Julius Centrum

An insider's view on Data Monitoring Committees

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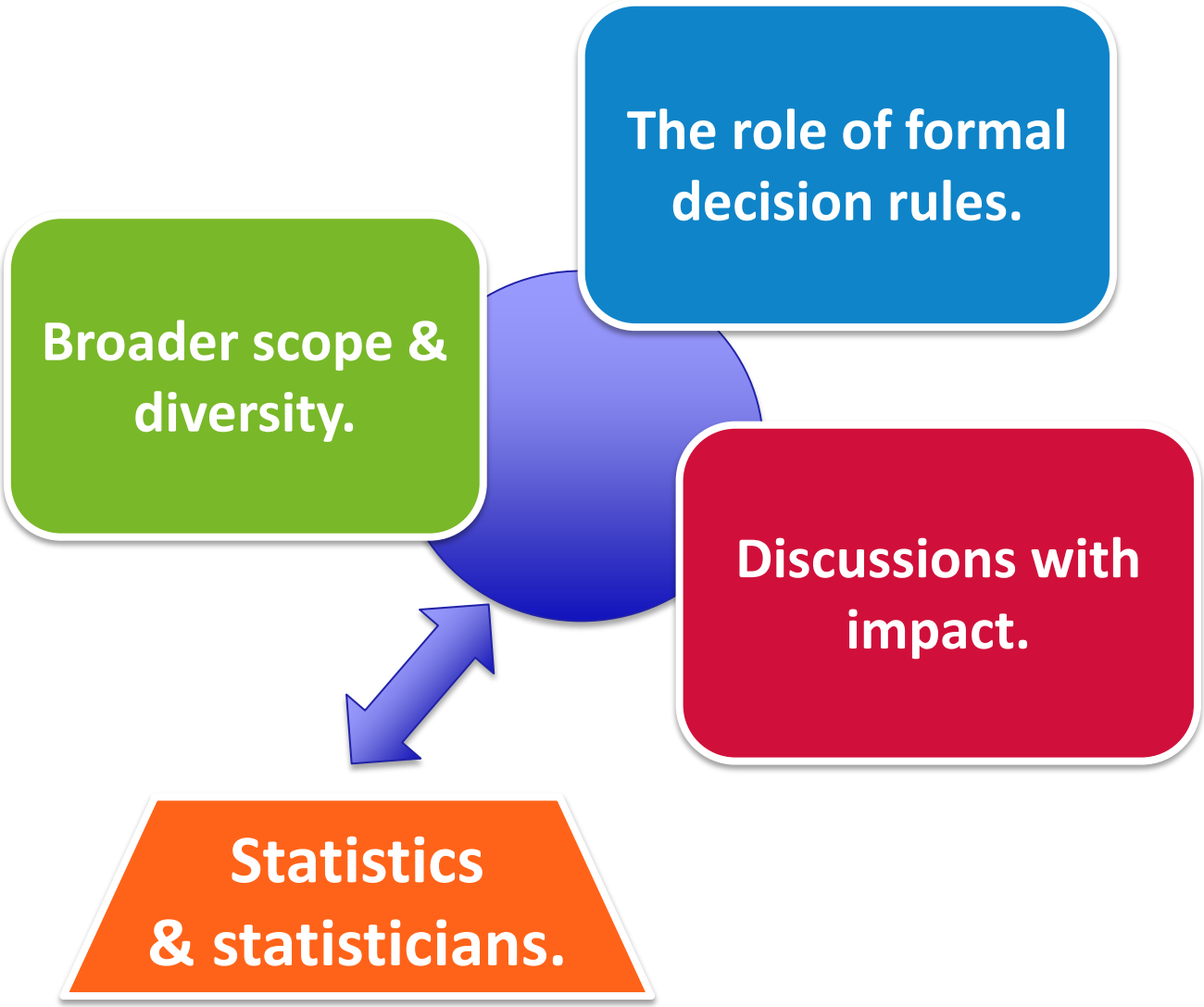
An insider's view on DMCs



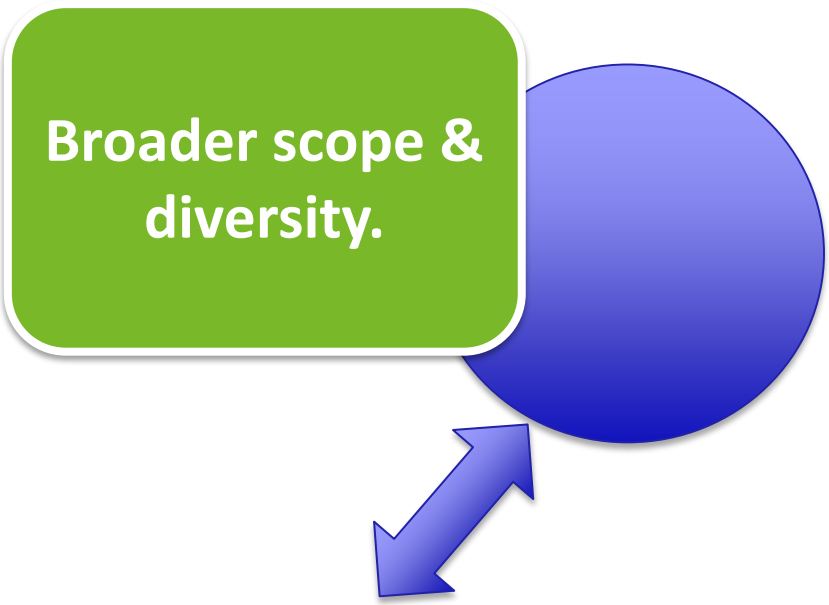
Data Monitoring Committee

"A clinical trial DMC is a group of individuals with pertinent expertise that reviews on a regular basis accumulating data *from one or more ongoing clinical trials*. The DMC advises the Sponsor regarding the *continuing safety* of current participants and those yet to be recruited, as well as the *continuing validity and scientific merit* of the trial [FDA, 2006]"

Data (and) Safety Monitoring Board

(**Independent**) Data Monitoring Committee (ICH – GCP)

An insider’s view on DMCs



Recent developments

- Type of trials with DMCs extended.
  - Less serious illnesses, “softer” endpoints.
- The same DMC overseeing multiple trials.
- Extending potential roles.
  - Adaptive design recommendations.
- Institutional DMCs
- Sponsors ?

DMC Rivastigmine for delirium treatment

“Study delirium prematurely halted”

A national clinical study into treatment of severely delirious intensive care patients was prematurely halted due to safety concerns. In the study part of the patients received “rivastigmine”, a drug currently available for treatment of symptoms of Alzheimers disease.

May 2010

Original trial:	400 intensive care patients, randomized 1:1
Objective:	Reduce duration of delirium
Interim analysis at:	54:50 patients.
DMC:	Primarily safety (safety stopping guidance)

DMC Rivastigmine for delirium treatment

	Rivastigmine (n=54)	Placebo (n=50)	p value
Primary outcome			
Delirium duration (days)	5·0 (2·7–14·2)	3·0 (1·0–9·3)	0·06
Endpoint of end of delirium (n=35 *vs* n=34)	4·0 (2·0–16·0)	2·5 (1·0–5·8)	0·06
Endpoint of hospital discharge (n=7 *vs* n=12)	6·0 (3·5–11·5)	6·0 (3·0–21·5)	0·95
Endpoint of death (n=12 *vs* n=4)	9·5 (4·8–11·8)	8·0 (1·0–9·0)	0·29
Secondary outcomes			

Mortality during treatment with the study drug seemed to be higher in the rivastigmine group (n=12, 22%) than in the placebo group (n=4, 8%; p=0·07, based on sequential testing). This result met predefined criteria to consider stopping the trial, and, according to the DSMB's recommendation, the study was immediately halted.

DMC Surgical intervention vs watchful waiting

Trial to compare immediate surgical intervention with watchful waiting in a particular disease.

Randomised (not blind), multicenter study.

Primary outcome: Quality of life after 6 months follow-up

Safety: Serious Adverse Events, with particular attention to events related to the surgical intervention (quality of procedure in different centers).

Potential early stopping for efficacy possible, but not likely.

DMC Surgical intervention vs watchful waiting

- Main safety concerns cannot be followed *group comparative*: limit to percentage complications, but take into account random fluctuation & content knowledge.

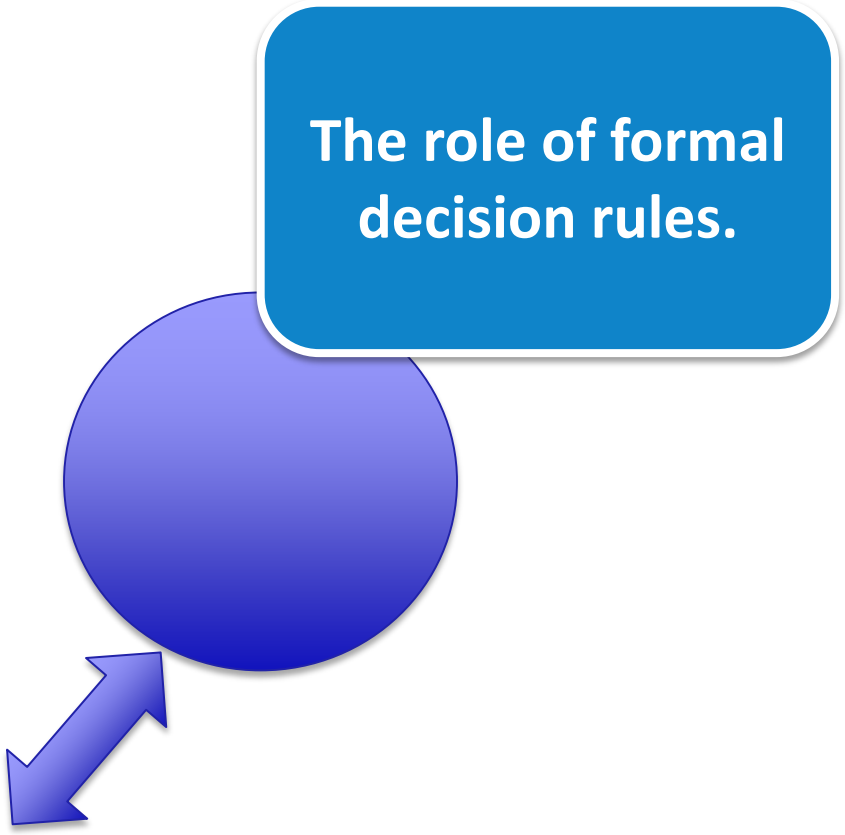
- Multicenter: quality of study impact (and surgery?) by (very) skewed recruitment across centers (you cannot just “drop” centers that only recruited one patient).

- Open character potential issue for conduct (e.g. switching to surgery).

DMC For a research consortium

- NVOG: Dutch Society for Obstetrics & Gynaecology
- National consortium for clinical research
- Research agenda set by NVOG
- Multiple (over 10) RCTs to answer pertinent questions for O&G practice
  - Surgical, Medical, Procedural, Devices
- Mutiple (academic) medical centers, multiple sponsors (hospitals, not companies)

An insider's view on DMCs



The role of formal decision rules

"No single statistical decision rule or procedure can take the place of the well reasoned consideration of all aspects of the data by a group of concerned, competent and experienced persons with a wide range of scientific backgrounds and points of view."

DMC Evaluating chemotherapy regimens*

Setting: First line cancer treatment.

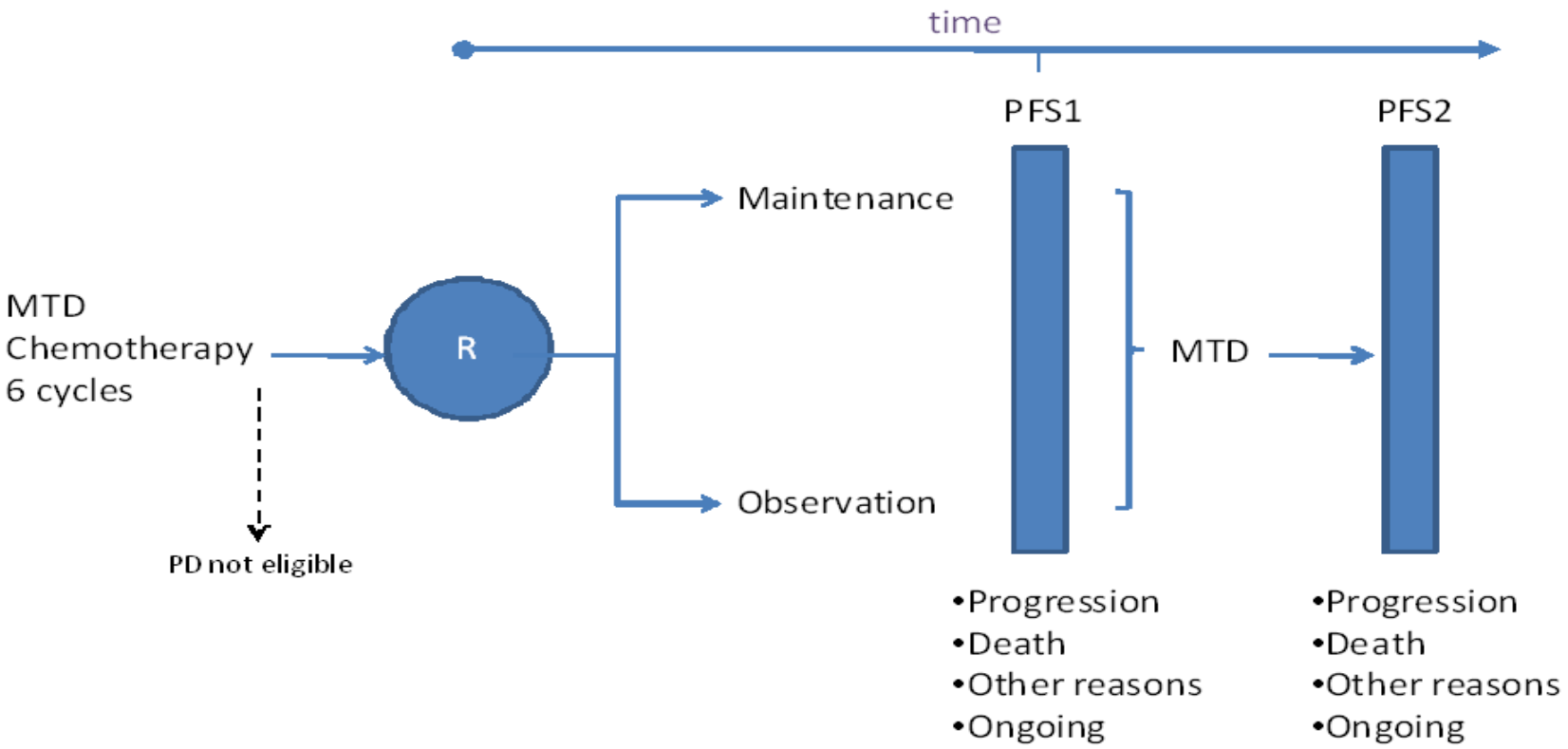
Comparison: Patients with at least stable disease after standard induction therapy are randomised between *observation* and *maintenance* treatment.

Upon first progression (PFS1), patients in both arms are to receive the induction regimen until second progression or death: PFS2.

Primary endpoint: PFS2

Secondary: OS, PFS1

* Derived from Real Life example, but data and aspects changed to retain confidentiality of interim data


time
PFS1
PFS2
Maintenance
MTD
Chemotherapy
6 cycles
R
MTD
Observation
PD not eligible
•Progression
•Death
•Other reasons
•Ongoing
•Progression
•Death
•Other reasons
•Ongoing

DMC Evaluating chemotherapy regimens

Sample size considerations

- Hazard ratio of 0.78 for PFS2: Total of 525 events to be observed across both arms for 80% power.

Interim analysis and Stopping rules

- One formal interim analyses of the primary efficacy endpoint by randomized treatment arm.

- After about half of the planned events (approx 260).

- Lan&DeMets alpha spending with OB&F type boundaries.

DMC Evaluating chemotherapy regimens

(First) Interim report.

- General: Somewhat more adverse events seen under Maintenance therapy compared to observation, but still positive benefit risk expected if efficacy can be shown.

- Follow-up of 350 patients (175 in each group). In total 215 PFS2 events observed. 120 events in Observation (68.6%) and 95 in Maintenance (54.3%).
  - Observed hazard ratio on PFS2 0.70 (p-value 0.02).
  - Observed hazard ratio on OS 0.73 (p-value 0.09).

- So>>>>>>?

DMC Evaluating chemotherapy regimens

- Overall Survival will be the most important endpoint of the study, in view of **convincing the clinical community**.

- The *unadjusted* comparison of overall survival needs to be 'convincingly' significant at the end of the study. To assure this, this comparison needs to be "comfortably" significant at the time of an interim analysis at which stopping is considered.

- A balance needs to be sought between stopping too early (ending without a convincing answer) and continuing too long (exposing too many patients to an inferior treatment)

DMC Evaluating chemotherapy regimens

(Second) interim analysis

- Recruitment challenging.
- Sample size re-evaluations between trial statistician and DMC.
- Trial stopped early, at 420 PFS2 events.
- Convincing results PFS2, OS consistent but less so.

The role of formal decision rules

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

THE CHANGING FACE OF CLINICAL TRIALS

Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John J.V. McMurray, M.D., James H. Ware, Ph.D., and Janet Woodcock, M.D., *Editors*

Data Monitoring Committees — Expect the Unexpected

David L. DeMets, Ph.D., and Susan S. Ellenberg, Ph.D.

An insider’s view on DMCs

Discussions with impact

- Considerations of effects outside the study
  - Sufficient evidence to convince broad community?
  - Will it prevent or trigger new studies?

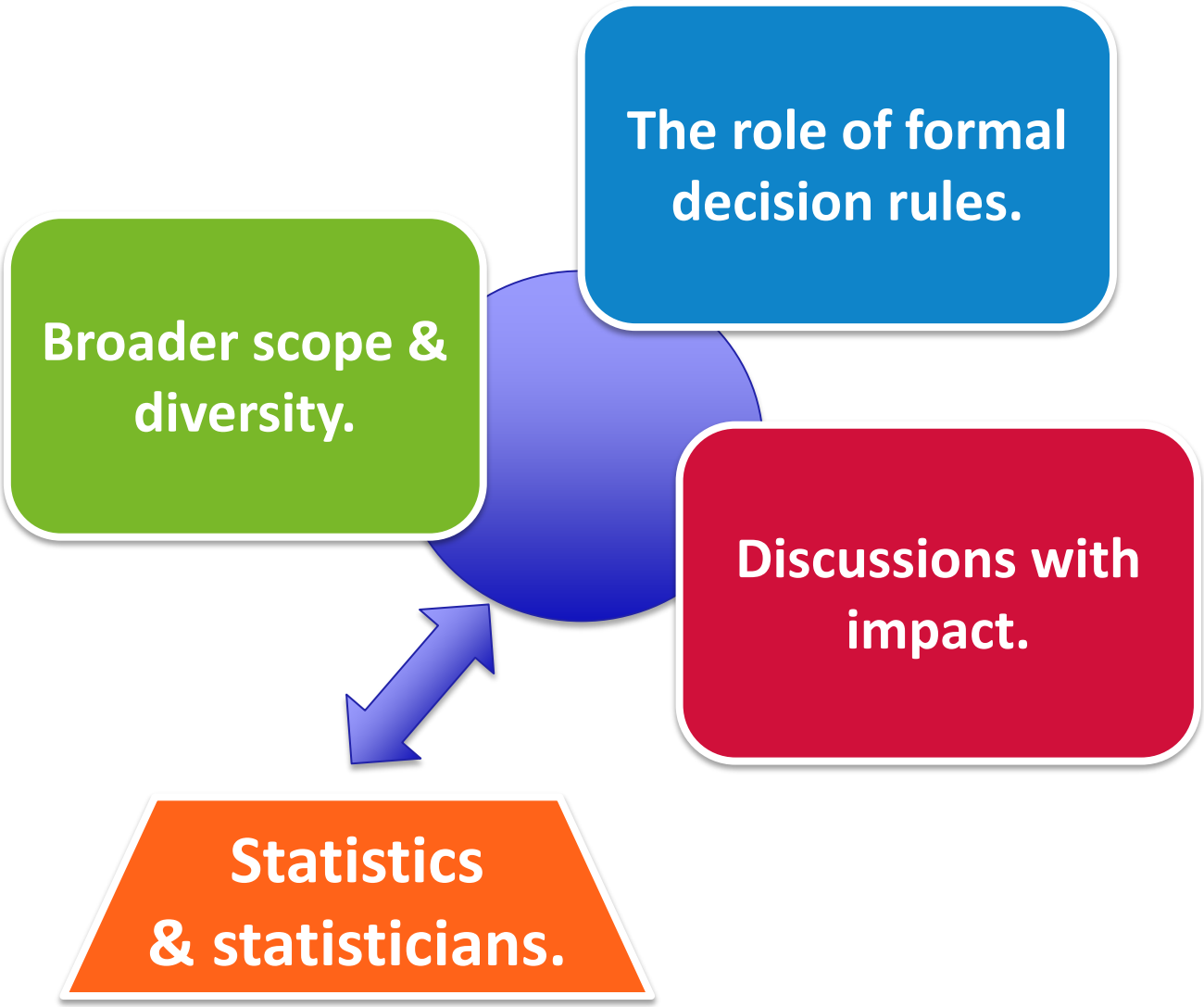
- Effect on innovation?
  - Few treatments are without risks of harm: balancing benefit and risk with large residual uncertainty.

- "Research waste": continued relevance of research question with evidence emerging elsewhere.

- Group dynamics of DMC as team with judgemental and choice dilemma tasks*

** Issues in data monitoring and interim analyses in clinical trials, Health Technology Assessment* 2005; Vol. 9: No. 7

An insider's view on DMCs



An insider's view on DMCs

- Statistical theory and practice of interim data monitoring crucial for DMCs – particularly for not stopping too early.
- Many advises of DMCs not 1-1 related to pre-defined critera.
- Statisticians important role:
  - To assess the data & To assist in keeping role of DMC clear.
- Assessing the complex (safety and efficacy) data & judging strength of evidence may need more attention.

Statistics & statisticians.