Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel
Federal Institute for Vaccines and Biomedicines

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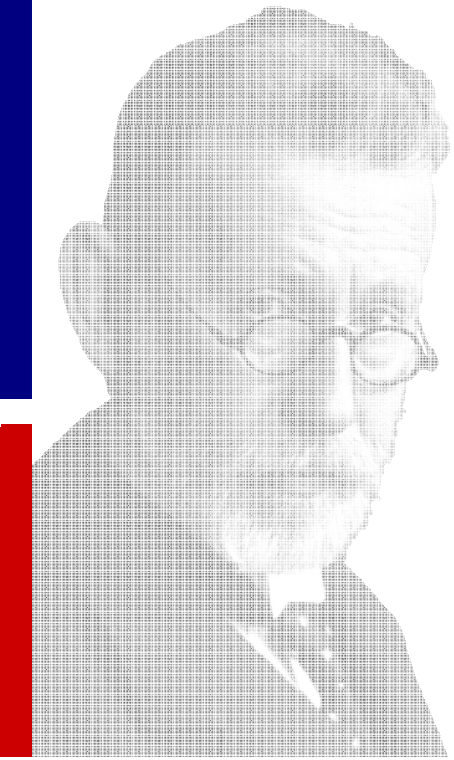


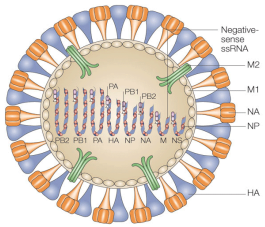
Clinical trial authorization
// challenges, complex study designs //

Benjamin Hofner, Brigitte Keller-Stanislawski, Elena Wolff-Holz,
Klaus Cichutek et al.

DGRA Annual Congress, 23 – 24 May 2019, 3.00 – 3.45 p.m.

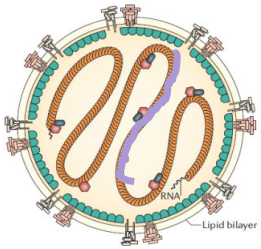
- Biomedicines, clinical trial authorization, national scientific advice, horizon scanning
- Challenges in first-in-human clinical trial authorization (CTA)
- Adaptive clinical trials
- Adaptive CTAs to Paul-Ehrlich-Institut (CTA)
- Some design-specific challenges
- Conclusions

pathogen

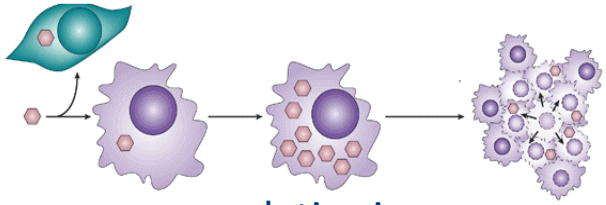


HA-, NA-, NP-Gene

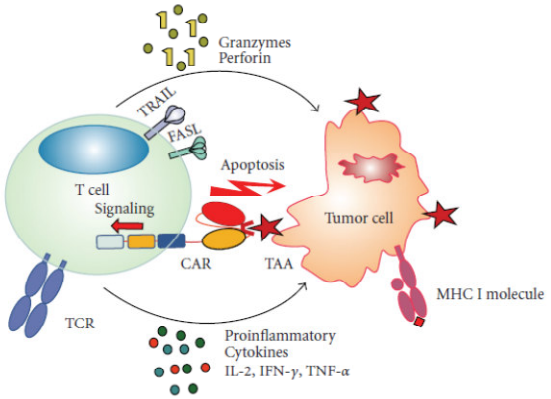
vaccine



vector vaccines



oncolytic viruses

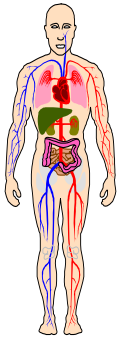


adoptive immunotherapy
in allergology and oncology

Regulation & Research

product type-specific know-how

monoclonal antibodies
in neurology, oncology (checkpoint inhibitors) and rheumatology



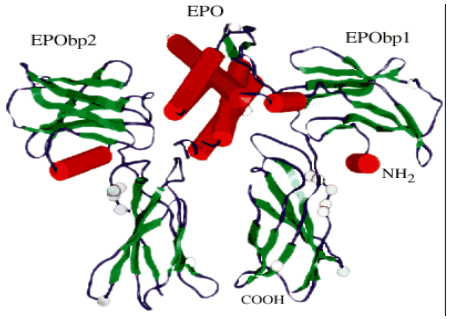
tumour sample

sequence expressed genome

identify individual mutations

RNA-Impfstoff

ATMPs and passively/actively personalised cancer immunotherapy



recombinant clotting factors, plasma-derived products

stem cell therapy
in hematology and tissue engineering

Standard clinical trial schedule

Stage of Development	Phase 1	Phase 2	Phase 3	Phase 4
End Point	Safety	Efficacy	Efficacy	Efficacy
Specific End Point	Safety Profile	Cardiac Output	Reduction in Mortality Rate	Reduction in Mortality Rate
Types of Studies	Different Indications; Single or Multiple Dose	Placebo Controlled; Dose Escalation	Placebo Controlled; Long Term Follow Up	Comparative; New Indications

- One medicine tested in one clinical indication

National scientific advice in preparation of clinical trials

- Germany is second in the world in hosting clinical trials
- Many clinical trials of biomedicines initiated by German and US Sponsors are carried out in the US and followed by Europe
  - Paul-Ehrlich-Institut satisfies many requests of these Sponsors for national scientific advice
- HMA agreed to pilot
  - a voluntary multi-national scientific advice
  - carried out by several member state medicines agencies together
  - on request of the Sponsor
  - similar to Voluntary Harmonisation Procedure for multi-national clinical trial authorisation in one step (apply at PEI)

German Research Foundation DFG

Replicability of results in medicine and biomedicine

Position Paper of the Working Group „Quality in Clinical Research“
of the DFG Senate Committee on Basic Issues in Clinical Research

- *The Lancet* „Increasing value, reducing waste“ initiated a discussion on quality of research as a basis for future product development.

- **Academic Institutions**: need to provide resources, basic infrastructures and time for an adequate management of their research data (continuity of personnel, attractive career options, education and advice).

- **Animal protection, ethics committees, regulatory agencies, data protection:** Further development of regulatory frameworks should keep in mind the importance of replicability and validation of scientific results.

- **Scientific journals, editors**: should allow publication of replication studies and negative results. Development of check lists and guidelines for validation and documentation of results should be promoted.

- **Scientific Organisations and the general public**: should acknowledge more realistically the potnetial of scientific results and knowledge (Erkenntnisgewinn) to cure human diseases. Over-interpretation of results cause pressure and inhibit careful research.

- **Funding agencies**
  - Regarding applications for research funding and their evaluation need for replicability and translational career key performance indicators should be taken into account.

// Challenges in first-in-human clinical trial authorisation //

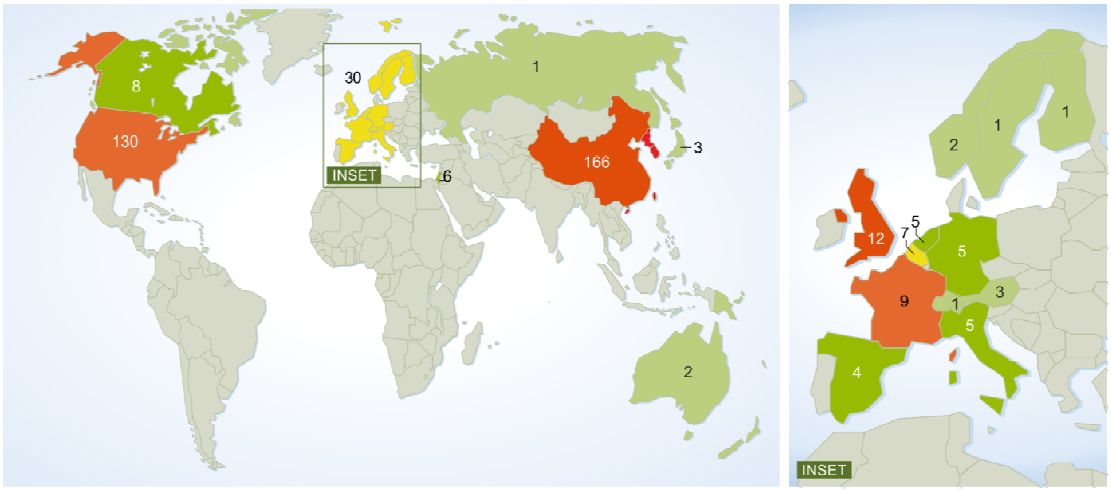
No. of CAR T cell clinical trials on the rise world-wide

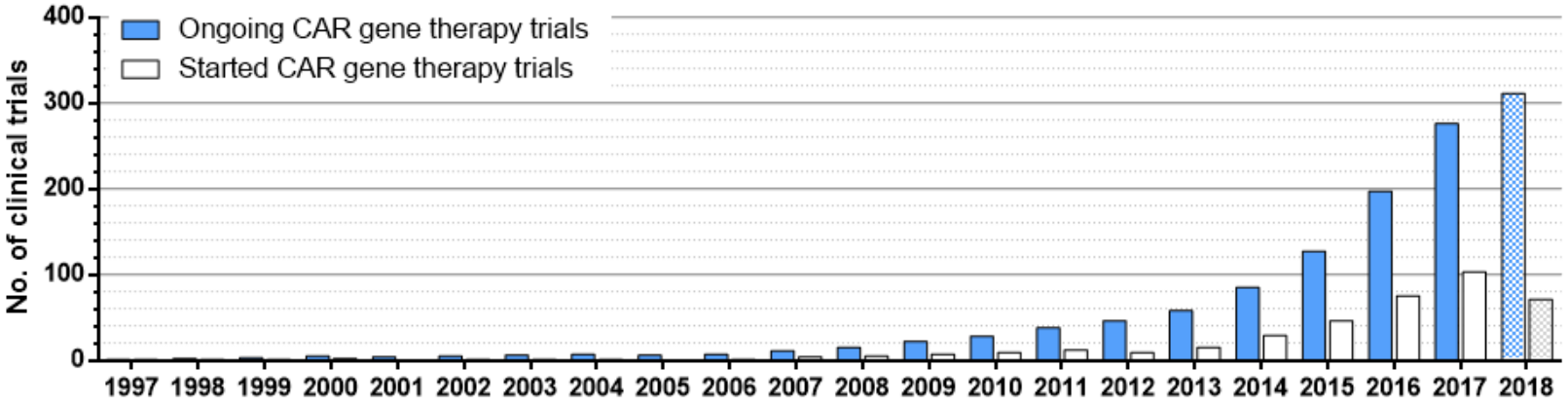
326 ongoing trials world wide ←w/o LFU→

- including 12 multi-national trials (≥2 countries)
- Europe is counted as one country
- for 4 trials no information on trial sites

28 registered trials in Europe

- including 9 multi-national trials (≥2 countries)
- 5 trials country not known
- at PEI 19 trials for DE are registered + 2 long-term follow-ups





Updated from:
Hartmann J, Schüßler-Lenz M, Bondanza A, Buchholz CJ, *EMBO Mol Med* , 8 2017.

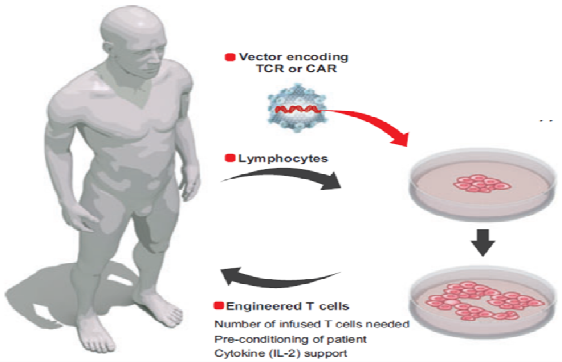
* For some trials information on start date is not included in the database

CAR T cell toxicities

Neurological events

Risk of leukapheresis

Risk of 2ndary malignancy?



Risks related to conditioning regimen

Risk of infections

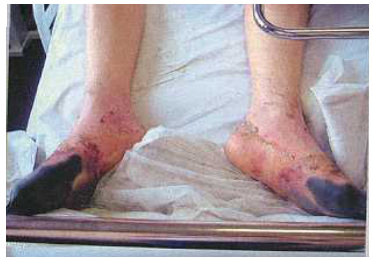
Risks related to the mechanism of action (e.g. cytokine release syndrome)

Prolonged cytopenias

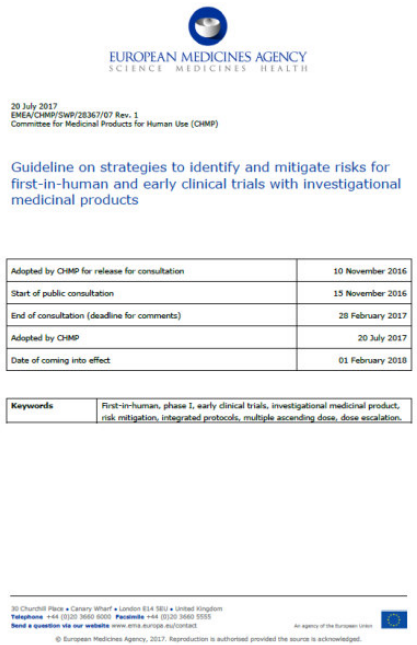
Hypogamma-globulinemia

Caroline Voltz, EMA
Martina Schüssler-Lenz

First-in-human clinical trial of CD28 super-agonistic antibody *'TGN1412'* in UK



www.pharmagossip.blogspot.com



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 July 2017
EMEA/CHMP/SWP/28367/07 Rev. 1
Committee for Medicinal Products for Human Use (CHMP)

Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products

Adopted by CHMP for release for consultation	10 November 2016
Start of public consultation	15 November 2016
End of consultation (deadline for comments)	28 February 2017
Adopted by CHMP	20 July 2017
Date of coming into effect	01 February 2018

Keywords	First-in-human, phase I, early clinical trials, investigational medicinal product, risk mitigation, integrated protocols, multiple ascending dose, dose escalation.

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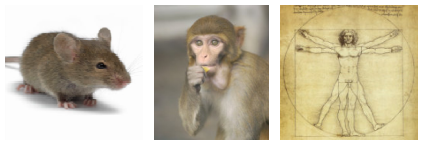
Send a question via our website www.ema.europa.eu/contact

An agency of the European Union

- Guideline prompted by occurrence of severe adverse reactions in the TGN1412 clinical trial in healthy volunteers in 2006
- Revision in 2017 after fatal adverse reactions in a trial in France
- Considerations on quality (potency, representativeness of material for non-clinical studies)
- Considerations on relevance of preclinical models
- Considerations on appropriate starting dose, dose escalation, multiple dosing
- Design considerations: choice of subjects, waiting times/staggered inclusion, integrated protocols, necessary safeguards when transitioning from single dose to multiple dose, stopping rules

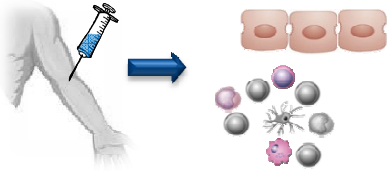
Regulatory research following the *'TGN1412'* FIH incident in UK

Predictive value of animal models?



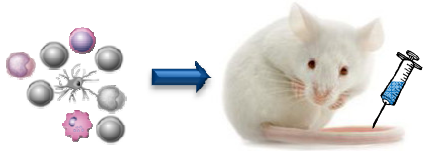
- Signaling in T cells from human and monkey origin differs (Waibler *et al*., PLoS One, 2008)
- *In vitro* method established to predict receptor occupancy (Waibler *et al*., JACI, 2008)

Molecular and cellular mechanisms?



- ICOS-LICOS interaction is critically involved in TGN1412-mediated T cell activation (Weißmüller *et al*., Blood 2012)

Novel animal models?



- TGN1412 induces lymphopenia and human cytokine release in a humanized mouse model (Weißmüller *et al*., PLoS One, 2016)

The role of Fc:FcR interaction?

- Strength of TGN1412:FcR interaction inversely correlates with FcR-mediated T cell effector function (Dudek *et al*., Eur J Immunol. 2019)

Therapeutic individualized tumour vaccines – actively personalized medicines

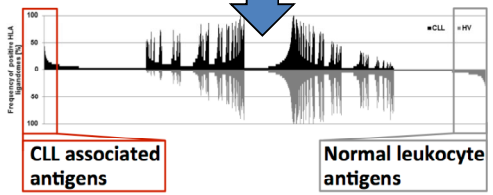
by **LC-MS/MS**

Proteomics

Bioinformatic analysis

Selection of peptides (***medicinal products***) relies on actual ***presentation of HLA ligands*** in patient tumour samples

HLA ligandome tumor tissue



Peptide Warehouse

off the shelf

Mutanome sequencing

- Prediction of patient-individual neo-expitopes
- Neo-Epitope selection and peptide design for manufacturing

Mutated Peptides

de novo **synthesis**

by **'epitope prediction'**

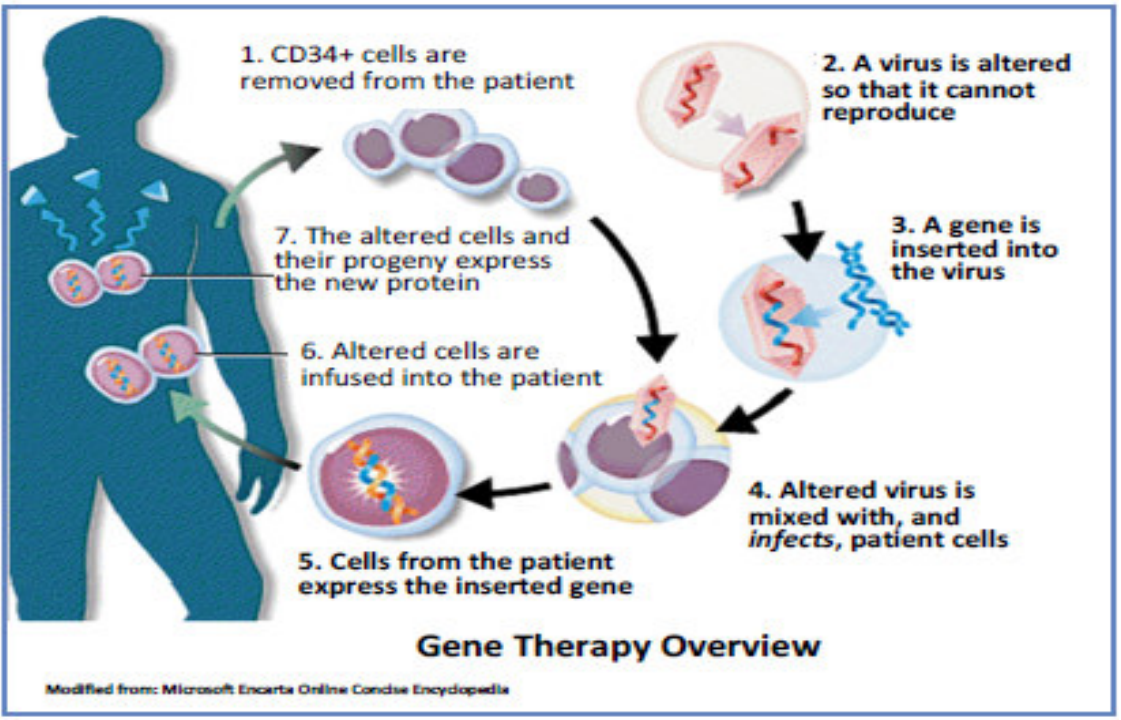
Genomics

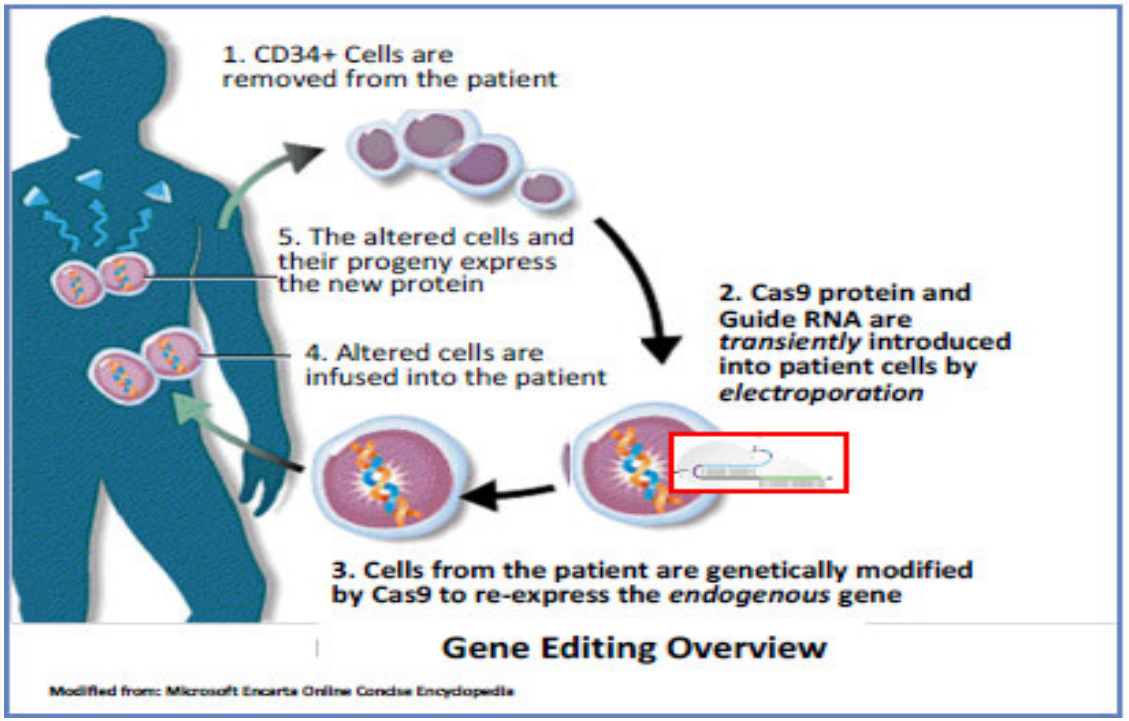
Bioinformatic Algorithms

Selection of individualised ***medicine*** entirely relies on **bioinformatic algorithms**

GAPVAC trial

Ex vivo gene editing using *'CRISPR/Cas'*





- *ex vivo* retroviral gene transfer into CD34-positive haematopoietic stem cells
- Strimvelis, ADA-SCID
- EU marketing authorisation in 2016

- *ex vivo* CRISPR/Cas9-modified CD34-positive haematopoietic stem cells
- indications β-thalassemia, sickle cell disease
- clinical trials authorised in EU/EEA member states

Horizon scanning:
genome editing using ‘CRISPR/Cas’ technology

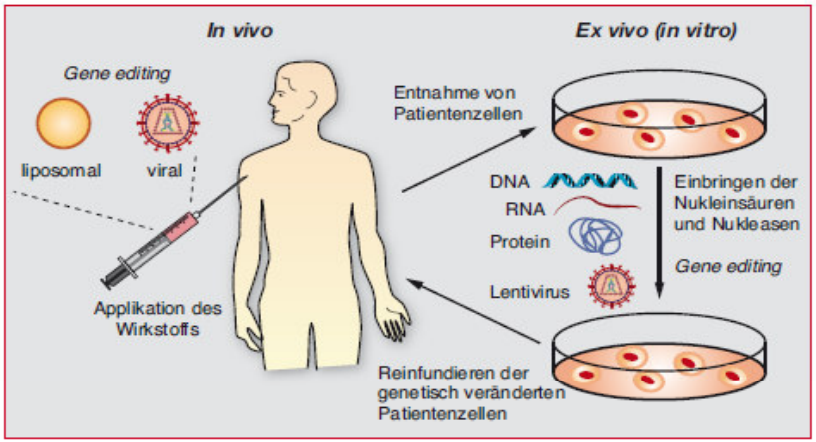


Abb. 2 Mögliche Therapie von Erkrankungen. *Bei der In-vivo-Methode wird dem Patienten das CRISPR/Cas-System in Form von Vektoren direkt appliziert. Diese Strategie setzt voraus, dass der Vektor mit den Komponenten des CRISPR/Cas-Systems die Zielzellen im Körper mit ausreichender Effektivität erreicht. Bei der Ex-vivo-Methode werden Zellen des Patienten isoliert und kurzzeitig in Kultur genommen. Dann werden die Zellen mit dem CRISPR/Cas-System genetisch modifiziert und dem Patienten re-infundiert.*

CRISPR/Cas-basierte Arzneimittel: Herausforderungen in der Regulation

CRISPR/Cas-based medicinal products: regulatory framework

Matthias Renner, Katrin Féchir, Juliane Rau, Silke Schüle, Martina Schüssler-Lenz, Zoltán Ivics

Abteilung Medizinische Biotechnologie, Paul-Ehrlich-Institut, Langen

EMA expert meeting on genome editing technologies used in medicinal product developments

Programme

18 October 2017
European Medicines Agency, London, United Kingdom

Meeting **room 3E**

Challenges reg. clinical trial authorisation by competent authority

- First-in-human studies pose risks
  - first human use of a new drug substance
  - known adverse reactions
  - unknown adverse reactions

- Biomedicines are complex
  - design
  - mechanism of action
  - manufacture
  - targets
  - clinical effects

- Common issues
  - suitability of non-clinical model
  - intrinsic toxicological properties of a drug substance
  - variability with actively personalized medicines (individual mixture)
  - on-target/off-tumour effects

// Adaptive and complex clinical trials //

Standard clinical trial schedule

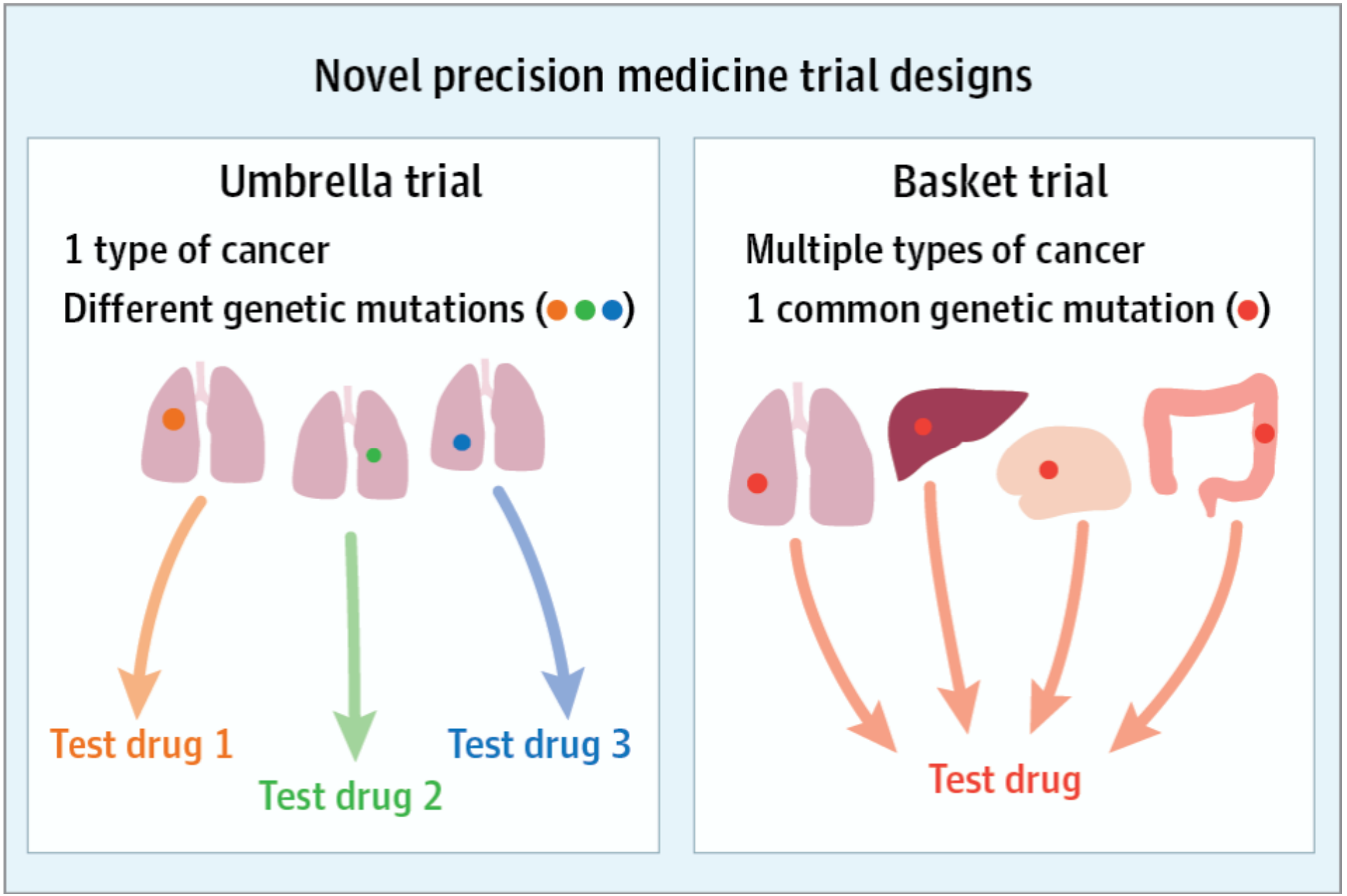
Stage of Development	Phase 1	Phase 2	Phase 3	Phase 4
End Point	Safety	Efficacy	Efficacy	Efficacy
Specific End Point	Safety Profile	Cardiac Output	Reduction in Mortality Rate	Reduction in Mortality Rate
Types of Studies	Different Indications; Single or Multiple Dose	Placebo Controlled; Dose Escalation	Placebo Controlled; Long Term Follow Up	Comparative; New Indications

- One medicine tested in one clinical indication

Adaptive clinical trials

- Basket and umbrella trials
- Adaptations of trial design based on interim analyses (platform trials/master protocols)
  - Learning in real time
  - More efficient use of resources (patients)
  - Speeding up clinical development
- Examples
  - Sample size adaptations (reduction or increase of sample size)
  - Continuing / closing of trial arms (interim analyses for futility / efficacy)
  - Seamless phase II/III design
  - Enrichment designs (e.g. adaptively enrich patients with specific biomarkers)
- **Issues**
  - High risk of bias and type 1 error inflation
  - Risk to overestimate effects

➢ Adaptive designs need to be **pre-defined in the protocol**


Novel precision medicine trial designs
Umbrella trial
1 type of cancer
Different genetic mutations (●●●)
Test drug 1
Test drug 2
Test drug 3
Basket trial
Multiple types of cancer
1 common genetic mutation (●)
Test drug

Key benefits of basket and umbrella clinical trials

If available at many cancer centers, umbrella and basket trials for molecular targets offer several major benefits for developing new treatment approaches:

- It is possible to identify options for small subgroups, perhaps even with a marker seen in only 1% or 2% of a broad cancer patient population.
- Patients and oncologists have an “actionable result” to suggest a plan of action when genetic testing panels report a rare mutation.
- Patients from many locations can participate in trials for their specific target without need to travel to distant sites.
- New treatments can be tested and potentially approved for commercial use faster.

Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials

February 2019

Clinical Trial Facilitation Group, Heads of Medicines Agencies (HMA)

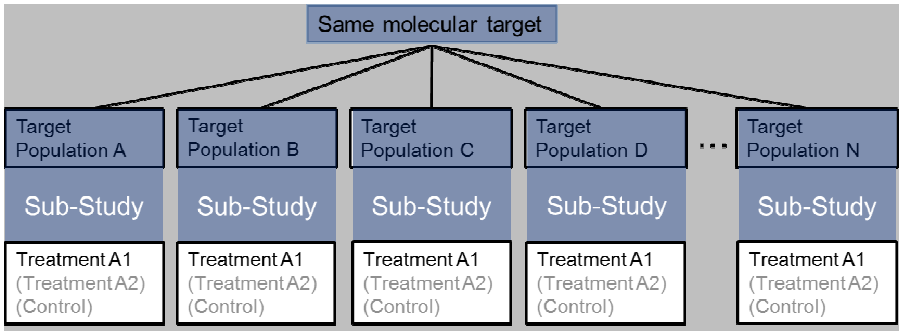
For the purpose of this guidance, a clinical trial is considered to have a complex clinical trial design if it has separate parts that could constitute individual clinical trials and/or is characterised by extensive prospective adaptations such as planned additions of new Investigational Medicinal Products (IMPs) or new target populations. In this document, the separate parts of a complex clinical trial design will be designated 'sub-protocols' and may be described by sponsors in separate protocols or within a common protocol as study cohorts or arms depending on the context.

The most common characteristic features of complex trial designs are thus sub-protocols, extensive adaptations and master protocols.

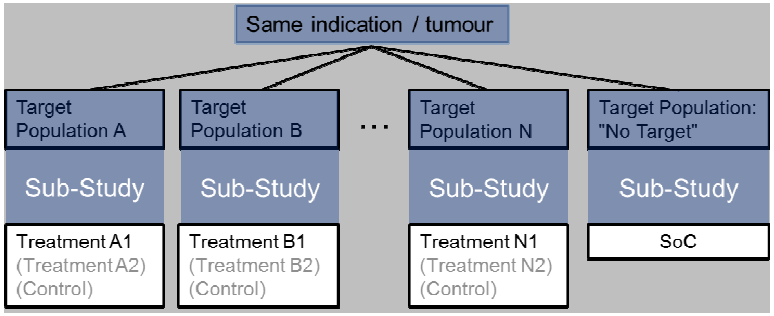
Common examples of complex clinical trial designs are basket, umbrella, and platform trials.

The EU/EEA competent authorities support the conduct of innovative design trials provided that each clinical trial addresses a specific scientific hypothesis and the sponsor has adequate oversight of the safety and integrity of the entire clinical trial.

Overview on general designs in master protocols

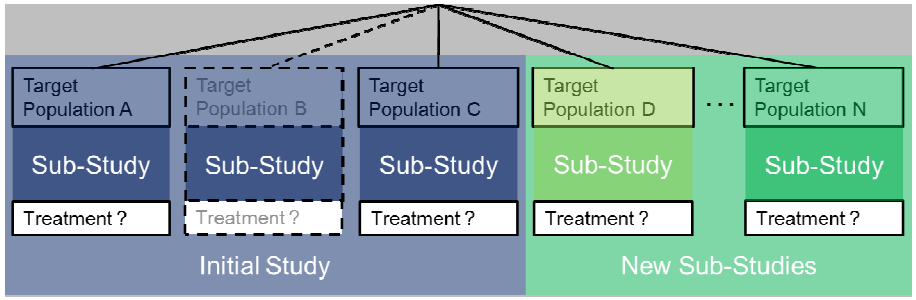


Basket trial
(same target, same treatment different indications)



Umbrella trial
(different targets, different treatments, same indication)

Platform trial/master protocol
(adaptive version of any of the above trials)



- Often trials do not fit exactly in any of the above schemes.
- Use design and analysis considerations to judge trial rather than names.

Current regulatory position on master protocols for complex clinical trials

Acceptability might depend on design issues, such as

- Phase of study (exploratory *vs* confirmatory)
- Rationale for master protocol (combined study *vs* a series of studies)
- Study design (dependent *vs* independent sub-studies)
- Planned analyses (pooled analysis *vs* separate analyses)
- Rationale for analyses (common indication *vs* separate indications)
- Adaptive design (adaptive *vs* fixed design; pre-specified *vs* ad-hoc; type of adaptions)

Important considerations

- Master protocols cannot be used to **lower regulatory standards**
  - Strength of pivotal evidence needs to be the same as with “regular” trials in the same indication one or two phase 3 studies, convincing statistically significant efficacy outcome

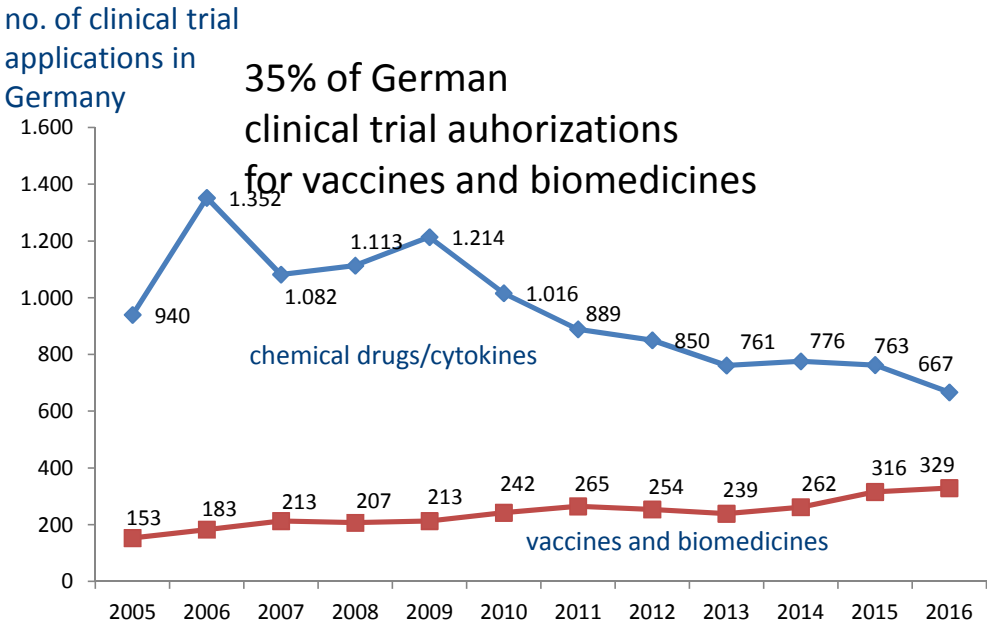
- Master protocols cannot be used to **reduce contact with regulators**
  - Initiation of new sub-trials must be submitted to NCAs[1)],
    - either as new protocol linked to the master protocol
    - or as substantial amendment
  - Seamless designs cannot be approved as a whole; Sponsors must provide a substantial amendment after first phase to update B/R

[1)]National agencies (NCAs) are directly responsible for the authorisation of clinical trials; Approval of marketing authorization applications usually centralised via EMA

// Current situation in clinical trial authorisation at Paul-Ehrlich-Institut (CTA) //

Current situation at Paul-Ehrlich-Institut

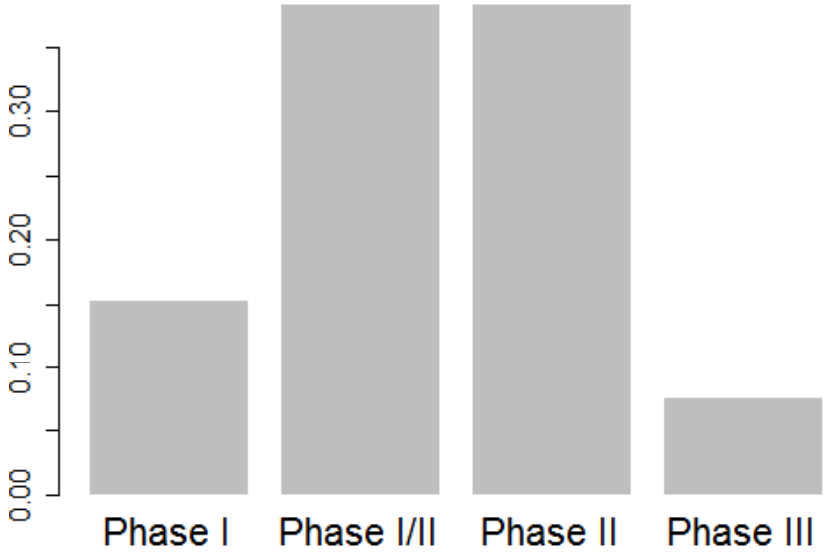
- Approximately 2 master protocols per months are submitted to PEI for CTA[1)]
  - 26 in 12.5 months (= since we started counting prospectively)
  - Per month we receive approx. 40 to 50 CTAs and resp. amendments in total.
  - ➢ Approx. 5% are master protocols (basket, umbrella or platform designed studies).



[1)]National medicines agencies (NCAs) are directly responsible for the authorisation of clinical trials;
evaluation of marketing authorisation applications usually via the centralised procedure coordinated by EMA;
marketing authorization granted by the European Commission.

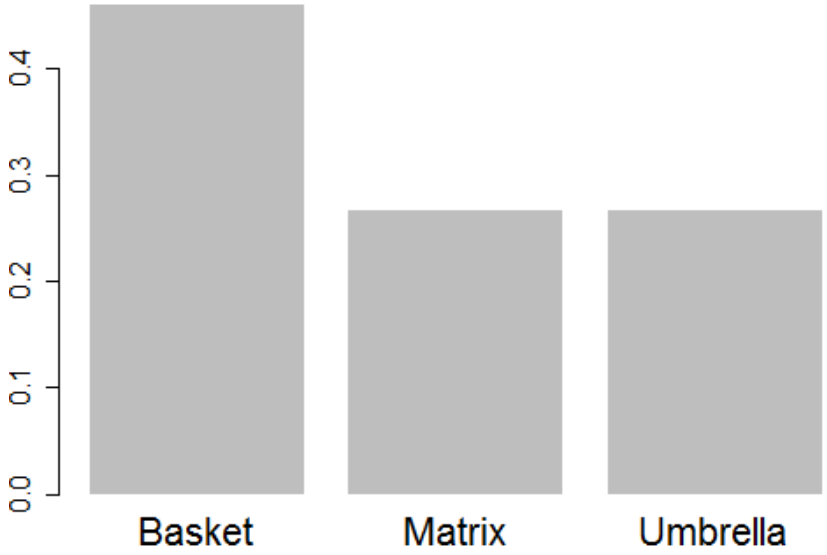
Types of master protocols authorised by PEI

Trial phase



- Mostly early phase trials
- Note that the fraction of pivotal trials might be higher than ~8%
  - see e.g. Keytruda in MSI-high/dMMR patients which received MA based on pooled trial results ("basket type") from uncontrolled Phase II data by FDA

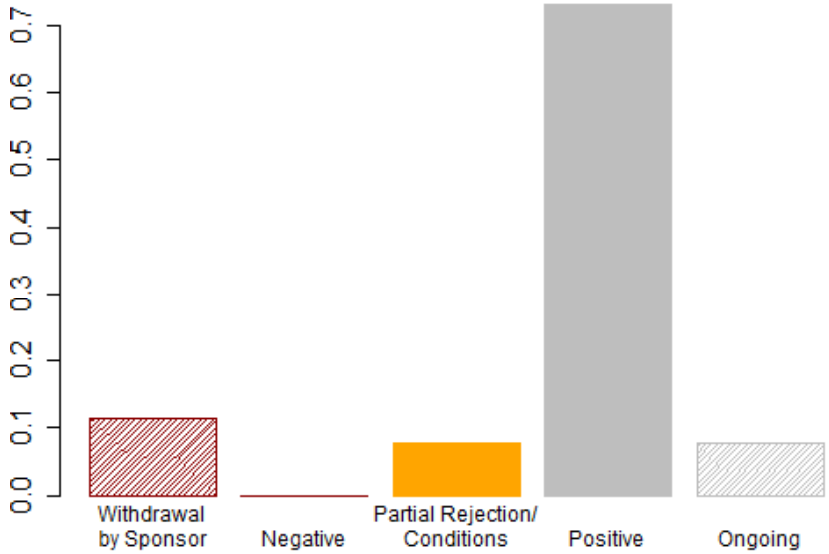
Type of trial



- Matrix trial = multiple indications, multiple treatments
- Some of the trials plan for modifications / new sub-studies / new study arms
  - so-called platform trials

Outcome of clinical trial applications with master protocols at PEI

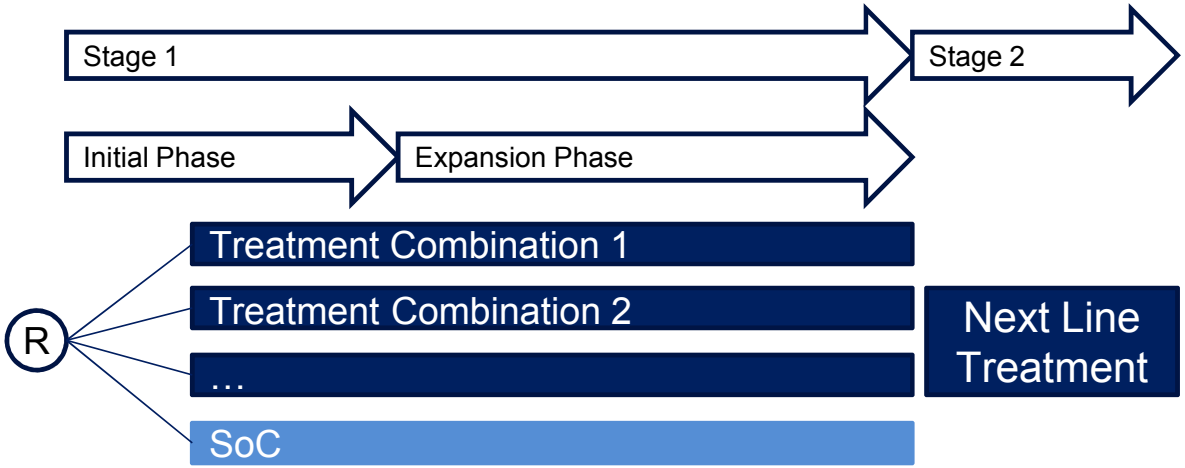
Outcome of clinical trial applications



- Most trials are authorized, some with conditions or partial rejections.
- Around 10% of the trial applications were withdrawn by the Sponsor.

Example 1

Randomised umbrella trial

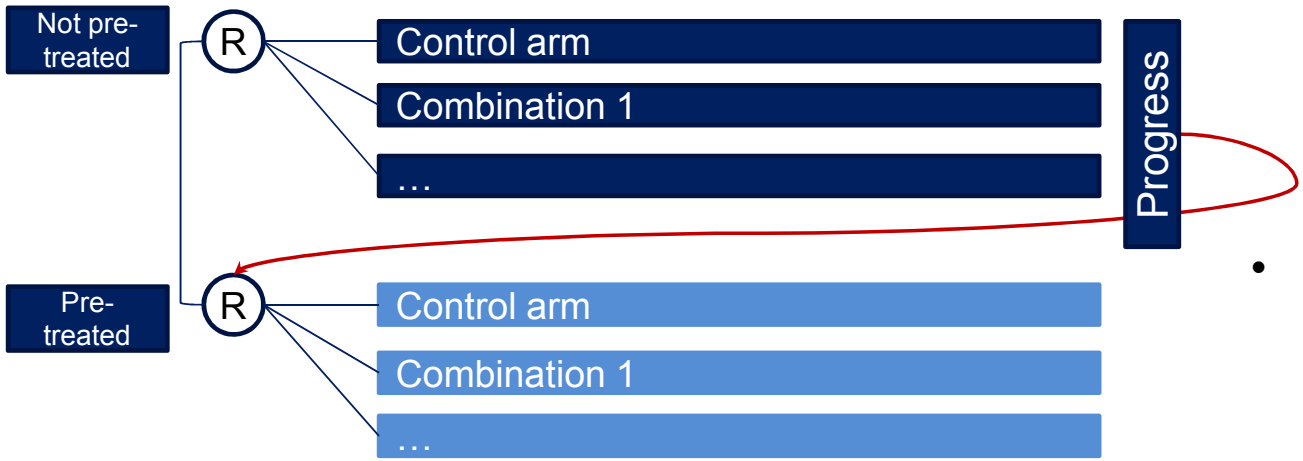


- Disease progression in Stage 1 > new treatment in Stage 2 (higher no. of participants, next-line treatments)
- DMC/DSMB is implemented to oversee the data quality/safety of the study
- Global in-/exclusion criteria
  + specific exclusion criteria exist for all study arms (but Standard of Care (SoC))
  - i.e., at randomisation an arm will be removed from the list of potential arms for that patient if exclusion criteria for a specific arm are met

Example 2

“Real” complex clinical trial using a master protocol

- The Sponsor proposes a Phase II study for oncologic indications
- Currently, one indication (phenotypically/histologically defined cancer) under investigation
- Two cohorts depending on pre-treatment with targeted therapies
- Sub-studies might have different in-/exclusion criteria



- Sub-studies are submitted as separate protocols

- Overarching statistical analysis plan and study design defined within master protocol
- Primary analysis:
  - separate analyses for each of the treatment arms
  - futility / efficacy boundaries depend on cohort (but not on treatment)
- Relative benefits (to control arm and among active arms) will be additionally assessed for decision-making

Summary of examples

- A wide variety of trial designs and analysis approaches exists under the label of master protocols
  - Umbrella
  - Basket
  - Platform
  - Examples 1-3 show further advanced adaptations

- “Master protocol”-like designs exist longer than the advent of corresponding terms and research (but were of course not called that way)

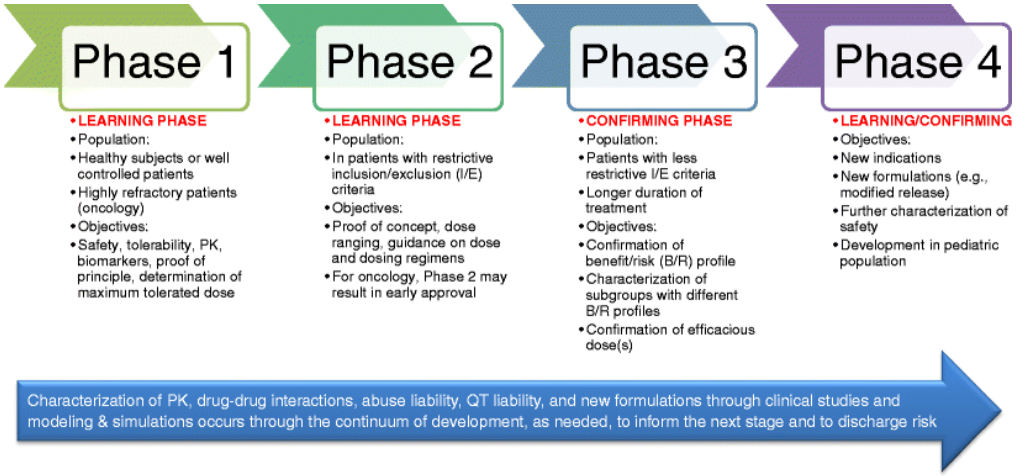
- **Cave:** Especially in orphan indications, the phase of study does not necessarily translate into its purpose
  - Phase I or II can be pivotal!

- **Cave:** Master protocols are the exception, not the norm

// Conclusions //

Further regulatory challenges in the conduct of adaptive clinical trials

- Sufficient characterisation and validation of biomarkers
  - Crucial even in early phases



- Complexity of study (negatively) impacts, e.g.,
  - patient information and informed consent
  - logistics
  - legal aspects
- Conduct of study
  - DMC / DSMB are important (irrespective of study phase)
  - Changes in ongoing study need to be approved by NCAs
  - Initiation of next phase (e.g. in seamless designs) needs to be approved by NCAs (via substantial amendment)
  - Whole study will be stopped if issues in one arm arise
- Risk of never ending studies
  - End of study must be pre-specified within the protocol

Take-home messages reg. adaptive/complex clinical trials

- Of note, discussion on adaptive trial designs is an *ongoing discussion*.
- Sound planning and scientific rationale required
- Master protocols are generally (more) acceptable for *exploratory studies*
  - ➢ Possibly acceptable as pivotal study if T1E is adequately controlled
- Pre-specification of possible adaptions helps to maintain study integrity, validity and T1E control
  - Data driven ad-hoc changes are considered problematic
- Consider existing EMA guidelines
  - Reflection paper on **adaptive clinical trials** (CHMP/EWP/2459/02)
  - Guideline on **subgroups** (EMA/CHMP/539146/2013)
  - Guideline on **multiplicity** (EMA/CHMP/44762/2017)
  - (Specific guidelines and position papers are in preparation)
- Especially for *confirmatory trials* scientific advice is highly recommended.

Acknowledgements

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- BfArM
  - Norbert Benda
- EMA Biostatistics Working Party "*Task force on master protocols*"
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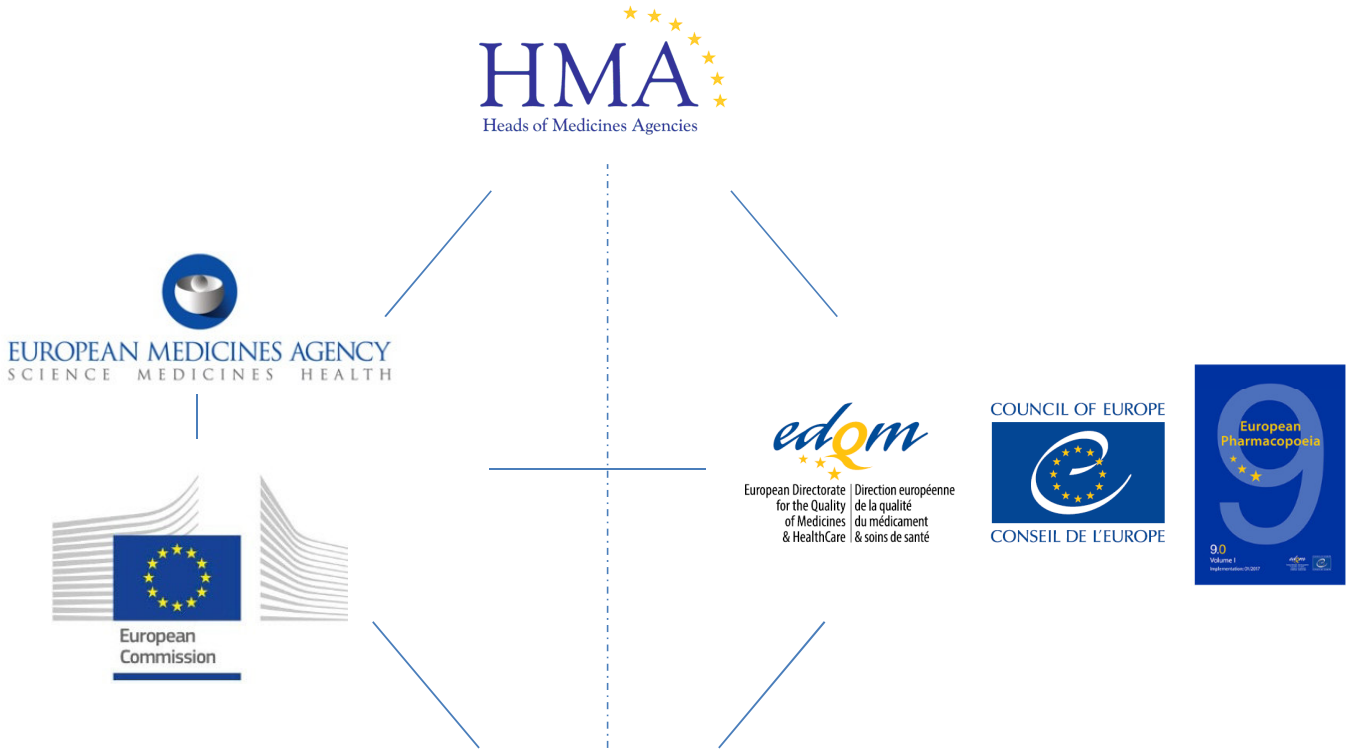
Medicines agencies regulate medicines in Europe



National competent authorities regulating medicines in Europe

Back-up slides


Questions?

General recommendations for applicants

- Provide sound scientific (and/or operational) rationale for master protocol
- Identify possible issues
- Pre-specify solutions within protocol, e.g.
  - ✓ provide operational measures to allow a safe and GCP-conform conduct of study
  - ✓ install a DMC/DSMB
  - ✓ pre-specify possible adaptions of the study design
  - ✓ pre-specify and discuss T1E control
  - ✓ pre-specify and discuss measures to prevent bias

Philosophy of the Paul-Ehrlich-Institut since 1896:

Evaluation of medicines & research

Founding director of todays Paul-Ehrlich-Institut
Nobel laureate Paul Ehrlich

Nobel price in Physiology & Medicine 1908

Retrieval of Diphtheria serum

Staining of tissues and cells:

- Organ-specific therapy
  => Medicines as Magic Bullets

Basic science:

- Founder of nowadays immunology
  => side-chain theory – formation of antibodies

Development of medicines:

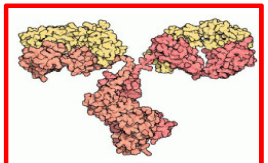
- Chemotherapy of infectious disease (before antibiotics)
  (Syphilis, Malaria, sleeping sickness)
  => Salvarsan

Experimental testing of medicines:

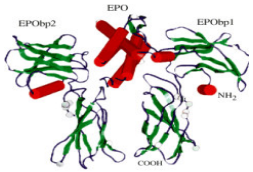
- Laboratory testing of efficacy correlates
  => Potency assay of diphtheria antisera

Paul-Ehrlich-Institut
Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel

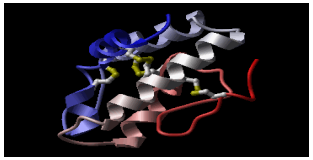
Antikörper, Proteine und Allergene



Antikörper und Sera



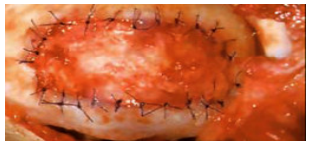
Gerinnungs-faktoren



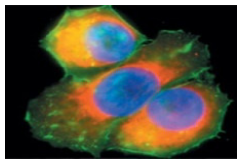
Allergene

Stammzellen, Gen- und Zellktherapeutika

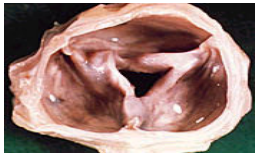
Transfusionsmedizin, haem. Stammzell-transplantation



Tissue Engineering-Produkte



Zell & Gentherapeutika



Gewebe-zubereitungen

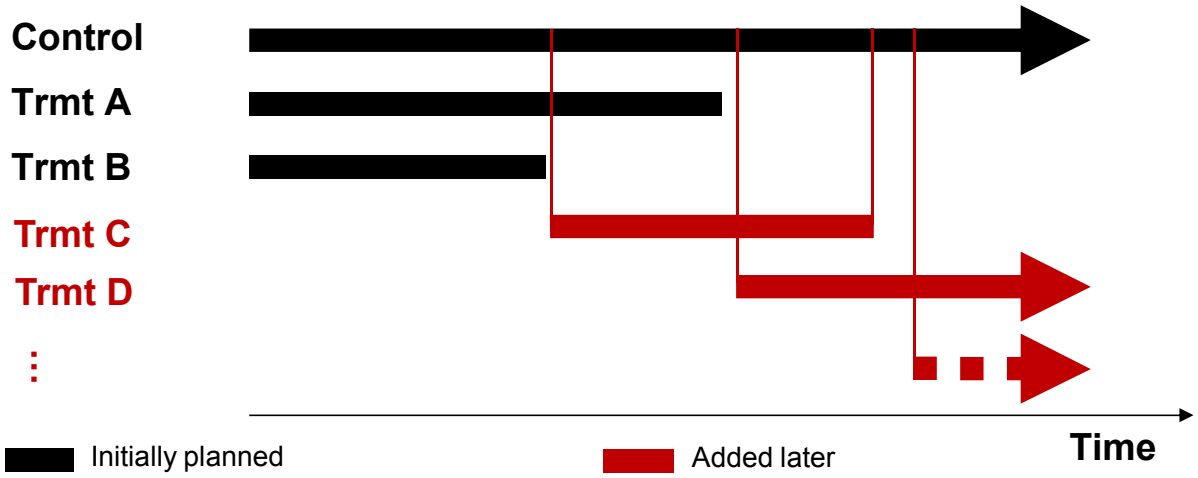
Impfstoffe

Impfstoffe (human & vet).

Vektor- & DNA/RNA-Impfstoffe

Shared control arm (especially in umbrella trials)

- How can we define a relevant control group?



  - Preferably use separate control arms per sub-study
  - If using a shared control,
    - use *concurrent* controls and
    - use only controls which *would have been eligible for the treatment arm*.
  - Pooling controls should be reflected carefully!

- Sufficient characterisation and validation of biomarkers
  - Crucial even in early phases
- Complexity of study (negatively) impacts, e.g.,
  - patient information and informed consent
  - logistics
  - legal aspects
- Conduct of study
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// Some design-specific challenges //

Pooling and transfer of evidence (especially in basket trials)

- Clinical rationale for pooling
  - is strongly required, at least if primary endpoint is based on pooled population
- Grounds for pooling might be challenged
  - Same prognosis?
  - Same effect size / homogenous effect in all sub-studies?
  - Same SOC / treatment possible in control arm?
  - Same effect with control?
- In general, pooling can be envisaged as supportive / exploratory analysis but might be difficult to justify as primary analysis.
- Same considerations apply for transfer of evidence (“borrowing”)

Overlapping target populations (especially in umbrella trials)

- Regulatory decisions (positive opinion reg. MA) are complicated if different molecular targets expressed in a patient
- E.g. in umbrella trials when patients express multiple biomarkers, allocation to sub-studies not uniquely defined
- ➢ If biomarker distribution in sub-study does not reflect population prevalence, bias might occur (see issues with pooling), e.g., due to
  - different prognoses or
  - different treatment effects

Example 3

Phase III basket trial

- The Sponsor proposes a Phase III study for an oncologic indication.
- The IMP is a monoclonal antibody targeted to PD-L1.
- Two independent cohorts are planned based on eligibility of backbone therapy

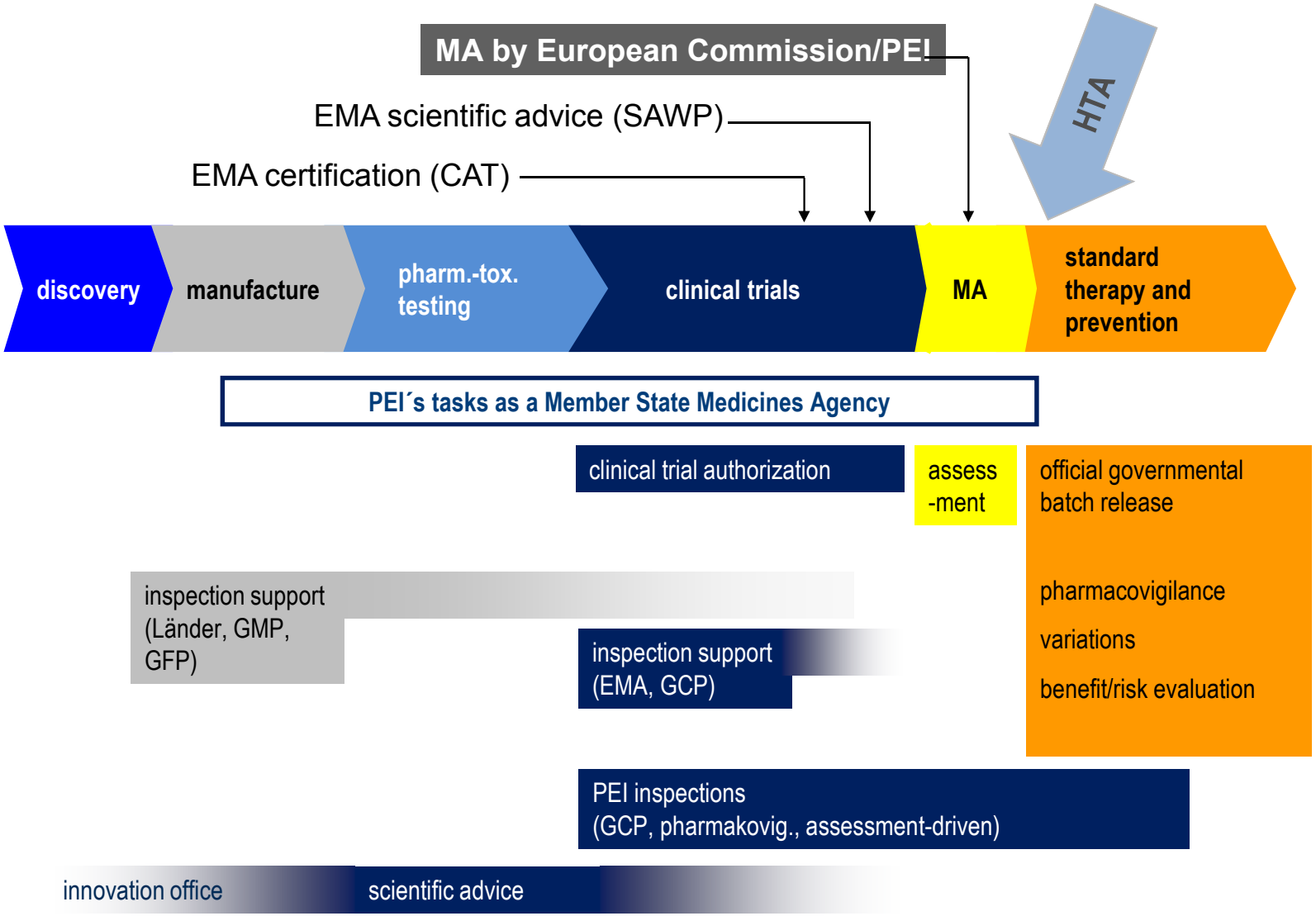
- Randomization is done per cohort (using the same methods).
- Analyses are (almost) identical for both cohorts but are conducted strictly separate with separate (but identical) objectives and hypotheses.
- Importantly, the Sponsor plans to use a separate significance level of $\alpha = 0.05$ (two-sided) for each of the cohorts.

➢ The Sponsor does not call this study a basket trial but all statistical and design elements equal a basket trial.

➢ Hence, one can conclude that this is a basket trial.

✓ It would be acceptable to conduct separate studies for each of the cohorts *or,* as done here, to use separate T1E control.

Regulatory support of medicines development



Current regulatory position on master protocols

Acceptability might depend on design issues, such as

- Phase of study (exploratory *vs* confirmatory): more likely acceptable in exploratory phase
- Rationale for master protocol (combined study *vs* a series of studies):
  acceptable if rationale for carrying out a combined study is convincing (e.g. identical target screening method such as NGS, identical methods of sample analysis from patients, etc.)
- Study design (dependent *vs* independent sub-studies):
  statistical analysis adequate to avoid type 1 error or bias
- Planned analyses (pooled analysis *vs* separate analyses)
- Rationale for analyses (common indication *vs* separate indications)
- Adaptive design (adaptive *vs* fixed design; pre-specified *vs* ad-hoc; type of adaptions)