Clinical trial designs appropriate for children

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Network Heart Diseases (ERN GUARD-HEART)

European Reference Network for rare or low prevalence complex diseases
Network Respiratory Diseases (ERN-LUNG)

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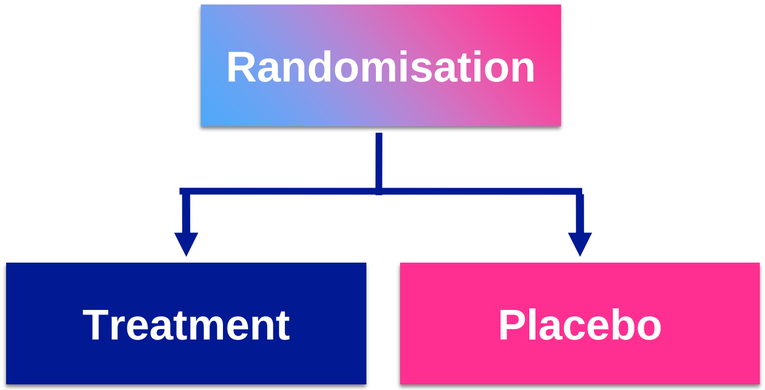
Parallel groups *vs.* small trials designs

- **It is generally accepted that an appropriate trial design includes a sufficiently large sample size and statistical power, and methods for minimizing bias to enable the results to be reliably interpreted.**

- **The randomized, parallel-group controlled clinical trial design is generally considered as the gold standard, but in some situations it is difficult to use this design.**

- **Small trials should enable a reasonable measure of the treatment effect to be obtained.**

- **The design should include an outcome that can be measured to determine change or ‘ success’ , via a baseline value and an ‘ under-treatment’ value for the outcome.**



Difficulties in pediatric trials (1)

- Drugs (including orphan drugs) are developed for treating rare diseases, and their efficacy and safety need to be evaluated but **due to the small number of potential trial participants, a standard randomized controlled trial is often not feasible**.

- In children the issue is not restricted solely to rare diseases as **the difficulty in recruiting sufficient numbers of patients is a problem** for even frequent diseases.

- This difficulty is mainly due to ethical and psychological considerations, which not only represent an obstacle to running clinical trials but also **to protecting the children**.

Difficulties in pediatric trials (2)

- These considerations need to be taken into account to **design trials which minimize the risk for individual patients** (e.g. **minimal numbers of samples** in pharmacokinetic/pharmacodynamic studies) as well for the whole pediatric population.

- Consequently, the **use of innovative methodologies enabling fewer patients to be recruited** could become the rule for dose finding and efficacy studies in our field.

Reasons for failure to demonstrate efficacy in the carvedilol trial for heart failure in children

Inclusion of CHD and cardiomyopathies - **different diseases - « mistake »**

The inclusion of patients with differing ventricular morphologies - **different diseases - « mistake »**

Use of a composite end-point - **none validated in pediatric heart failure - ignorance**

The assumptions made regarding the potential of clinical improvement over the study period - **50% improvement with standard of care - ignorance**

The distribution of heart failure severity present in the study population - **71% of patients in NYHA-FC II - pusillanimity**

The doses used in the trial - **plasma concentrations lower than in adults - not a real reason, the trial is made for this purpose**

Shaddy RE et al.JAMA 2007

Anticoagulation

1. Trials should focus on high-risk childhood patient populations, potentially including single ventricle patients across the various stages of palliation, patients with Kawasaki disease and coronary aneurysms, children and adolescents with ventricular assist devices, children and adolescents with heart failure, younger children who have undergone cardiac catheterization procedures, and children who require indwelling catheters.

2. In addition to exploring drug efficacy for thromboprophylaxis, there is a need to develop agents for treatment of venous and arterial thrombosis in children and adolescents with congenital or acquired heart disease.

3. Head-to-head safety and efficacy studies are needed to compare newer anticoagulation agents with existing agents such as heparin, low molecular weight heparin, aspirin, and warfarin.

4. Attempt to define additional endpoints beyond incidence of thrombosis and bleeding that impact clinical care and patient quality of life. For example, studies are needed to validate biomarkers as surrogate endpoints; these may prove especially useful for head-to-head comparison studies.

Do Adult Medications Work in Children and if Not, Why Not?

1. Design of clinical trials
2. Different response to medication
3. Different disease
4. Different substrate

The specific question of anticoagulation in children

- (1) the heterogeneous nature of congenital and acquired heart disease that can result in both venous and arterial thrombosis;
- (2) the fact that coagulability often varies depending on the underlying clinical condition, thus probably necessitating separate studies for each individual condition;
- (3) a broad range of developmental considerations that can affect dosing and safety, such as potential adverse effects on bone development or increased fall risk in younger patients;
- (4) the absence of validated biomarkers and the fact that there is no clear established quantitative relationship between blood activity levels (eg, activated partial thromboplastin time levels or anti-factor levels) and clinical outcomes;
- (5) challenges related to performing head-to-head studies with existing agents such as warfarin (which requires therapeutic drug monitoring) or low molecular weight heparin (which must be administered as a subcutaneous injection).

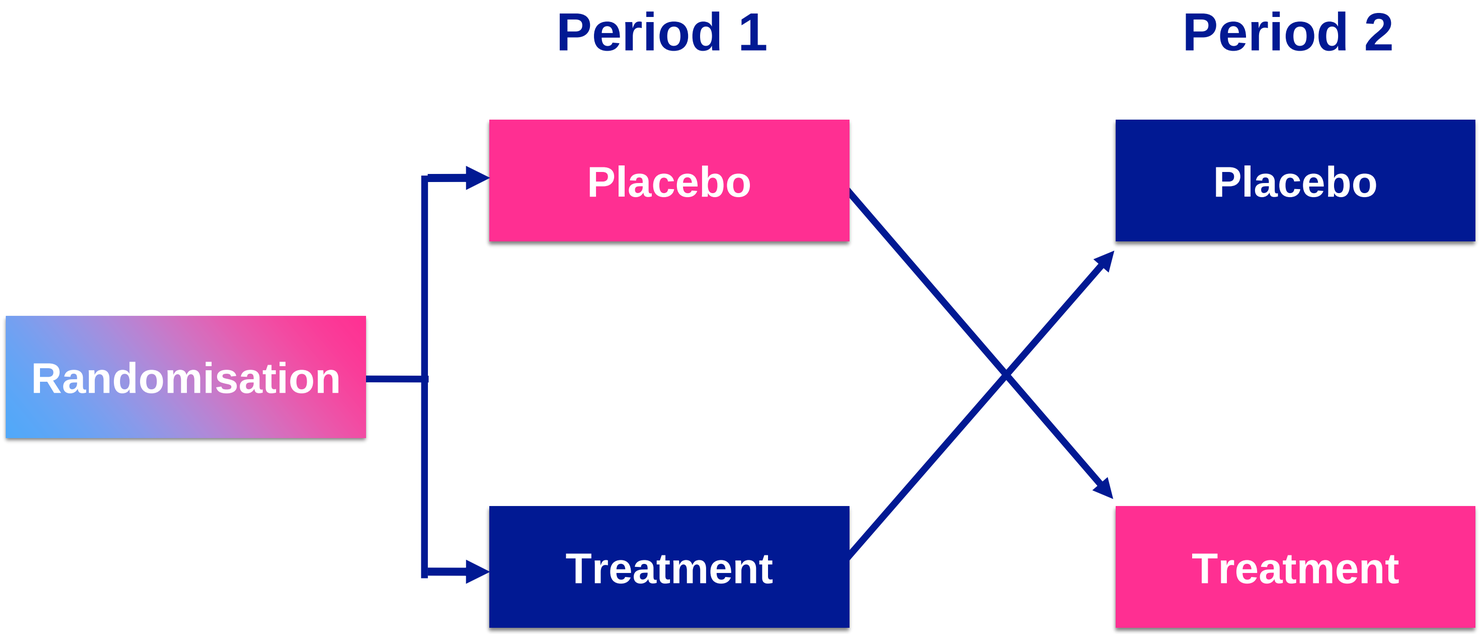
How to improve design of therapeutic trials in pediatric heart diseases ?
Population related issues : enrichment strategies

- **Strategies do decrease population heterogeneity**
  -inter- and intra-patient variability **to increase study power**

- **Prognostic enrichment strategies**
  -choosing patients with a greater likelihood of having a disease-related endpoint event (for event-driven studies) or a substantial worsening/improvement in condition (for continuous measurement endpoints) **to increase absolute effect difference between groups**

- **Predictive enrichment strategies**
  -choosing patients more likely to respond to the drug treatment than other patients with the condition being treated **to reduce the number of patients in the trial**

Cross-Over
Latin square
N-on-1



For all intra-patient designs,

- **the disease must be stable,**
- **the patient' s health status must be identical at the beginning of each treatment period.**

There can be a carry-over effect, if the treatment effect from the previous period is still present during the following period.

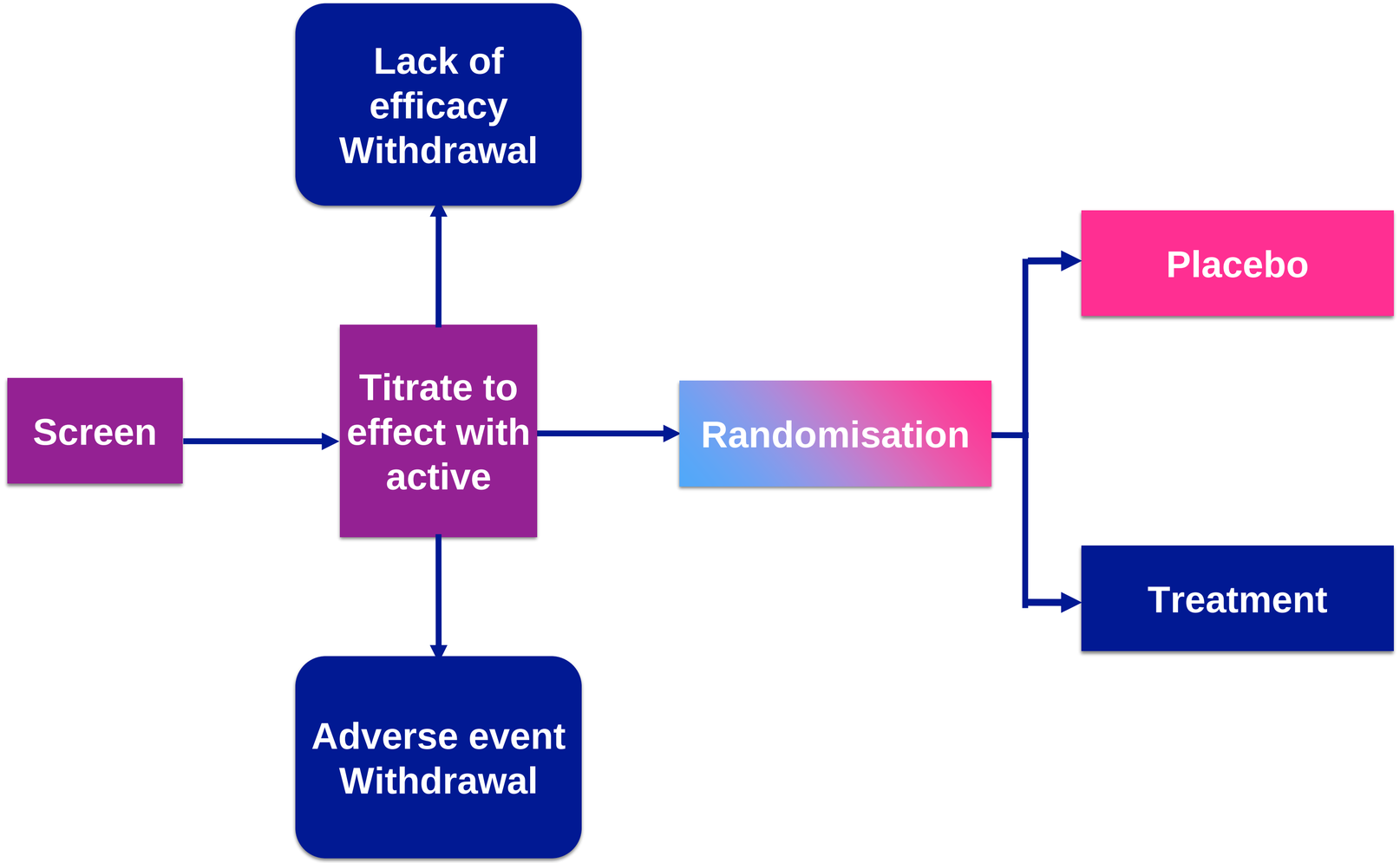
Minimizing time on inactive treatment or placebo

Randomized withdrawal

Early escape

Randomized placebo phase

Stepped wedge designs



- **Identifies a subgroup of patients who can successfully achieve a pre-defined level of response.**
- **Aims to evaluate the optimal duration of a treatment in patients who respond to the treatment.**

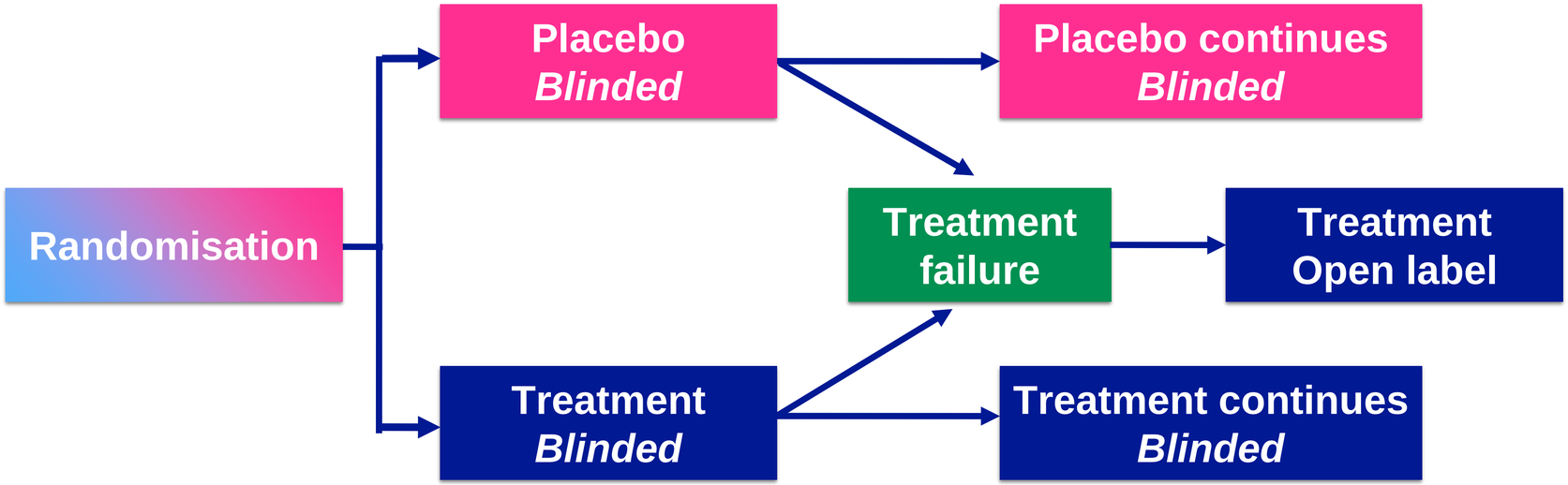
Minimizing time on inactive treatment or placebo

Randomized withdrawal

Early escape

Randomized placebo phase

Stepped wedge designs



- **Reduces the time on placebo or in treatment failure.**
- **Difficult to define a binary failure/success outcome.**
- **Analyse failure rate, so minimizes exposure to ineffective treatment**
- **Only short-term efficacy evaluated.**
- **Loss of power if significant number of patients ‘escape’**

Adaptive randomisation (play the winner, drop the looser designs)

- A study that includes prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (interim) from subjects in the study

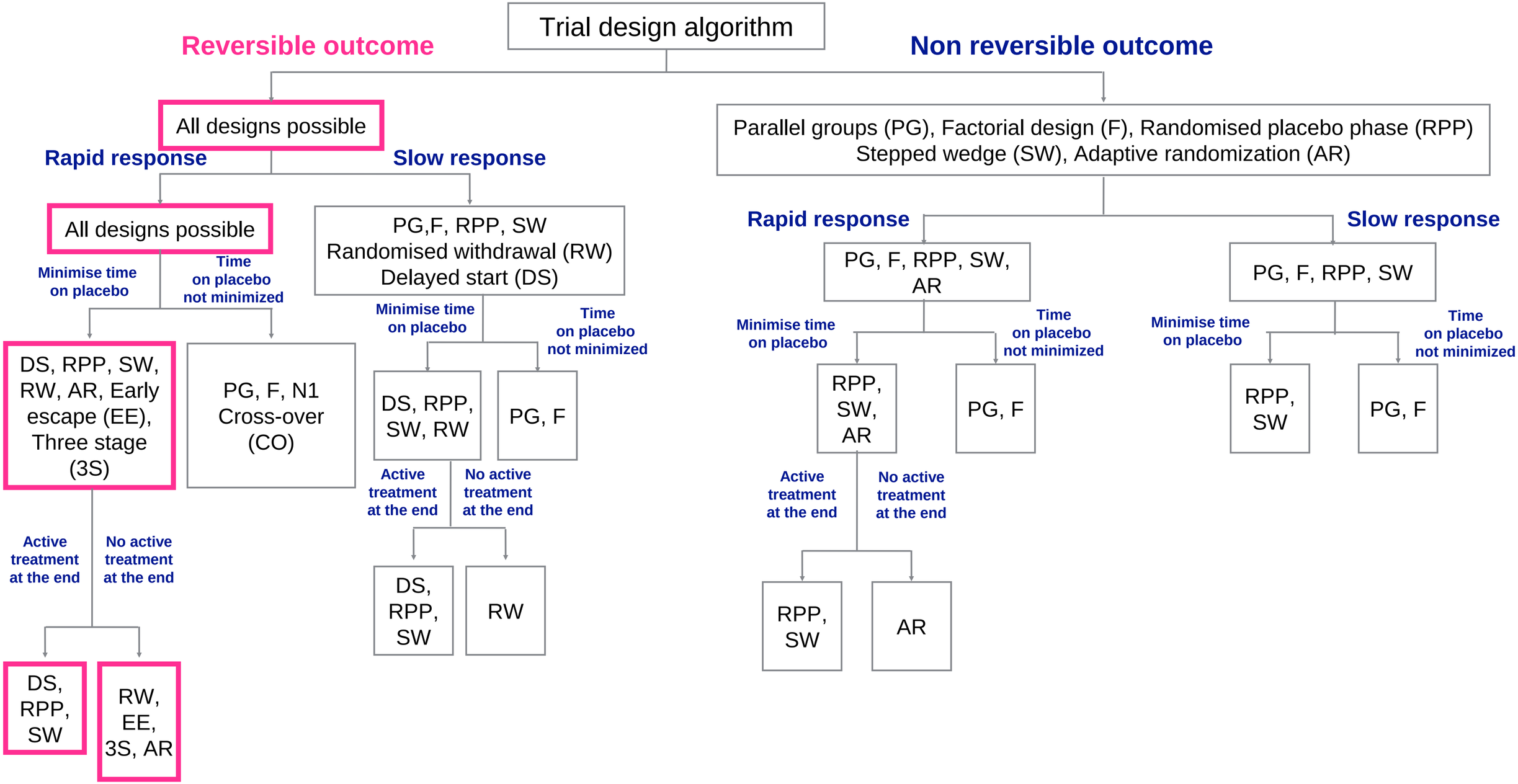
- The purpose is to make **RCT more flexible, efficient and fast without undermining its validity and integrity**

- Adaptive randomization design
- Sample size re-estimation
- Drop the loser
- Play the winner
- Adaptive dose finding
- Hypothesis adaptive design

Limited to trials with binary response

Decision nodes
How to chose a specific trial design ?

1. Reversible or irreversible outcomes
2. Fast (defined as up to a few weeks) or slow response to treatment
3. Possibility of minimizing the time on placebo
4. Possibility that all patients received active treatment by the end of the trial
5. Possibility of performing intra-patient or inter-patient comparisons.



Cornu et al. Orphanet J Rare Dis 2013;8:48

The trial design depends on the expected outcome/endpoint

End-points

- **Consistently & readily measurable**
- **Sensitive**
- **Well defined & reliable**
- **Clinically meaningful**

…a direct measure of how a patient functions, feels or survives …

Robert Temple, FDA

The specific question of anticoagulation in children

- **What is “a clinically meaningful endpoint” ?**
- **Two problematics:**

1. Treatment of thrombosis - venous or arterial

2. Prevention of thrombotic events

Therapeutic trial endpoint
Treatment of thrombosis
One single end-point

- **Resolution**
- **No progression**
- **No recurrence**

Duration of trial ?

Time matters

Thromboprophylaxis

Event-driven: until the number of events is obtained

Limited in time: ranking

Patient matters

Thromboprophylaxis and treatment

Patients reported outcomes

Quality of life

as single end-points in head-to-head trials

as part of a composite end-point

How to facilitate, accelerate and obtain clinically meaningful informations in future trials ?

Leveraging existing resources

- **Necessary informations for new compounds**
  - **Efficacy proven in adults if the disease is comparable**
  - **PK**
  - **Safety short-term**

- **Large registries**
  - **Natural history**
  - **Standard of care**
  - **Clusters of patients**

- **Role of Role Pediatric Trial Networks**

- **Include advocacy groups in drug development**

Thank you

Collective ignorance is the motivation
Curiosity is the strength
Research is the path

Individual experience is the brake
Indifference is the weakness
Authority argument is the threat