on their size (and quality)

Rare Tumors

- ~~***Randomised Trials***~~
- Biological & Preclinical Studies
- Case-reports
- Uncontrolled studies
- Studies with surrogate endpoints
- Studies on other similar cancers
- Studies on the same cancer in different stages
- Others?

Prior evidence and clinical trials

Need to develop and validate new (meta-analytic) approaches to summarize prior information in rare tumors

Requirements

- Explicit
- Quantitative
- Reproducible

Meta-analyses in rare tumors

- NEED TO USE INFORMATION FROM STUDIES <100% VALID AND <100% PERTINENT TO THE QUESTION OF INTEREST, i.e.
- Different cancers, treatments, endpoints

Prior evidence in Bayesian statistics

If no direct information/evidence ?

- Indirect (pertinent) evidence

- **Studies of questionable validity?**
- **Pubblication bias?**

Differences between the present and the proposed approach

- Present :
  - Rational but informal integration of the available knowledge
- Proposed
  - Formal, explicit and quantitative integration of the available knowledge
    - Verifiable quantitative methods
    - Sensitivity analyses
    - Focus on summary effect estimates

Efficacy trials in rare tumors

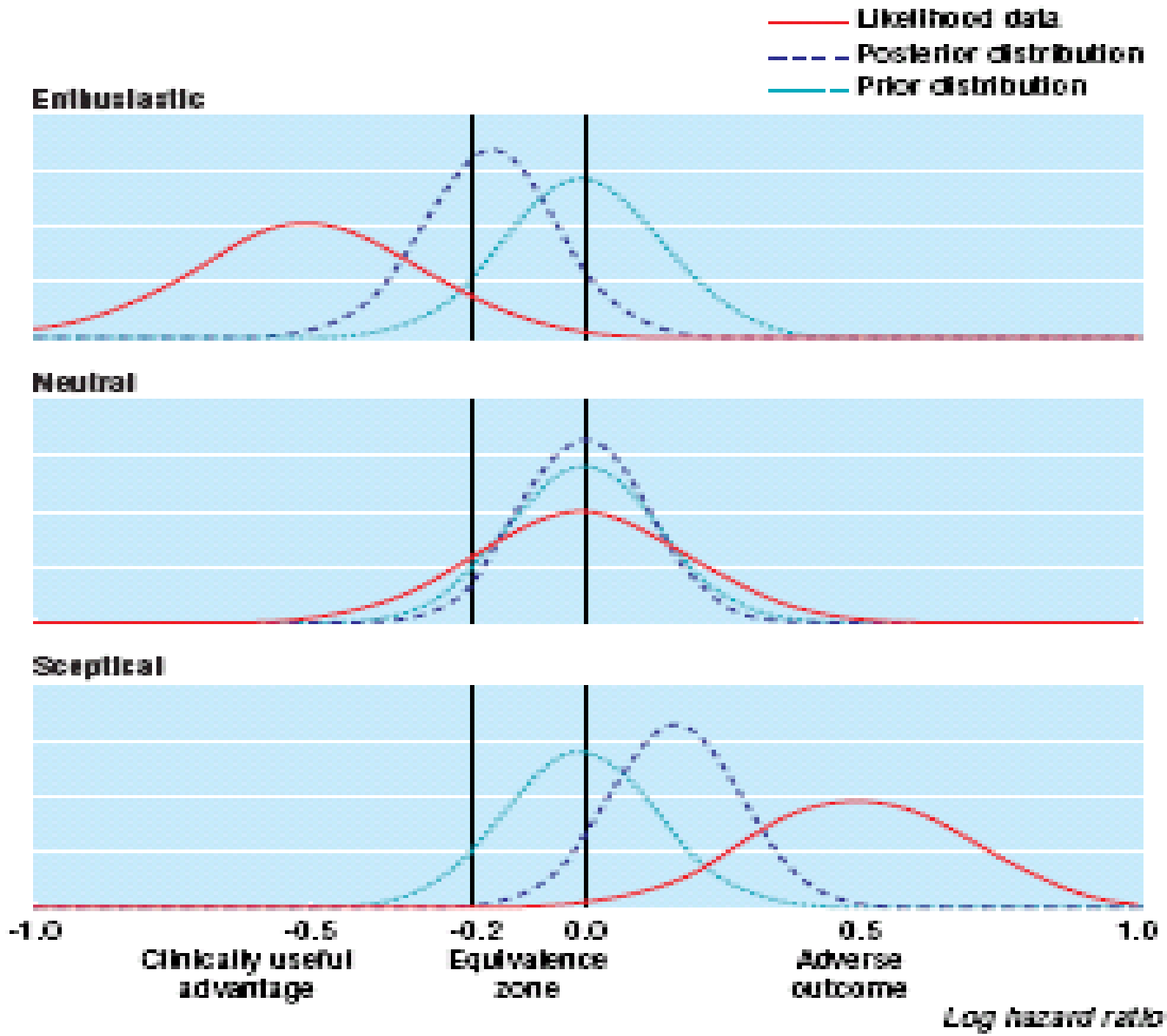
- Uncontrolled efficacy (phase III) trials of high quality
- Randomized activity (Phase II) trials followed by uncontrolled efficacy trials (with historical controls
- RCT's with surrogate endpoints
- **Adaptive, Bayesian, activity/efficacy RCT's based on unconventional Systematic Reviews**

Once the available evidence has been summarised, it is possible to estimate the probability that the new treatment, when compared to the standard is:

a) Definitely worse: Stop
b) Much better: RCT not ethical, confirmatory uncontrolled trials (e.g. GIST)
c) **Neither : RCT necessary and ethically justified**

How to use this approach in **planning** a new RCT

1. Realistic sample size projection (e.g. 50 events)
2. Review of the (pertinent?) literature
3. Construction of the prior
4. Consider possible scenarios for hypothetical results of the trial (e.g optimistic, neutral and pessimistic)
5. Update prior to give hypothetical posterior distributions
6. Examine possible impact of the new trial


Likelihood data
Posterior distribution
Prior distribution
Enthusiastic
Neutral
Sceptical
-1.0
-0.5
-0.2
0.0
0.5
1.0
Clinically useful advantage
Equivalence zone
Adverse outcome
Log hazard ratio

How to use this approach in **analysing** a RCT

1. Summarize study results
2. Combine trial results (likelihood) and prior distribution to obtain posterior probability distribution of treatment effect
3. Decision
   - Adequate evidence against: Stop
   - Adequate evidence in favor: Stop
   - **Still large uncertainty: Study Continues**