Methodological challenges
Designs of clinical studies

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Considerations for design

- RCT remains the gold standard
- n-of-1 design: this is a sequence of different treatments in one and the same patient.
  - Has the feel of cross-over design
  - Question: how does that work in oncology?
- Play with the type I error (or even type II error). For example:
  - One sided testing: can be acceptable
  - Higher type I error (alpha): this will never be found, because the trial will not be repeated
  - More optimistic alternative hypothesis: this has the same practical effect as increasing the type II error (beta): only a really strong improvement has good chances of being identified. Look more at the confidence interval.

Considerations for design

- Single-arm/non-comparative approaches
- The fact of having some responses is an improvement in itself
- The fact of stopping progression is an improvement in itself
- Robust historical data is available with small between trial variability (not likely, but happens)

There is no current standard …

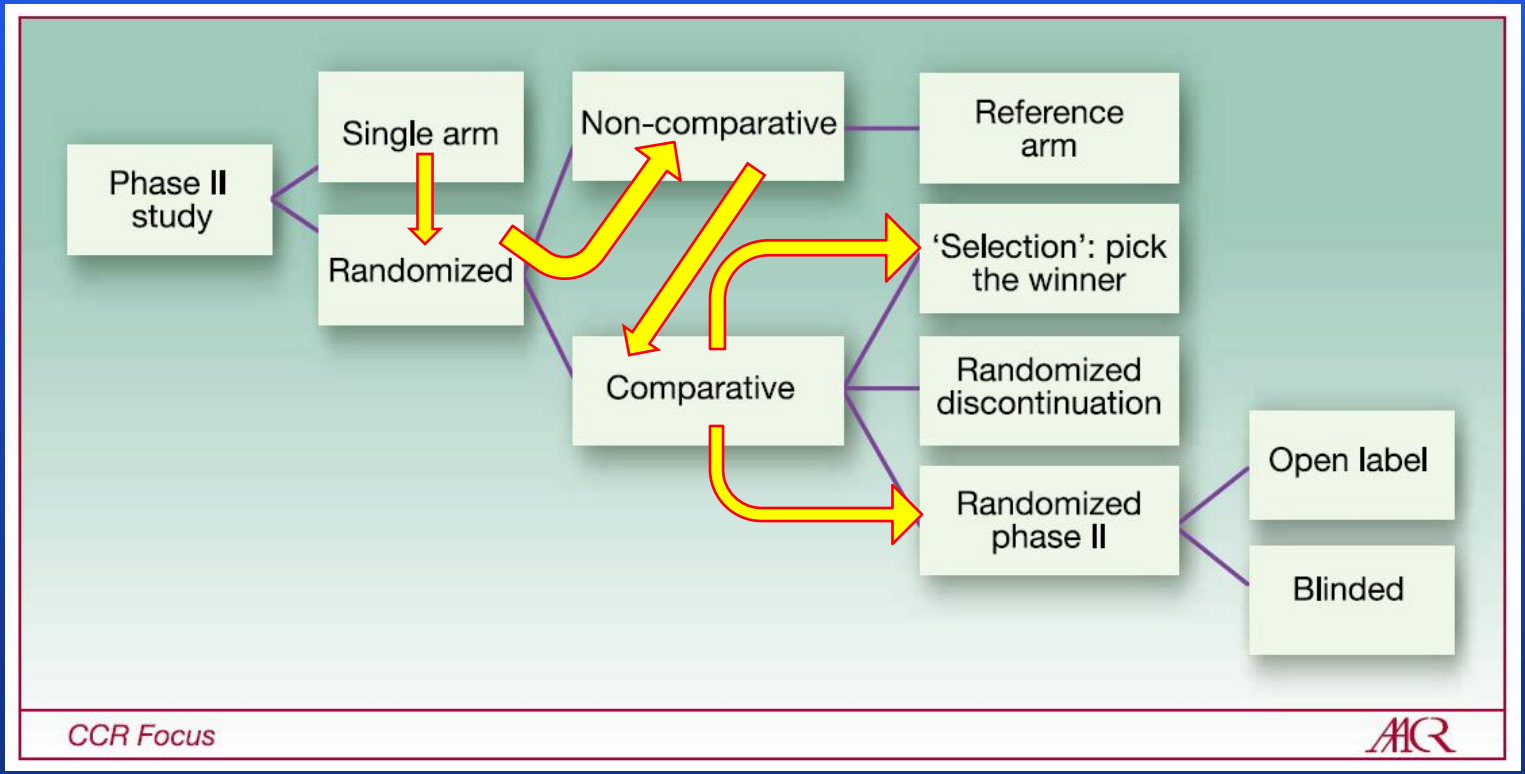
I would then (still) suggest a randomized approach with either a Phase II selection design, or a play-the-winner (adaptive randomization) approach

Other cases:

- Maybe it is worthwhile to incorporate in the plans a trial / decision point where disagreement is settled
- If the standard is wait-and-see, that can be randomized against

Example of evolution: how we see Phase II trials

- Trying to improve the Positive Predictive Value
- Accommodate many objectives: moving to an amalgam of approaches



Seymour et al. CCR 2010

Suggestion

- When there are less patients … then per patient more information needs to be collected
- Patient as their own control:
  - Make trials where patients are followed much longer, following patients and their consecutive treatments ‘forever’. (Similar to n-of-1 approach)
  - Obtain detailed information of disease evolution (e.g. tumor measurements) pre-treatment. Because rare cancer trials are done in specialized hospitals, this may be achievable. Can give much more info than e.g. usual RECIST (which has 1 baseline).

Alternative endpoints

- **Continuous endpoint of change in tumor size**
  - **Instead of binary response**

Karrison et al, Design of Phase II Cancer Trials Using a Continuous Endpoint of Change in Tumor Size: Application to a Study of Sorafenib and Erlotinib in Non–Small-Cell Lung Cancer, JNCI, 2007

Wason et al, Reducing sample sizes in two-stage phase II cancer trials by using continuous tumour shrinkage end-points, EJC, 2011

- **"Growth modulation index": ratio of time to progression under previous treatment relative to time to progression under new treatment**
  - **Paired failure-times within each treated patient**

Mick et al, Phase II clinical trial design for noncytotoxic anticancer agents for which time to disease progression is the primary endpoint, CCT, 2000

Suggestion (continued)

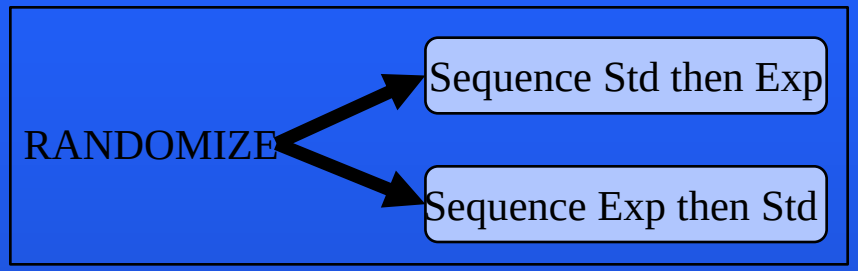
- Consider drawing from other cancer types with similar expression of genetic damage
  - EMA guidance: "… For example, in studies investigating the activity of a compound targeting a specific, molecularly well-defined structure assumed to be pivotal for the condition(s), it might be possible to enrol patients with formally different histological diagnosis, but expressing this target. …"

Suggestion (continued)

- Make more use of interim testing (or adaptive designs)
  - Usually in rare cancer types accrual is somewhat slower/longer, so more information on the enrolled patients is available at time of interim analysis, as compared to quickly enrolling trials
  - Any predefined plan of taking decisions can be investigated for its operating characteristics

Alternative designs

- **Cross-over design**
  - **Paired failure-times within each treated patient**
  - **Underlying assumptions for carrying out such studies almost never valid in cancer studies (carry-over effect)**



- **3-stage design**

Honkanen, A three-stage clinical trial design for rare disorders, SiM, 2001

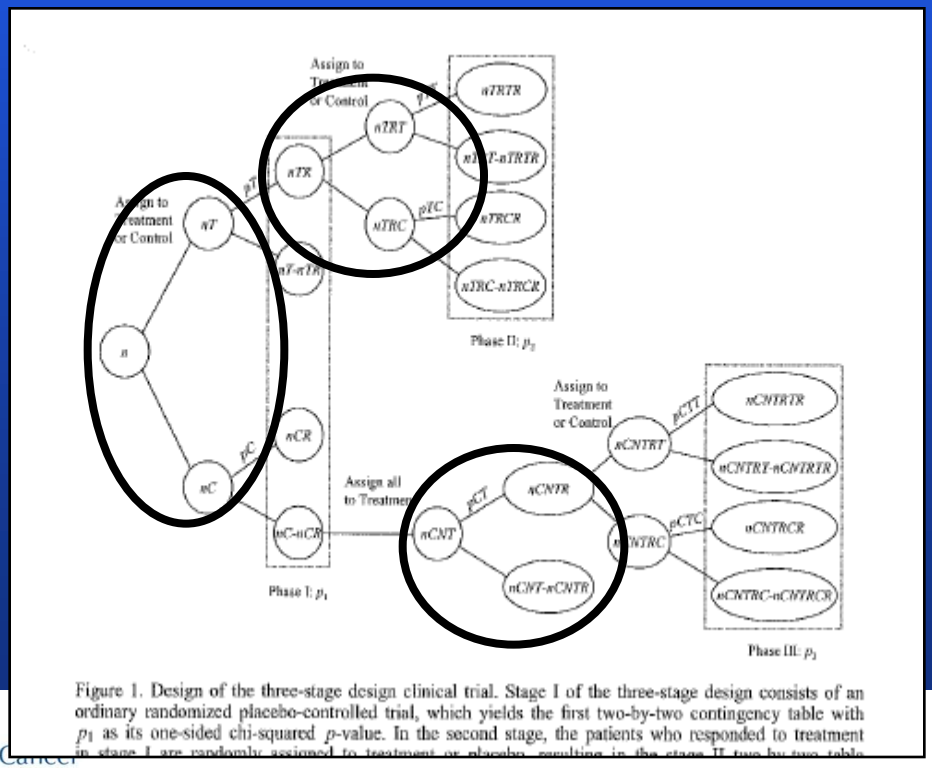
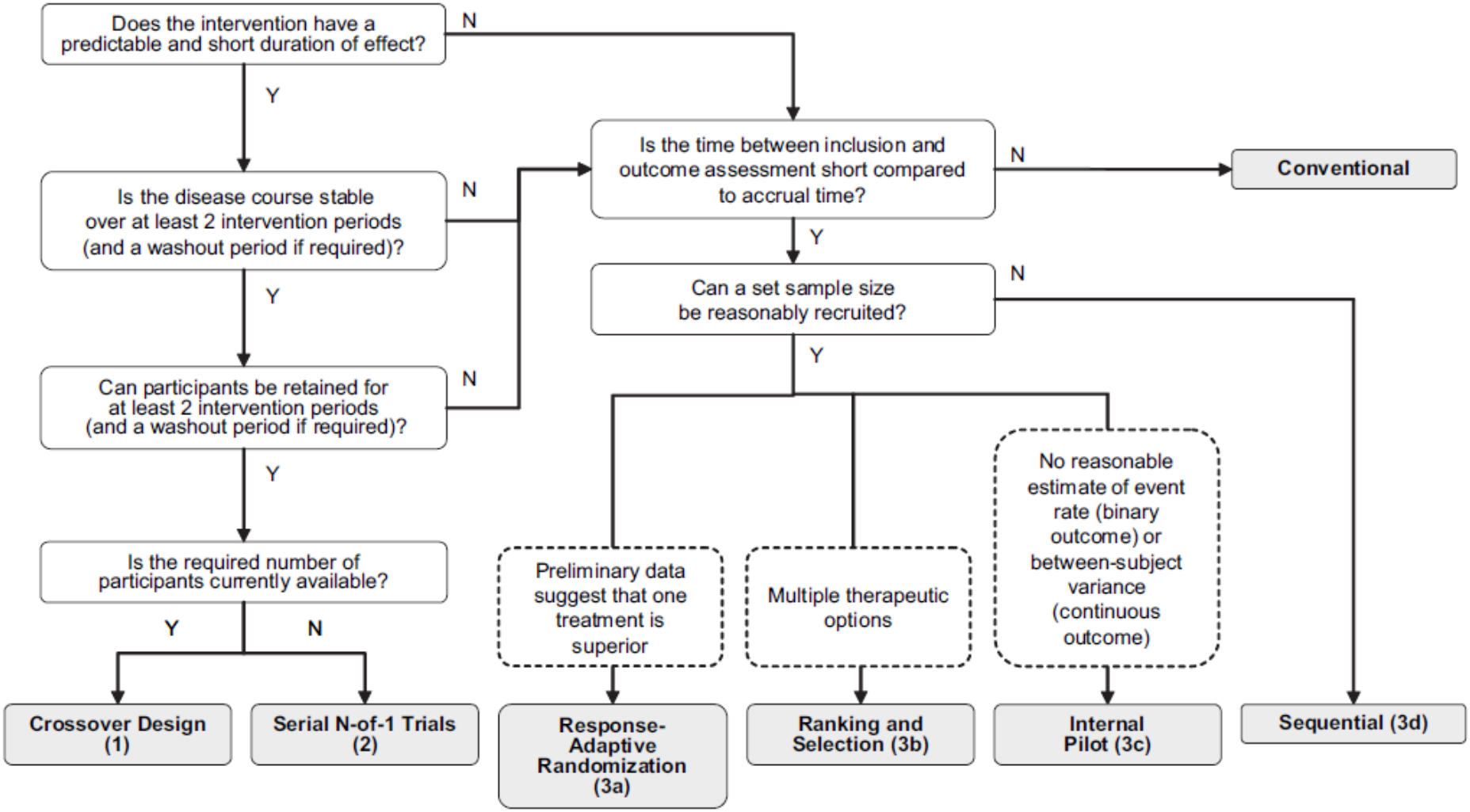


Figure 1. Design of the three-stage design clinical trial. Stage I of the three-stage design consists of an ordinary randomized placebo-controlled trial, which yields the first two-by-two contingency table with p_1 as its one-sided chi-squared p-value. In the second stage, the patients who responded to treatment in stage I are randomly assigned to treatment or placebo, resulting in the stage II two-by-two table

From Gupta et al.



Acknowledgements

- Consensus notes from Gynecologic Cancer Intergroup Harmonization Committee, Statistical Subcommittee (ASCO 2011, Jim Paul et al.)
- Catherine Fortpied

Reading

- A framework for applying unfamiliar trial designs in studies of rare diseases, S. Gupta et al., Journal of Clinical Epidemiology 2011
- Clinical trials and rare diseases, S. Lagakos, NEJM editorial 2007
- Trials in rare diseases: the need to think differently, Billingham et al. Trials 2011
- Evidence-Based Medicine for Rare Diseases: Implications for Data Interpretation and Clinical Trial Design, Behera et al. Cancer Control 2007

Back-Up

Looking for new common ground

- Trials with a high level of patient startup work
  - Screening many to obtain some eligible patients
  - Splitting according to markers
  - High workload to include patients
  - Timelines to enter a patient
- Think about:
  - Trials spanning several phases of development
  - Trials with multiple additional analyses / endpoints
  - TR analysis and planning of such analysis
  - Biobanking
  - Tools to perform complex logistics

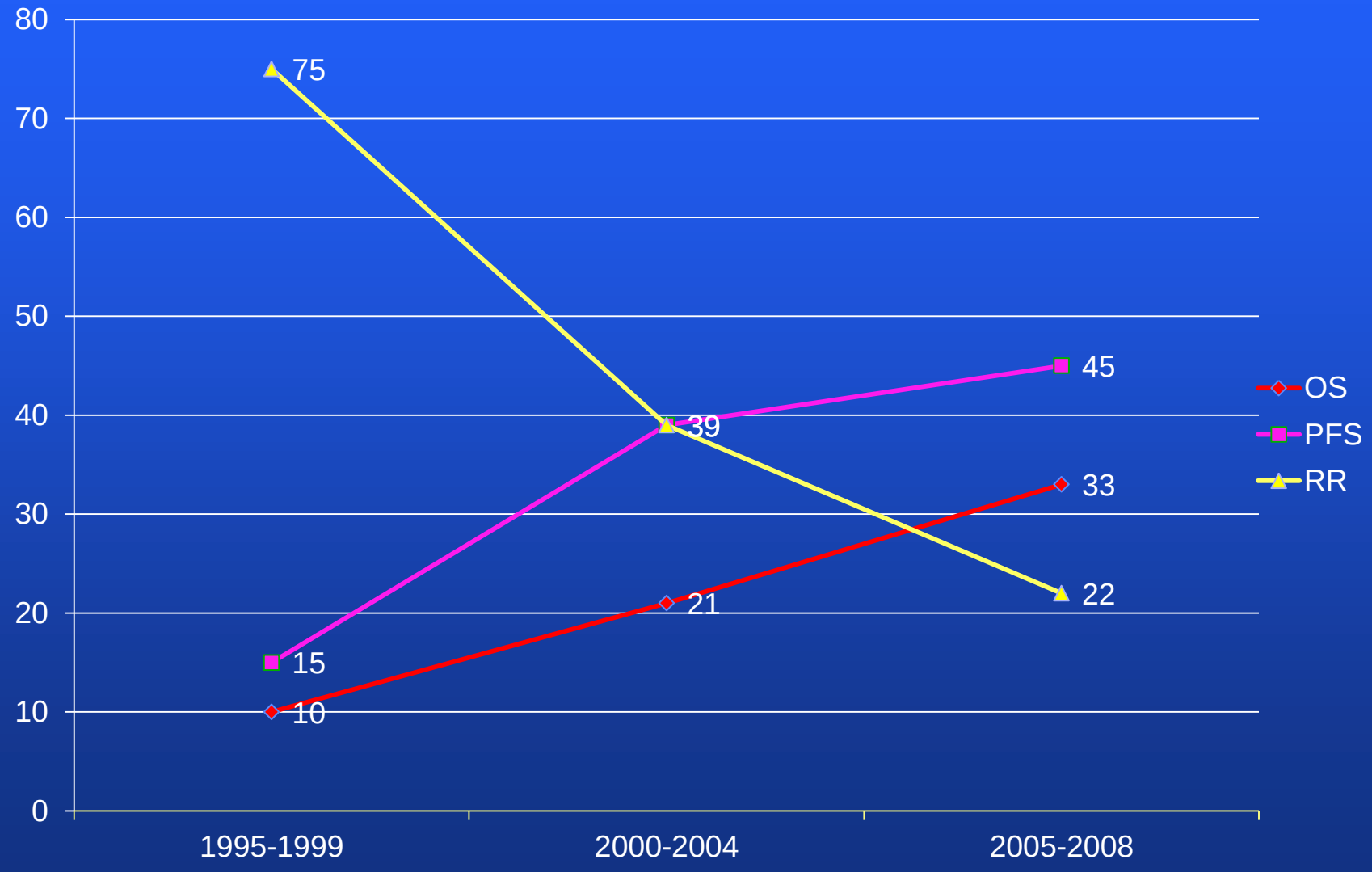
Buzzword: Adaptive designs

- We are learning to plan and run these complicated trials in an acceptable way
  - Appropriate use of IDMC
  - Appropriate use of adaptive elements in the design
- Word of warning: adaptive designs are not the solution to manage the unexpected. But adaptive elements can be very interesting to manage the complicated.
- We are already using many adaptive ideas in our trials (all phases).
- Keys here are: think and discuss upfront and monitor during the trial

FDA table of endpoints

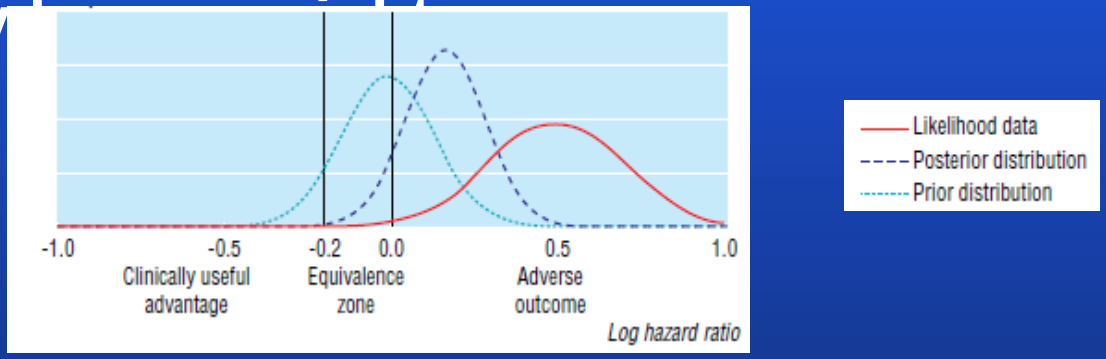
Endpoint	Regulatory Evidence	Study Design	Advantages	Disadvantages
OS	Clinical benefit	Randomized	Direct measure of benefit, easy, precise	**Large studies, crossover / followup Tx affects**, noncancer deaths
Symptoms	Clinical benefit	Randomized, **blinded**	Patient perspective of direct clinical benefit	Blinding hard, missing data, clinically relevant effect, validated tools lacking
DFS	Surrogate	Randomized, **blinded**, **blinded review**	Smaller, shorter	**Not stat. validated as surrogate for OS / not precise, open to bias / many definitions**
RR	Surrogate	**Blinded**, **blinded review**	1-arm possible, smaller, shorter, attributable to drug	No direct measure of benefit / no comprehensive measure of drug activity / only subset of benefiting pats.
CRR	Surrogate	**Blinded**, **blinded review**	1-arm possible, smaller, shorter, durable CR = benefit	No direct measure of benefit / no comprehensive measure of drug activity / small subset of benefiting pats.
PFS	Surrogate	Randomized, **blinded**, **blinded review**	Smaller, shorter, SD included, crossover / other Tx not affecting, objective & quantitative	**Not stat. validated as surrogate for OS / not precise, open to bias /many definitions / frequent assessments / need to balance timing x arms**

Evolution of endpoints leading to EMA oncology approvals



Alternative designs (cont'd)

- **Bayesian design, formally incorporating historical data into the design**
  - **Involve prior beliefs which may not be universally accepted**
  - **If we conduct a small trial, the choice of the prior may carry**



Tan et al. Strategy for randomized clinical trials in rare cancers. BMJ. 2003