Ethical view on complex clinical trials

EU NT Training: Joint assessment according to the new clinical trial regulation 536/2014 from the view of ethics committees and national regulatory agencies

Bonn, 2nd and 3rd April, 2019

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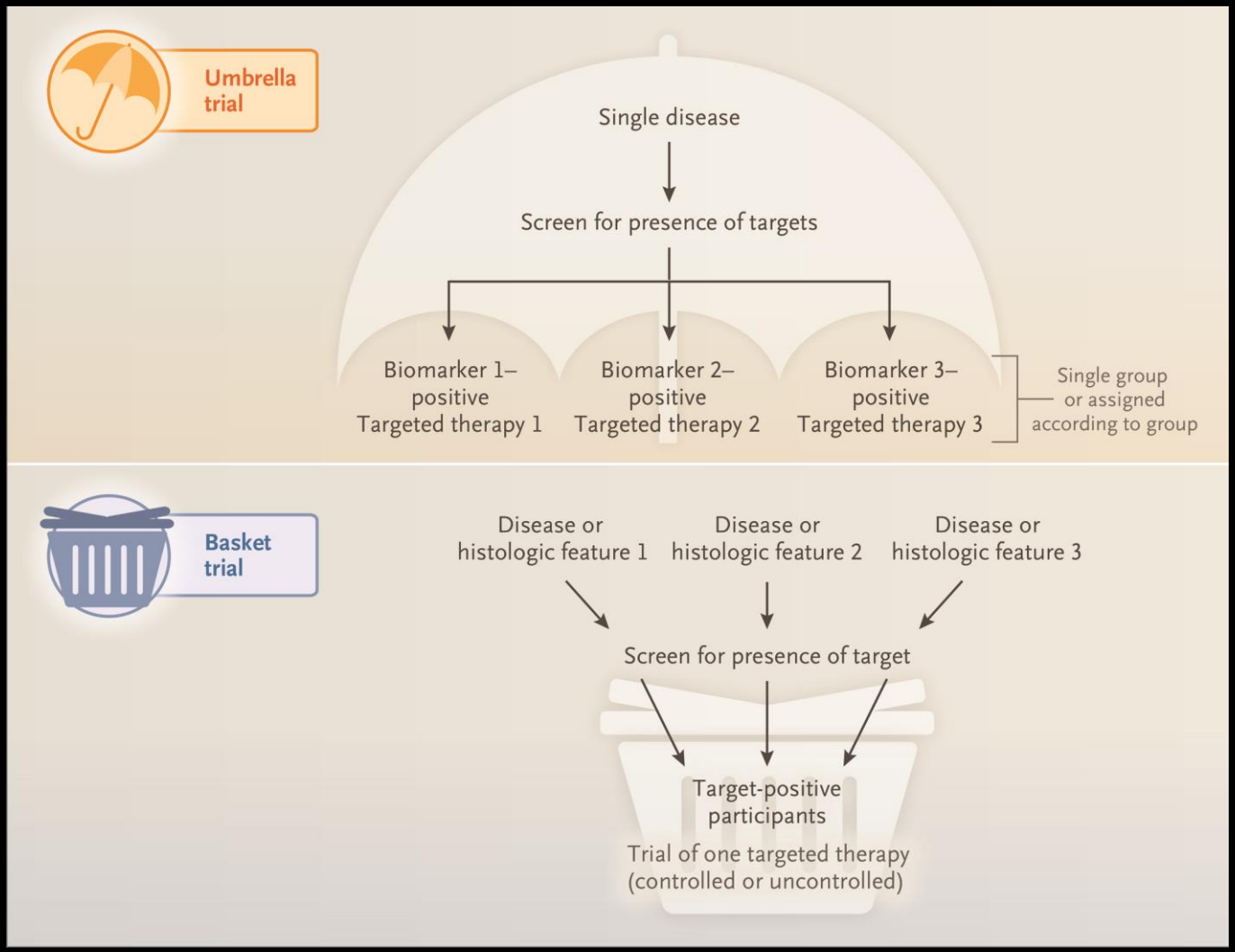
Structure

- Introduction – Background: Master Protocols (MPs) und Adaptive Designs (ADs)
- Biometric Aspects
- Ethical Aspects
- Practical Aspects
- Conclusions

Scientific Background

- Rapid progress in the molecular analysis of diseases.
- Increasing numbers of molecularly defined sub-entities of various diseases, particularly cancers.
- Hypotheses, that molecular subtypes are more relevant than histology or traditional disease entities.
- Huge number of new pharmacological substances and potential modes of action.
- Dissatisfaction with the current phase I – III clinical trial system, too slow and too many futile trials.

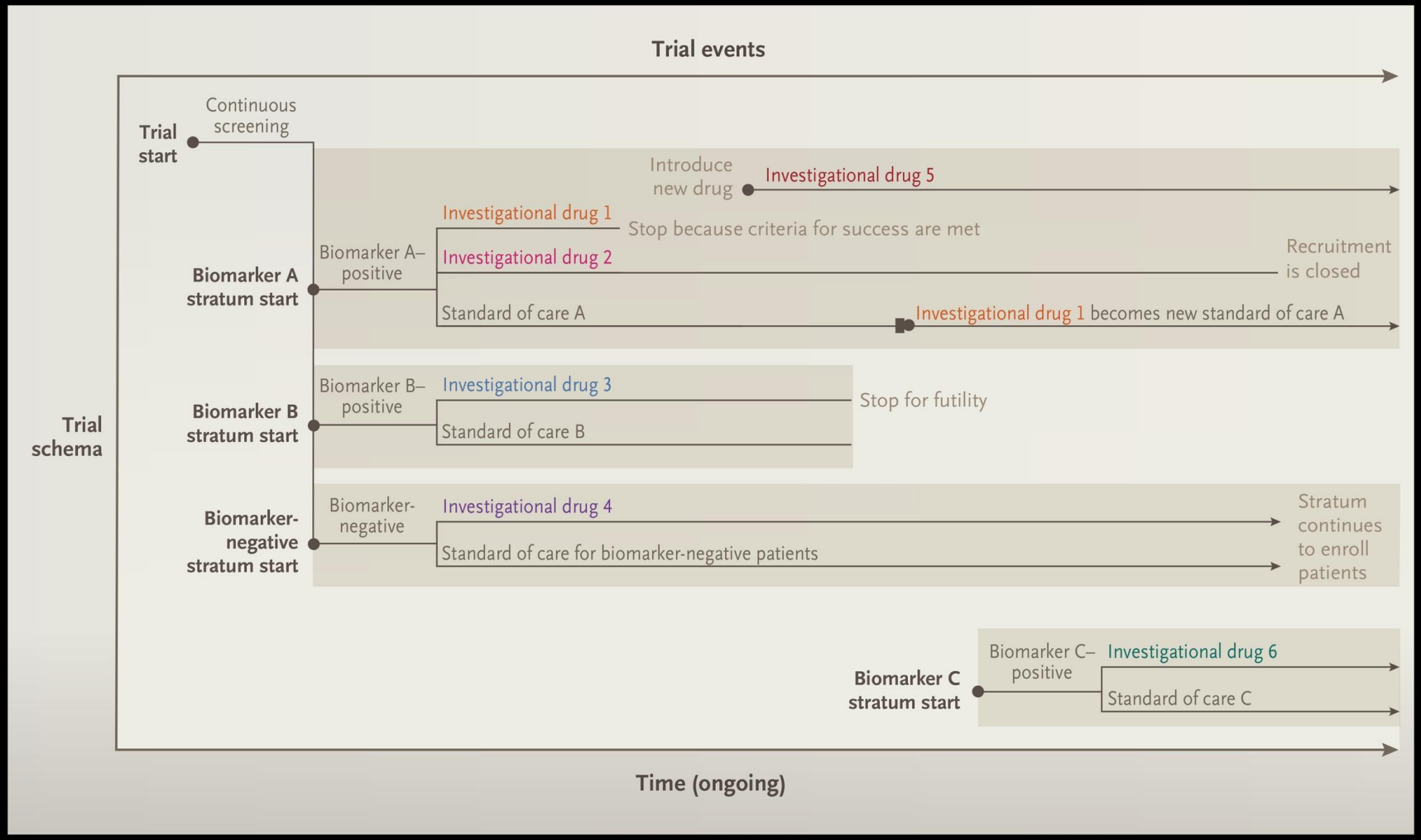
Umbrella Trial and Basket Trial.



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

The NEW ENGLAND JOURNAL of MEDICINE

Potential Design of a Platform Trial Involving a Single Disease.



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

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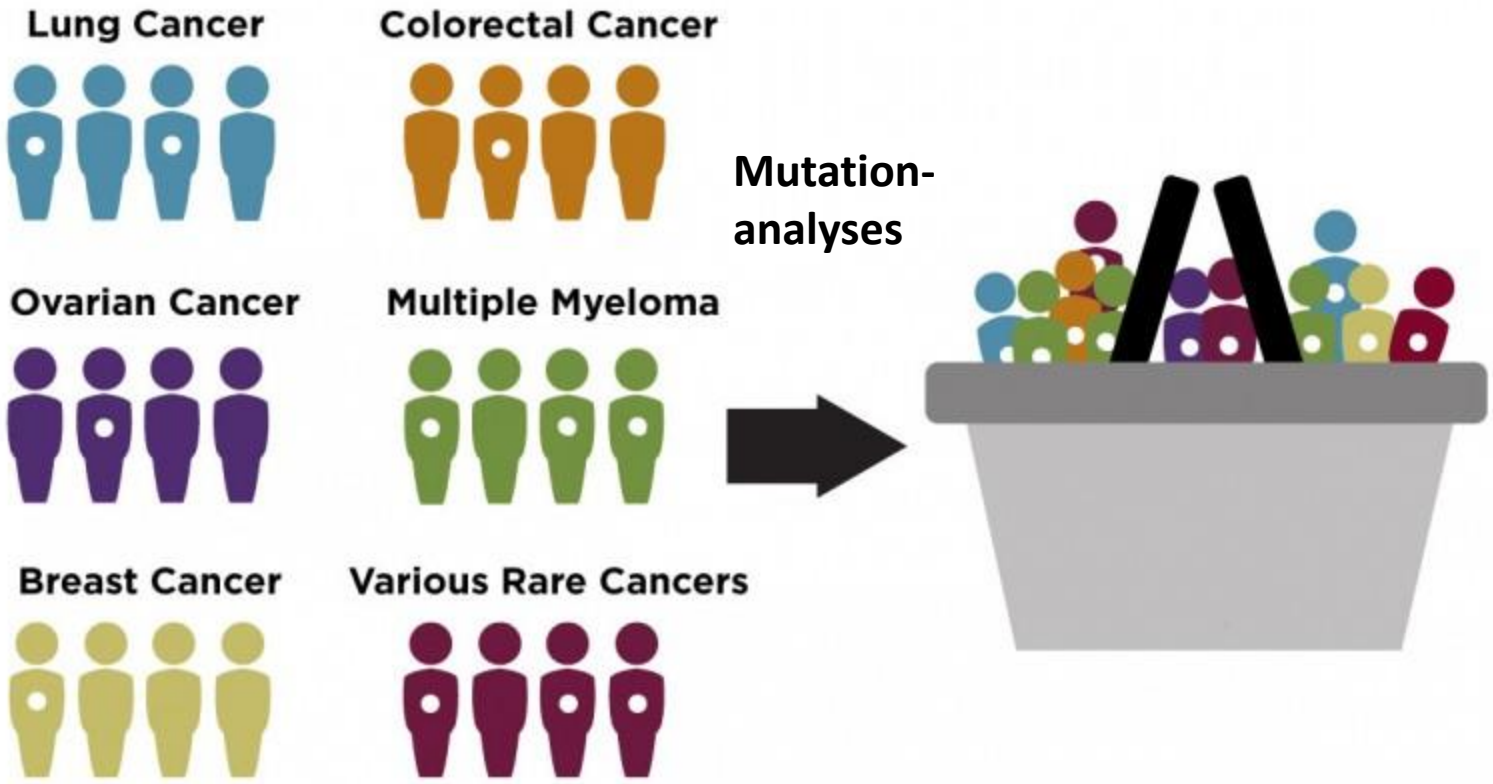
Types of Master Protocols.

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

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

Basket / Bucket trial design



2015: 1st publication of a basket trial (NEJM).

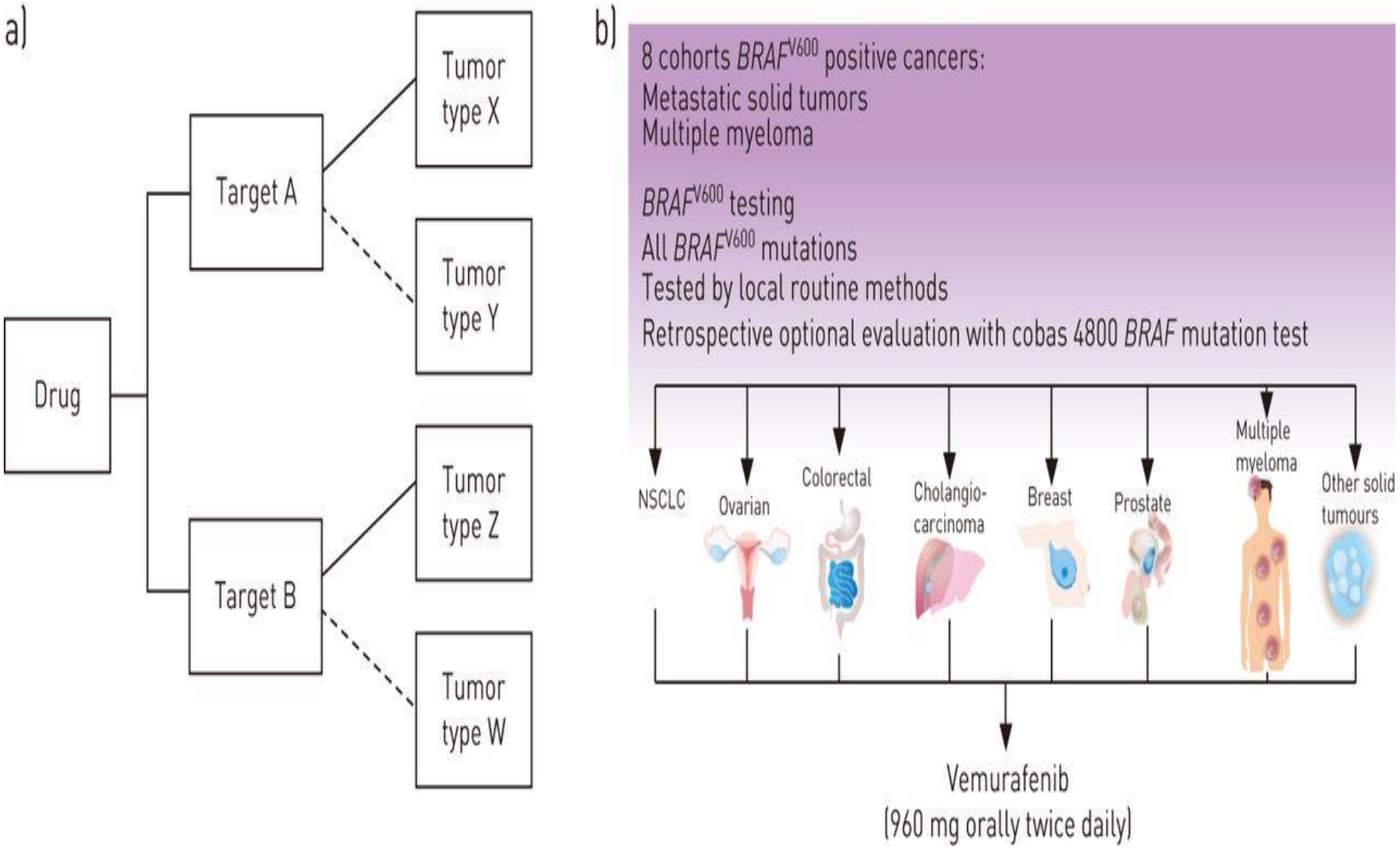
Basket / Bucket trial design

Objectives: Evaluation of a targeted therapy in pts. with genetically defined characteristics, independent of the disease / cancer type.

- Combinable with randomisation and prolongation of study cohorts*
- Allows for the inclusion of very rare diseases.
- Combinable with stopping rules à la phase II/III trials →* Adaptive Design

Example: Vemurafenib tested in 9 different cancers with BRAF V600-mutation.

Schematic example of a basket trial.

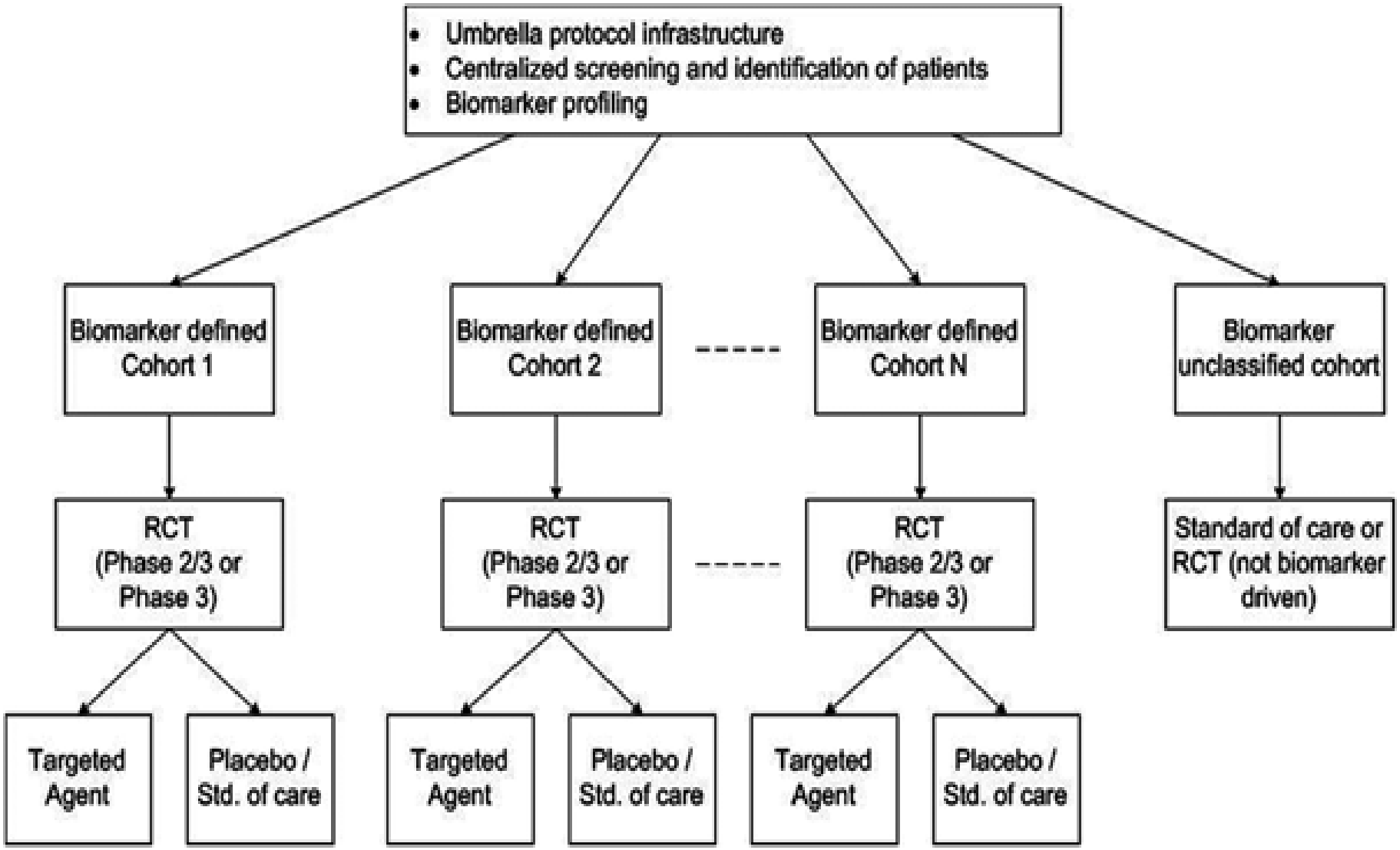


 Jessica Menis et al. Eur Respir Rev 2014;23:367-378

Basket / Bucket trial design

- One trial protocol only, but with complete sub-group protocols incl. eligibility criteria, stopping rules, risk-benefit assessement and informed consent material for each disease entity
- Valid biomarkers and cutpoints essential
- Targeted treatment may differ re efficacy & safety across diseases. -> no global analyses.
- No shared control group -> different diseases
- May be useful for phase I/II studies

Das Umbrella Trial Design



Mandrekar SJ et al. 2015 ASCO Educational Book e144

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Umbrella Design

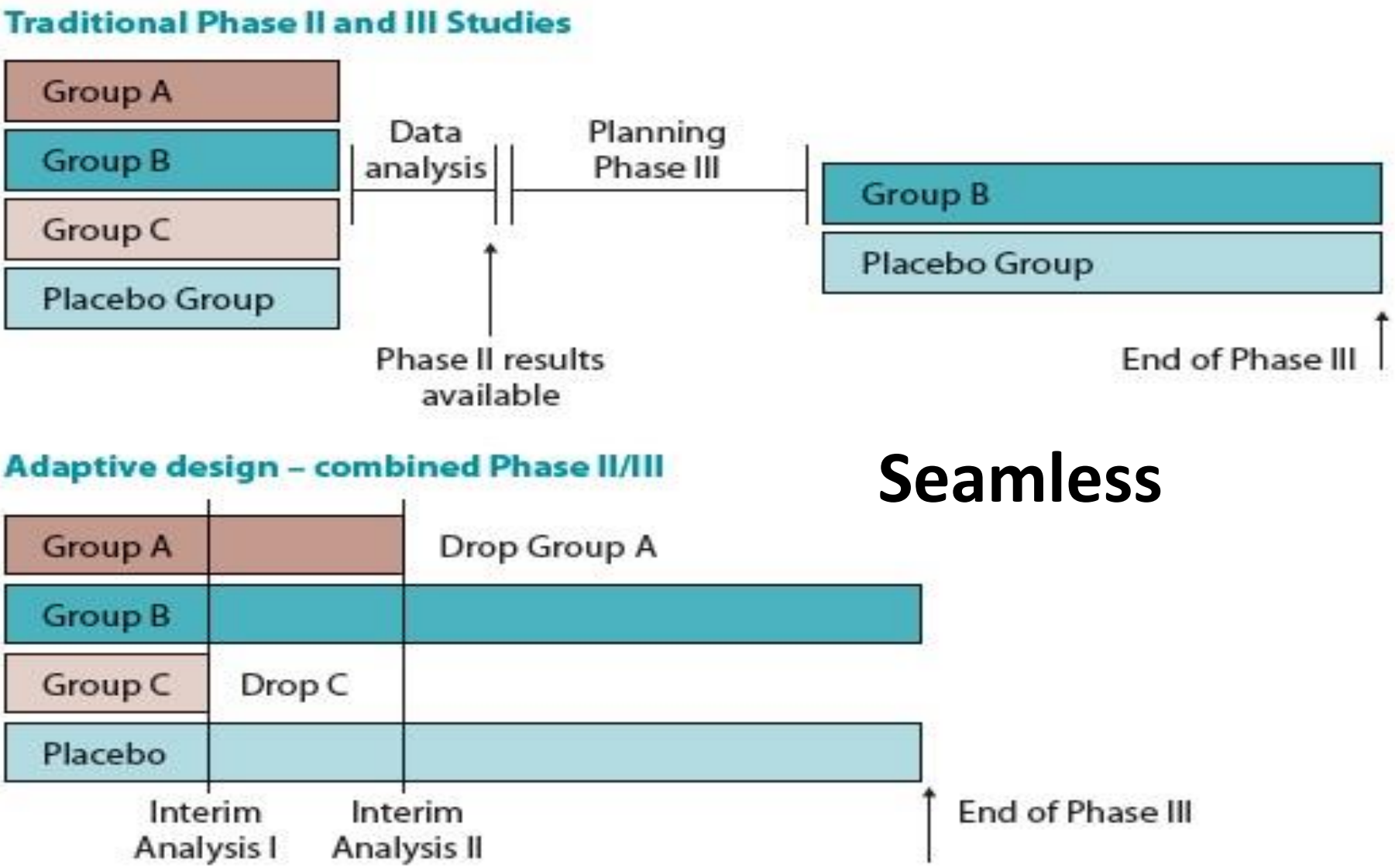
<u>Approach:</u> One disease gets molecularly analysed, each subtype receives a different targeted treatment, either in a cohort (phase I or II) or in a RCT (phase III)

- **One trial protocol for as many targeted treatment options as available.**
- **Suitable for all phases, flexibel for ADs; similar to an Enrichment-Design.**
- **Often used with surrogate endpoints only.**
- **Often control groups can be pooled.**
- **Advantages from a patients‘ and biometrical point of view.**

Master protocols - Interim result

- **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, coordiniation 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.**

Promise of Adaptive Designs (ADs) - Speed-up



Seamless

http://www.liftstream.com/blog/wp-content/uploads/2012/11/untitled.jpg

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 

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.

Inspection Order of Ethics-Committees

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

Adaptive Designs – Definition FDA

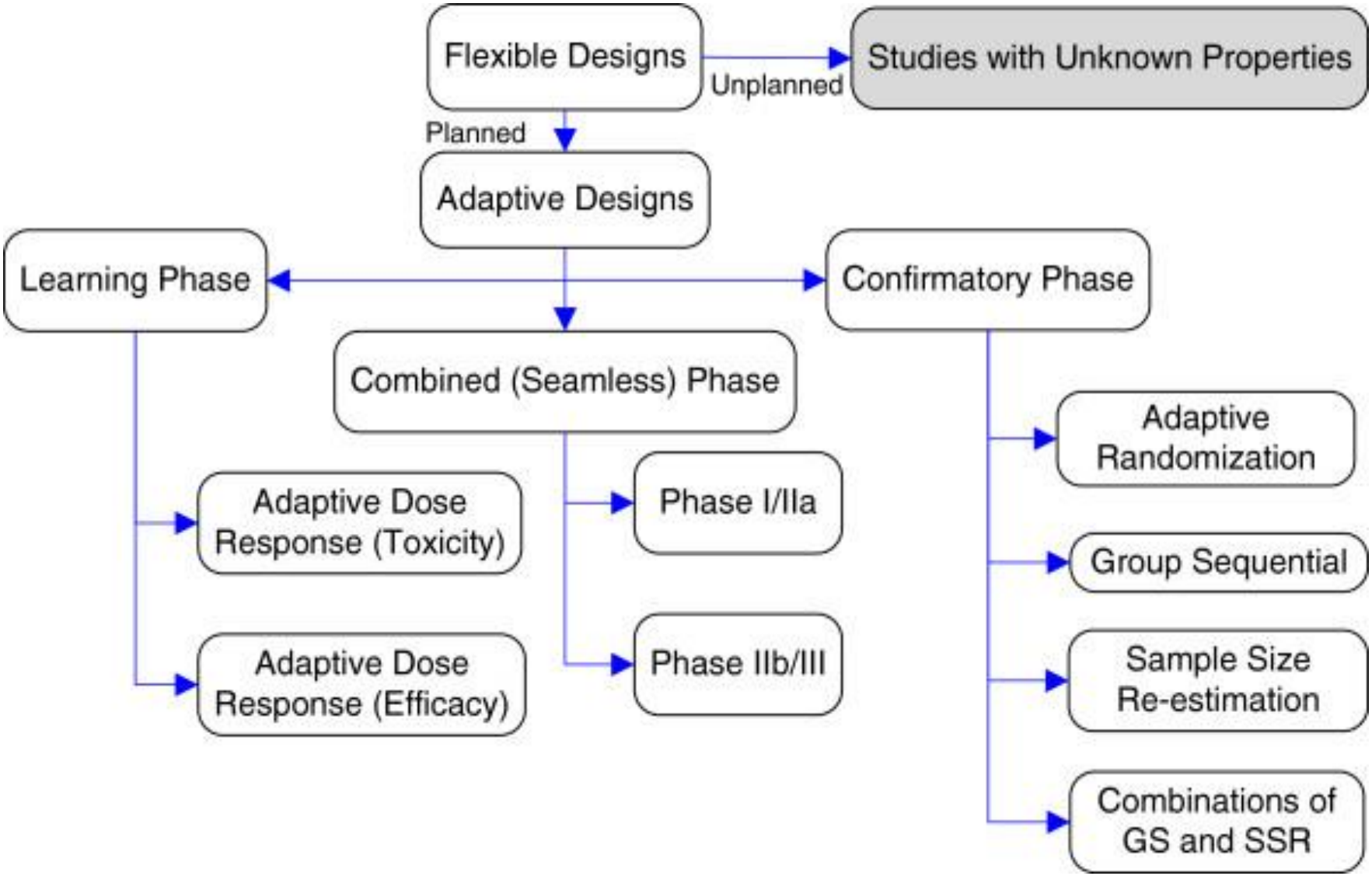
An ***adaptive design clinical study*** is defined as a study that includes a **prospectively planned** opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data) from subjects in the study. Analyses of the accumulating study data are performed at **prospectively planned** time-points within the study, can be performed in a fully blinded or in an unblinded manner, and can occur with or without formal statistical hypothesis testing.

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. This requirement ist stressed by CTFG 2019 too.***

Scheme of Adaptive Designs



Kairella JA et al. Trials 2012,13:145

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Adaptive Designs: Requirements

Any adaptations have to be *prospectively* defined and should be based on traceable blinded interim analysis only, otherwise the study cannot be considered as an *‚adequate and well-controlled effectiveness (A&WC) study‘* .

Even prospectively planned ADs may increase the risk of bias !

The FDA accepts, based on prospectively planned, blinded interim analyses, adaptations re

- the eligibility criteria
- the sample size*
- secondary endpoints without an association with efficacy parameters
- groupsequentiel 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

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 planned to be 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) ?

Ethics Committees Checklist

- Clear description and justification of CCT-design?
- Scientific integrity given? Prospectiveness?
- Quality of trial conduct and clinical feasibility ensured?
- Safety of trial subjects maintained?
- Data integrity maintained?
- Reassesment of benefit-risk balance at critical steps throughout clinical trial warranted?
- Companion diagnostics validated?
- Data transperency issues considered?

Ethics Committees Checklist

- Up to date informed consent material provided?
- DMC/DSMB with competent and independent members provided?

Practical Issues

- MPs ask for a central competent and powerfull 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 voluminess 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 offer intersting new concepts for clinical research.
- They are highly complex however and a challenge for all stakeholders.
- ADs increase the risk of bias.
- All adaptations have to be prespecified in the study protocol.
- It is not yet clear how the legal requirements re patient information can be properly met.
- When planning a MP/AD early scientific advice of EMA and competent REC is advised.

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