EURORDIS
Rare Diseases Europe

Session 2
Methodological principles

How to conduct a clinical trial

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CONTENTS

- The “Gold standard” – randomised, controlled trial (RCT)
- Planning and designing clinical trials
- Study protocol
- Non-standard situations (orphan and paediatric)

RANDOMISATION

- Study participants are identified based on clear criteria defined in advance (screening)
- Participants fulfilling study criteria are divided in (allocated to) treatment groups randomly
  - Example: one computerised system – interactive phone-based mechanism
- Neither participants nor study investigators can influence treatment allocation

ADVANTAGES OF RANDOMISATION

- Avoids selection-based bias (systematic error) – possibility that treatment outcome is influenced by selection
  - e.g. less severely affected patients receive well-known "control" therapy
- Makes sure that treatment groups within a clinical trial are balanced (similar) and that only the treatment is different

ADVANTAGES OF RANDOMISATION

- Randomisation may take account of important factors affecting treatment outcome, e.g. Risk factors, to make sure groups will be balanced
  - Stratified randomisation – e.g. Strata “smoker”, “non-smoker”
- If in spite of randomisation there are differences between treatment groups, these are easier to account for in data analysis
  - e.g. Mean age higher in one group – “imbalance”

DISADVANTAGES?

- Randomisation does not guarantee that the study setting is free from bias, particularly if
  - The participant, the investigator or both know what treatment the individual will receive (open-label study) this can affect
    - Treatment compliance
    - Receiving other treatments
    - Dropping out of study
    - Adverse events – adverse reactions
    - Subjective evaluation of outcomes
  - **Studies should be conducted ”double-blind” whenever possible**

Non-standard situations

- Conventional and unconventional development
- Orphan medicinal products for rare diseases
- Medicines for use in children
  - Minimise exposure to placebo
  - Minimise exposure to potentially ineffective or harmful therapy
- CHMP guideline on clinical trials in small populations (CHMP/EWP/83561)
- Note for guidance on clinical investigation of medicinal products in the paediatric population (CPMP/ICH/2711/99)

CONTROLLED

- Control group is a “yardstick” against which efficacy and safety of experimental therapy can be evaluated
- Control treatment (comparator) may be
  - Placebo
  - Standard care + placebo
  - Best supportive care
  - Established therapy – authorised or not authorised, but widely known and used

BLINDING

- Decreases risk of bias resulting from knowledge of treatment assignment
- Single-blind
  - e.g. Infusion treatment: patient and nurse/pharmacist know which treatment is given
  - Investigator blinded to treatment
- Double-blind
- Double-dummy

BLINDING

- Blinded central adjudication committee
  - Verifies outcome, e.g. Tumour response, myocardial infarction
- Frequent and distinct undesirable effects may break blind
- Independent data monitoring committee (IDMC/DSMB) can have access to unblinded data
  - Safety monitoring
  - Interim analysis – efficacy, safety
    - Can recommend early study closure

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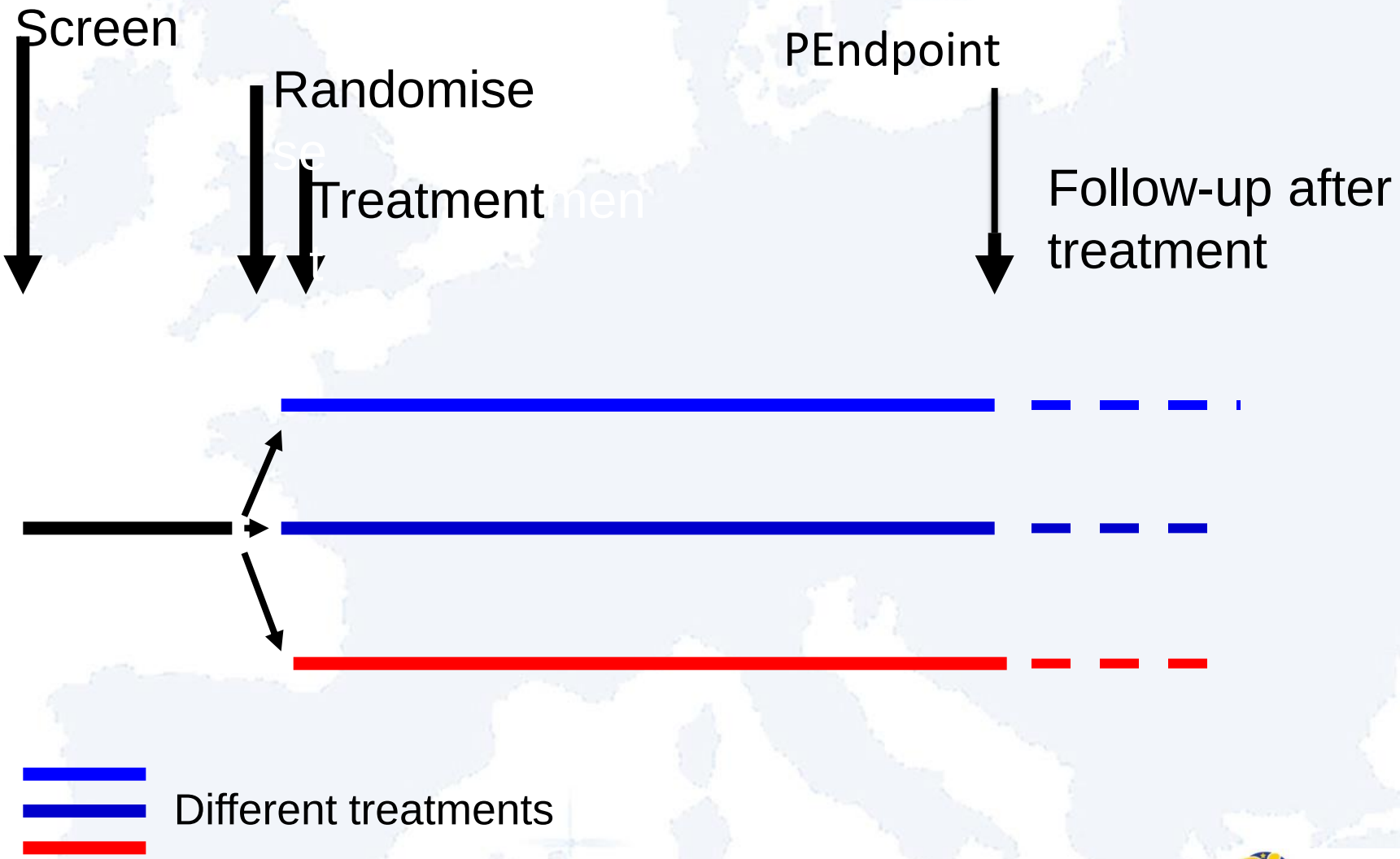
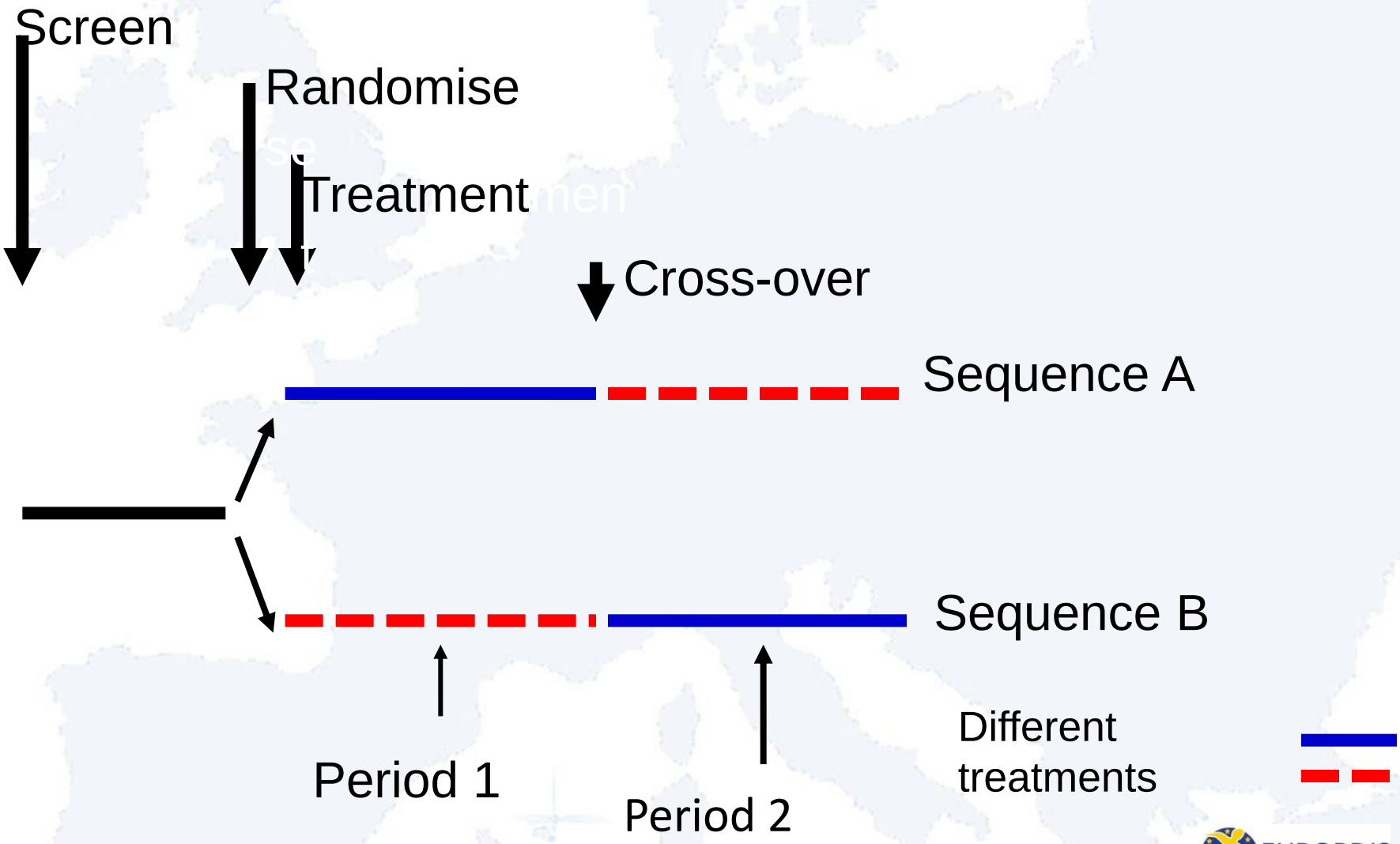
PARALLEL GROUPS DESIGN



CROSS-OVER DESIGN (2 X 2)



STUDY PROTOCOL

- Study “cookbook”
- Protocol amendments – substantial/non-substantial
- Protocol adherence – protocol violation
- Describes
  - Study objectives – primary and secondary
  - Study design
  - Treatments and procedures
  - Number of subjects
  - Inclusion and exclusion criteria

STUDY PROTOCOL

- Describes
  - Outcome measures/endpoints – primary and secondary
    - Primary measure decisive for interpretation of study
    - Depending on the study goal, e.g.:
      - Is the treatment effective?
      - Is the treatment safe?
    - Secondary measures intended to provide more information, support primary measure
  - Assessment of safety
  - Statistical methods

STUDY PROTOCOL

- Describes
  - Case report forms (CRF)
  - Study monitoring
  - Protection of patients
    - Informed consent
    - Institutional Review Board/Ethics Committee approval
  - Data handling and record keeping
  - Financing and insurance

OUTCOME MEASURES/ENDPOINTS

- Often called variables
- Objective or subjective
  - Objective: impartial – based on observation/physico-chemical measure, low degree of interpretation
  - Subjective – important measure of perceived benefit/harm

CLINICAL OUTCOMES/ENDPOINTS

- Objective:
  - “Hard” endpoints: e.g. Stroke, dialysis treatment, death
  - “Soft” or ”surrogate”: e.g. Blood pressure, laboratory measure of kidney function
    - Surrogate is known to predict ”hard” clinical outcomes
    - Certain magnitude of change is known to be important
  - Biological markers
    - Surrogate value unknown
    - Mirror presence and activity of disease
      - e.g. erythrocyte sedimentation rate, urine protein content

CLINICAL OUTCOMES/ENDPOINTS

- Subjective, e.g.
  - Patient or investigator-reported outcomes
  - Pain
  - Symptoms of depression
  - Function – activities of daily living
  - Quality of life
  - Require use of recognised instruments (rating scales)
- Studies often use a mixture of endpoints
- Choice depends on clinical context, disease and treatment and the questions the study is asking

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STANDARD AND NON-STANDARD SITUATIONS

- In priciple, development of orphan medicinal products and medicines for children are standard situations
- Development of medicines in these situations follows the principles of evidence-based medicine – as in common diseases
- Development of orphan medicinal products and medicines for children may set specific limitations to what is possible and reasonable
- Development may therefore require non-standard solutions

LEVELS OF EVIDENCE

- Meta-analyses of good quality RCT
- Individual RCT
- Meta-analyses of observational studies
- Individual observational studies
- Published case studies
- Anecdotal case studies
- Expert opinion

All have value – added value when combined

LEVELS OF EVIDENCE

- Key questions:
  - Is it possible to do a RCT?
  - Is a small RCT better than a larger study without control group?
  - Risk of bias?
  - How accurate will the result be?
  - What evidence is needed for initial marketing authorisation?
  - What evidence is needed post-marketing?

ADAPTIVE STUDIES

- Design of ongoing study can be adapted (changed) based on pre-defined rules
- Adaptations done based on interim analysis of data
- Adaptations: number of patients, add/discontinue treatment arm(s), eligibility criteria
- Seamless, adaptive Phase 2/Phase 3 can combine dose-finding and confirmatory phase
  - More data from smaller number of subjects compared to separate studies

Sequential studies

- Enrol patients and analyse emerging data repeatedly until a reliable positive/negative conclusion about treatment possible
- Treatment effect must emerge rapidly
- Study stopping boundaries defined in advance
  - Benefit
  - Harm
  - ”Futility”

STUDIES IN SMALL POPULATIONS – KEY FACTORS

- Standardised data collection – prospectively planned, documented in protocol and adhered to:
  - Maximising collection of important information
  - Keeping study participation burden acceptable
  - Avoiding loss-to-follow-up

STUDIES IN SMALL POPULATIONS – KEYFACTORS

- Understanding the natural course of disease, how this may change over time
- Understanding sources of possible misinterpretation (confounders)
  - e.g. Enzyme replacement therapy decreases heart complications
    - Is this due to enzyme replacement or improved supportive therapy?
- Understanding sources of variable response to therapy
  - Disease stage, age, gender, other therapies, etc.

STUDIES IN SMALL POPULATIONS - EFFICACY

- How is efficacy measured?
  - Cure
  - Survival
  - Time to disease progression
  - Progression-free survival
  - Reversal of organ dysfunction
  - Disease stabilisation
  - Surrogate endpoint – must predict benefit
  - Symptom relief
  - Quality of life
  - Biomarker, surrogate value unknown

Often a combination of measures pointing

To the same direction and "making sense"

STUDIES IN SMALL POPULATIONS COMPARATOR

- What is the most appropriate comparator?
- What is an acceptable comparator?

- Placebo?
- Best supportive care?
- Available therapy = active comparator?
- Historical control group?
- No control group?

- What is the desired outcome?

- Superior efficacy?
- Non-inferior efficacy?
- “Clearly effective”, although no control group available

TO CONCLUDE

- Randomised, controlled, blinded studies provide best scientific evidence of benefit and risk
- Increasing ethical issues and debate on use of placebo - recognised by authorities, too
  - But there are also ethical issues if research methods cannot provide reliable answers
- Use of active comparators will increase
  - Increasing demand to show better efficacy compared to available therapies
  - New therapy which is “only” not inferior to current therapy is a very challenging outcome

TO CONCLUDE

- Strike a balance: what is necessary – what is possible
- What seems cumbersome and not practical may turn out to be possible and *vice versa*
  - Repeated dialogue needed between sponsor-investigators-patient groups-regulators
- Methods are available to improve efficiency of clinical trials in small populations
- Development should be discussed in advance with regulators in scientific advice/protocol assistance