



Ethical issues with seamless and adaptive Master Protocols

CTFG-Meeting, Bonn 24.10.2018

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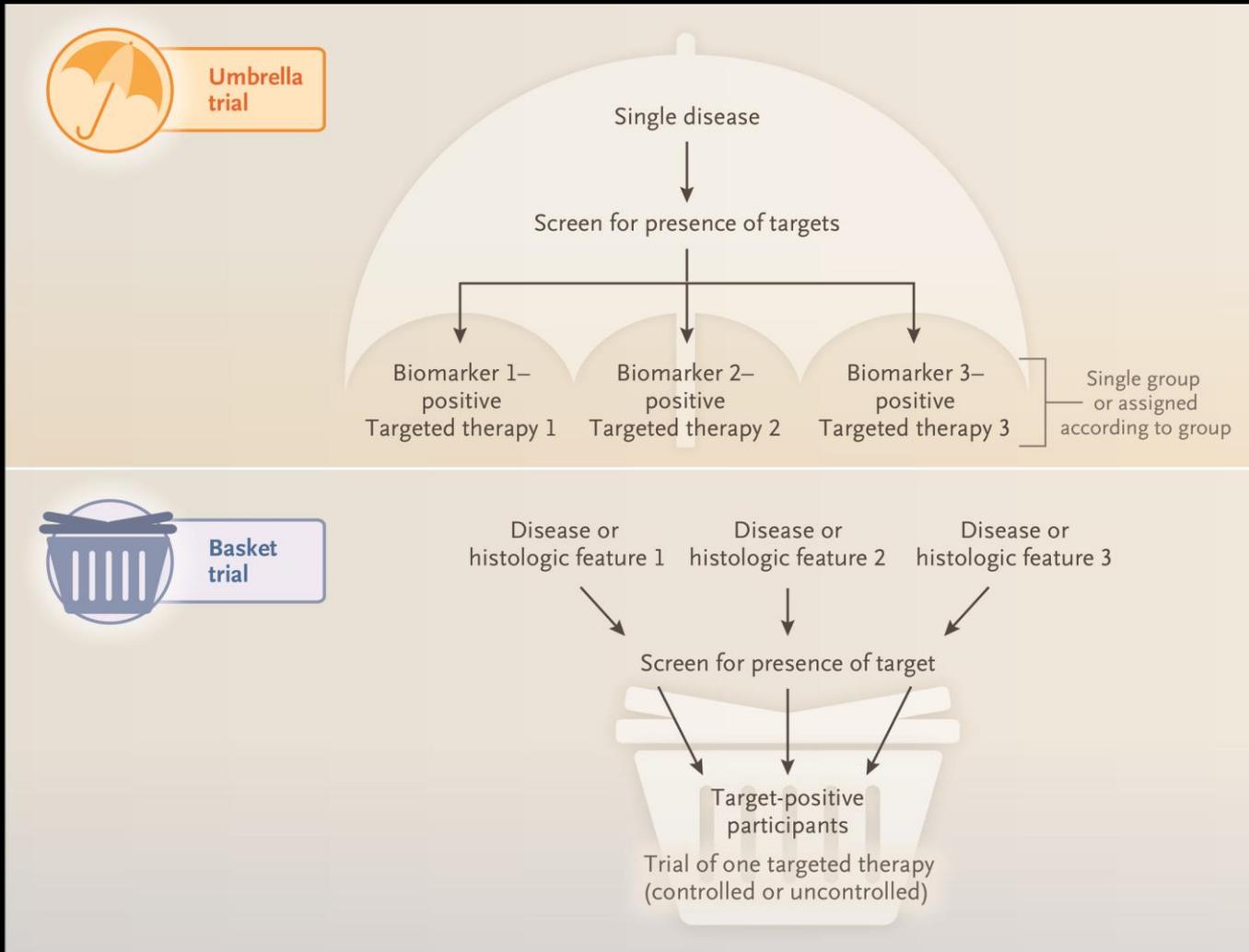
Preliminary note

- This presentation reflects my personal opinion and not necessarily the viewpoint of the Association of Medical Ethics Committees in Germany or of EUREC.
- No Conflicts of Interest to declare.

Inspection Order of Ethics-Committees

- *The scientific quality of the investigation*
- The lawfulness
- *the ethical acceptability*
- the medical acceptability

Umbrella Trial and Basket Trial.



Woodcock J, LaVange LM. N Engl J Med 2017;377:62-70



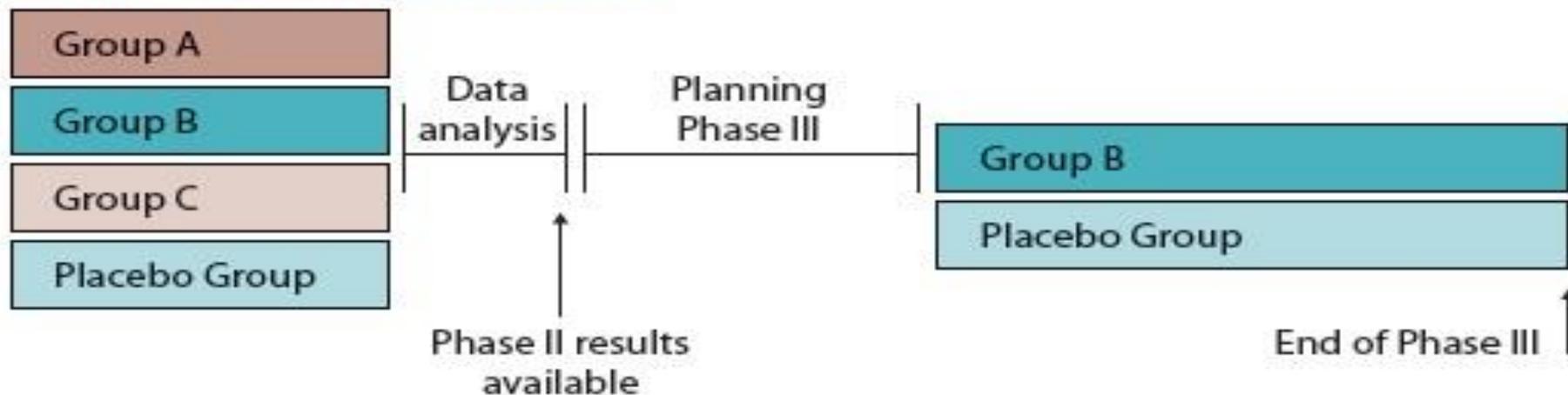
Types of Master Protocols.

Table 1. Types of Master Protocols.

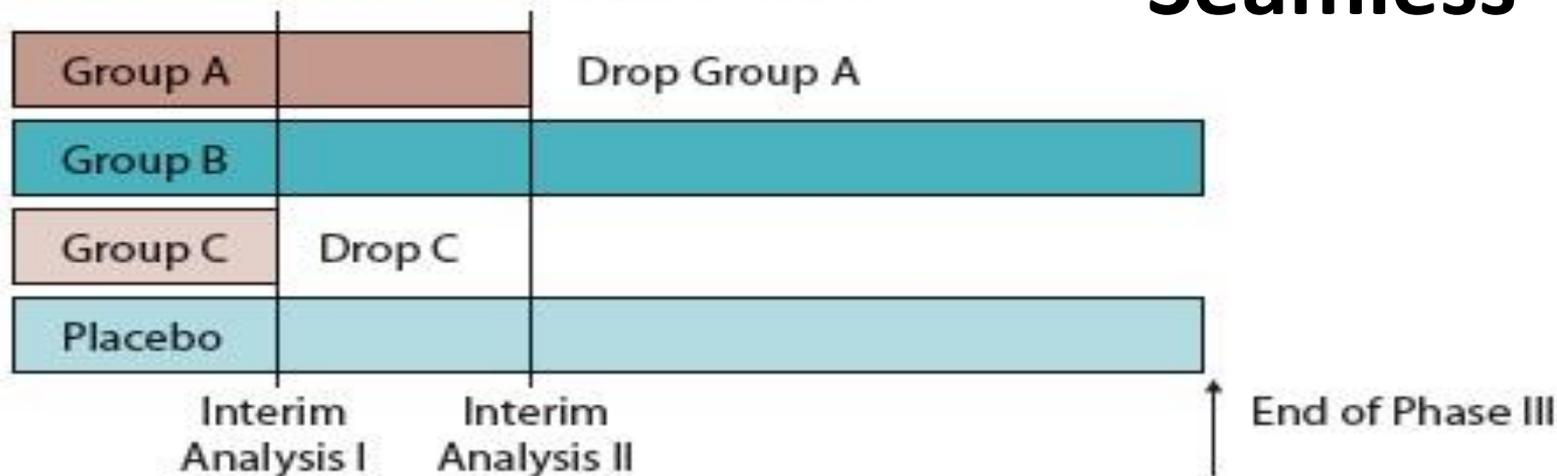
Type of Trial	Objective
Umbrella	To study multiple targeted therapies in the context of a single disease
Basket	To study a single targeted therapy in the context of multiple diseases or disease subtypes
Platform	To study multiple targeted therapies in the context of a single disease in a perpetual manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm

Promise of Adaptive Designs (ADs) - Speed-up

Traditional Phase II and III Studies



Adaptive design – combined Phase II/III



Seamless

Master protocols - characteristics

- **Umbrella-Trials:** Potential for advantages for patient care and combinable control groups.
- **Basket-Trials:** Less obvious advantages given that a basket trial is highly complex and a challenge re logistics, coordination etc. Single trials may be easier to do.
- **All master protocols are typically combined with adaptive design elements. → a.a.r. Risk of bias increased.**

Adaptive Designs (ADs)

Adaptive (engl.) = learning

Aim: To combine the ‘explorative’ and the ‘confirmatory’ part of a study (program) in such a way that valid, bias-free results (and drug approval) are achieved with less patients and in less time.

→ **Seamless drug trials/development**

Traditional vs. adaptive approach

Traditional:

- A priori hypotheses and endpoints
- Sample size estimation
- Fixed trial protocol, small risk of bias

Adaptive Design:

Prospectively planned modifications of the trial protocol , based on first results

→ Risk of bias 

Adaptive Designs – Definition EMA

A study design is called 'adaptive' if statistical methodology allows the modification of a design element (e.g. sample size, randomisation ratio, number of treatment arms) at an interim analysis with *full control of the type I error*.

→ AD has to be prospectively planned.

Acceptable are, based on prospectively planned, blinded interim analyses, adaptations re

- the eligibility criteria
- the sample size*
- secondary endpoints without an association with efficacy parameters
- groupsequential plans und futility
- the Data Analysis Plan*

DSMB/DMC essential, where required blinded

FDA: Adaptive Design Clinical Trials for Drugs and Biologics. 2010

* only aggregated data analyses permitted

Adaptation: Risks

Not only the astute investigator can often draw conclusions from the type of adaptation re efficacy / safety of the IND. By this the integrity of the trial conduct and the data is at risk.

Validity at risk → endangers the legitimacy of the trial from an ethical point of view.

Ethical Issues: Adaptive Randomisation

Outcome adapted randomisation means that the ratio, typically 1:1, gets modified in favour of the currently superior treatment towards 2:1, or 3:1 or 4:1.

Advertised ethical gain: less pts. get allocated to the alleged inferior treatment und → faster recruitment.

But:

- ✓ The Equipoise-assumption gets abandoned.
- ✓ How to measure superior? Primary or secondary outcomes ? ADRs? RBA?

Ethical Issues: Adaptive Randomisation

But:

- ✓ Required sample size increases for 12-33% when randomisation ratio gets 2:1 or 3:1*.
- ✓ May risk the comparability of the treatment groups
- How to explain it to the patients ?
- ✓ Increased risk of therapeutic misconception.
- ✓ Bias by modified physicians' behaviour and attitudes
- ✓ **Results in less valid and robust results !**

*Hey SP et al. Neurology 2014;82:77-79.

Ethical issues of ADs, MPs and Seamlessness

- **How to guarantee that the patient information (leaflet) provides at all times comprehensive, accurate and up to date information, e.g. re safety, given that the study is adaptively planned and seamless ?**
- **How to guarantee that the risk-benefit assessment is kept up to date and that decisions re continuation or stop of the study are properly performed, given the considerable time pressure?**
- **How to safeguard the methodological integrity of the study and the data (bias, type I error) ?**

Practical Issues

- **MPs ask for a central competent and powerful infrastructure, e.g. for the molec. screening, administration, and organisation.**
- **Seamless Designs shorten the time available for the analysis und interpretation of the data → Risk for wrong assessments and interpretations.**
- **Often excessively complex and voluminous protocols (>500 p.) – serious problem for authorities, RECs, investigators und sponsors.**
- **MPs not planned for in the current laws and regulations.**

Conclusions

- **MPs and ADs are highly complex and a challenge for all stakeholders.**
- **ADs increase the risk of bias and raise serious ethical issues.**
- **All adaptations have to be prespecified in the study protocol.**
- **It is not clear how the legal requirements re patient information can be properly met.**
- **When planning a MP/AD early scientific and ethical advice of the NCA and the competent REC is advised.**