N-of-1 trial Recommendations for Precision Treatments in Monogenic Epilepsies

An EpiCARE – research and care project

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Small clinical trials

- Small clinical trials are often necessary for rare diseases
- There are number of alternative trial designs to the usual parallel group
- Importance to choice the most appropriate design

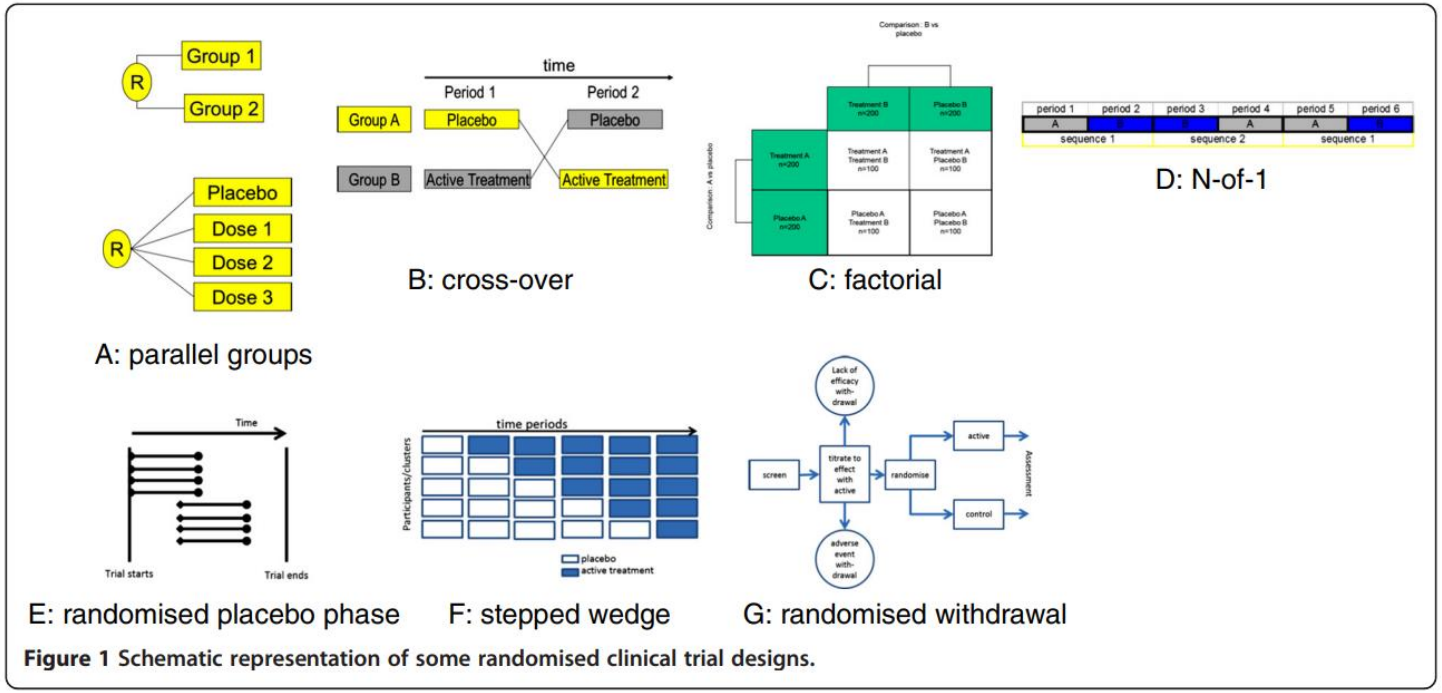

Figure 1 Schematic representation of some randomised clinical trial designs.

Cornu et al. Orphanet Journal of Rare Diseases 2013, 8:48
http://www.ojrd.com/content/8/1/48

ORPHANET JOURNAL OF RARE DISEASES

REVIEW Open Access

Experimental designs for small randomised clinical trials: an algorithm for choice

Catherine Cornu[1,2,3*], Behrouz Kassai[1,2,3], Roland Fisch[4], Catherine Chiron[5], Corinne Alberti[6,7,8], Renzo Guerrini[9], Anna Rosati[9], Gerard Pons[10], Harm Tiddens[11], Sylvie Chabaud[12], Daan Caudri[11], Clément Ballot[3], Polina Kurbatova[3], Anne-Charlotte Castellan[3], Agathe Bajard[1,2], Patrice Nony[2,3] and the CRESim & Epi-CRESim Project Groups

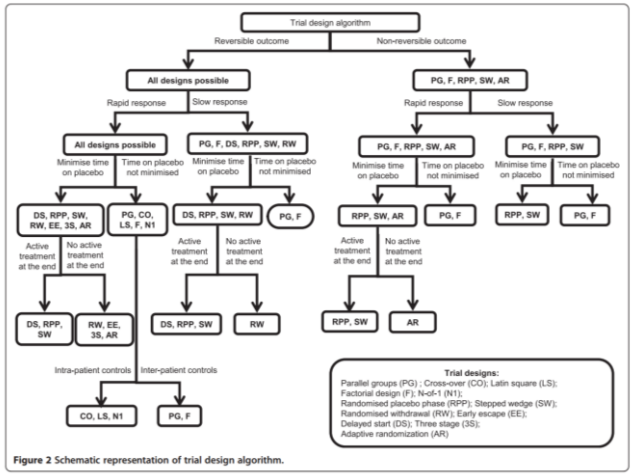

Figure 2 Schematic representation of trial design algorithm.

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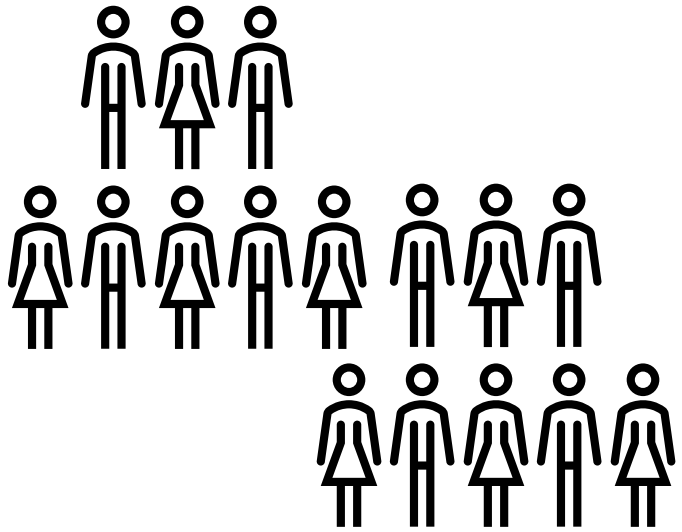
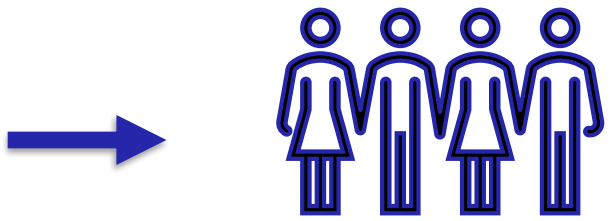
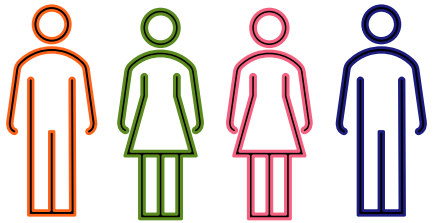
Rare monogenic epilepsies



Childhood Epilepsy
< 3 years of age or 1-5 years old



>25% monogenic epilepsy



8 genes → 80% of cases

➢ **200 genes**
Ion channels
Synaptic transmission
Growth-related pathways

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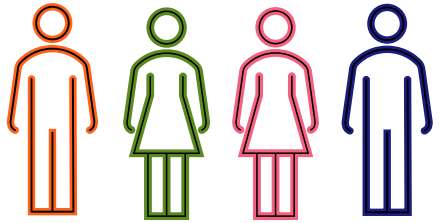
Rare monogenic epilepsies



- Rare – 1:40,000 live births
- Interpatient heterogeneity
- 45% Pharmacoresistant
- Therapeutic alternatives
- Lack of evidence

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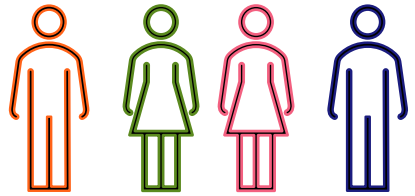
precision treatment in monogenic epilepsies



- precision treatment target the underlying molecular mechamism affected by the mutation
- case-series or retrospective studies ≠ high-quality evidence
- often trial-and-error approach, with no predefined monitoring plan or outcome measurement
- clinical trials are hampered by interpatient heterogeneity and low disease prevalence

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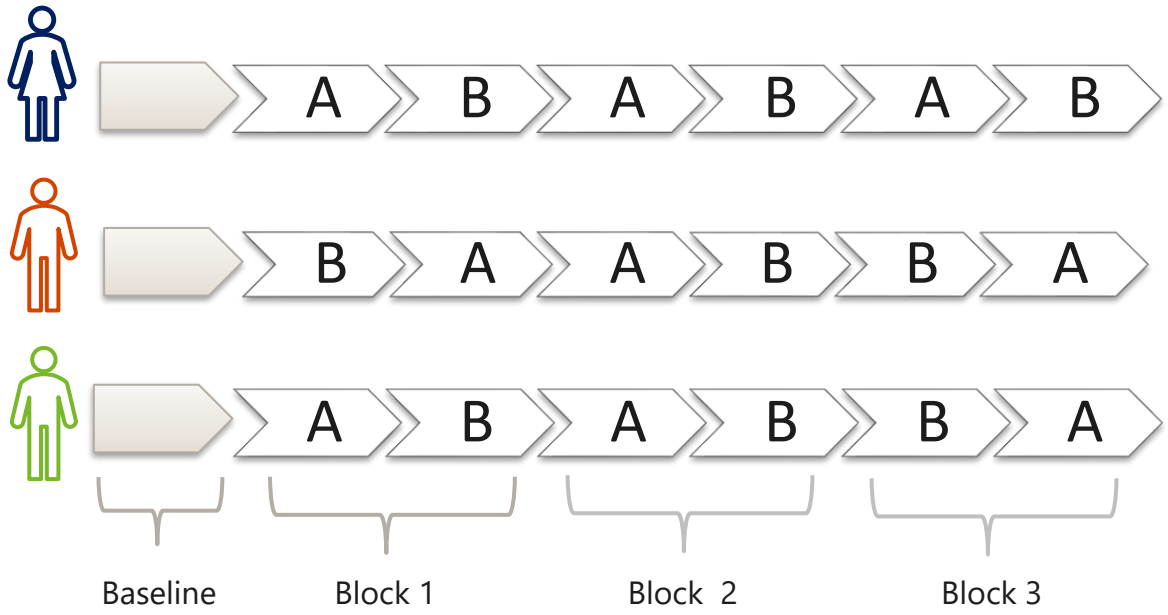
N-of-1 trials – an individual patient as the sole unit of observation



efficacy

adverse effects

patient centered outcomes

follow-up

Repeated measurements

Several cross-over randomized blocks

- N-of-1 trials are suited for :
  - chronic or stable disease
  - quick on-and-offset of a treatment
  - a measurable outcome in a short period of time

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project setup

retrospective study on selected monogenic epilepsy syndromes

- Explore past experience with precision treatments:
  - dosages
  - clinical outcomes
  - adverse effects
- define patient populations that *may* benefit from **precision treatment**

comprehensive analysis of the use of precision treatments in monogenic epilepsy syndromes

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retrospective study

Gene	Precision treatment
DEPDC5/NPRL2/NPRL3	mTOR inhibitors
GRIN2A/GRIN2B/GRIN2D	NMDA receptor inhibitors (GoF variants) Memantine
GRIN1	NMDA receptor positive allosteric modulator (LoF variants)
KCNA2	4-aminopyridine (GoF variants)
KCNQ2	potassium channel openers (LoF variants) retigabine analogues (Ezogabine) gabapentine
KCNT1	quinidine (other KCNT1 blockers) (GoF variants)
GABRB3	vinpocetine in case of LoF variants (consider others)
CACNA1A	acetazolamide/ 4-aminopyridine (consider others)
CACNA1E	topiramate

project setup

retrospective study

- explore:
  - dosages
  - clinical outcomes
  - adverse effects
- define patient populations that may benefit from precision treatment

tailored
N-of-1 approaches
reccomandations

Main topics:

- baseline monitoring
- outcomes measurements
- variations in disease phenotype
- different treatment characteristics
- Type of randomization and blindings
- ethical aspects - IRB
- logistical support (local pharmacies and industry)

duration of the trial blocks

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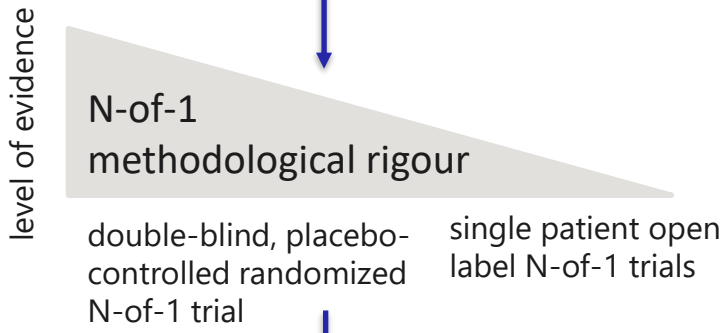
project setup

retrospective study

- explore:
  - dosages
  - clinical outcomes
  - adverse effects
- define patient populations that may benefit from precision treatment

tailored
N-of-1 approaches

- baseline monitoring
- outcomes
- phenotype
- treatment characteristics
- ethical aspects
- logistical support



prospective
N-of-1 trials

use of PCOMs

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prospective n-of-1 trials

protocol open-label, randomized
n-of-1 trials in clinical care

- memantine – GRIN2A GoF-related epilepsy
- everolimus – (non-surgical) GATOR1-related epilepsy

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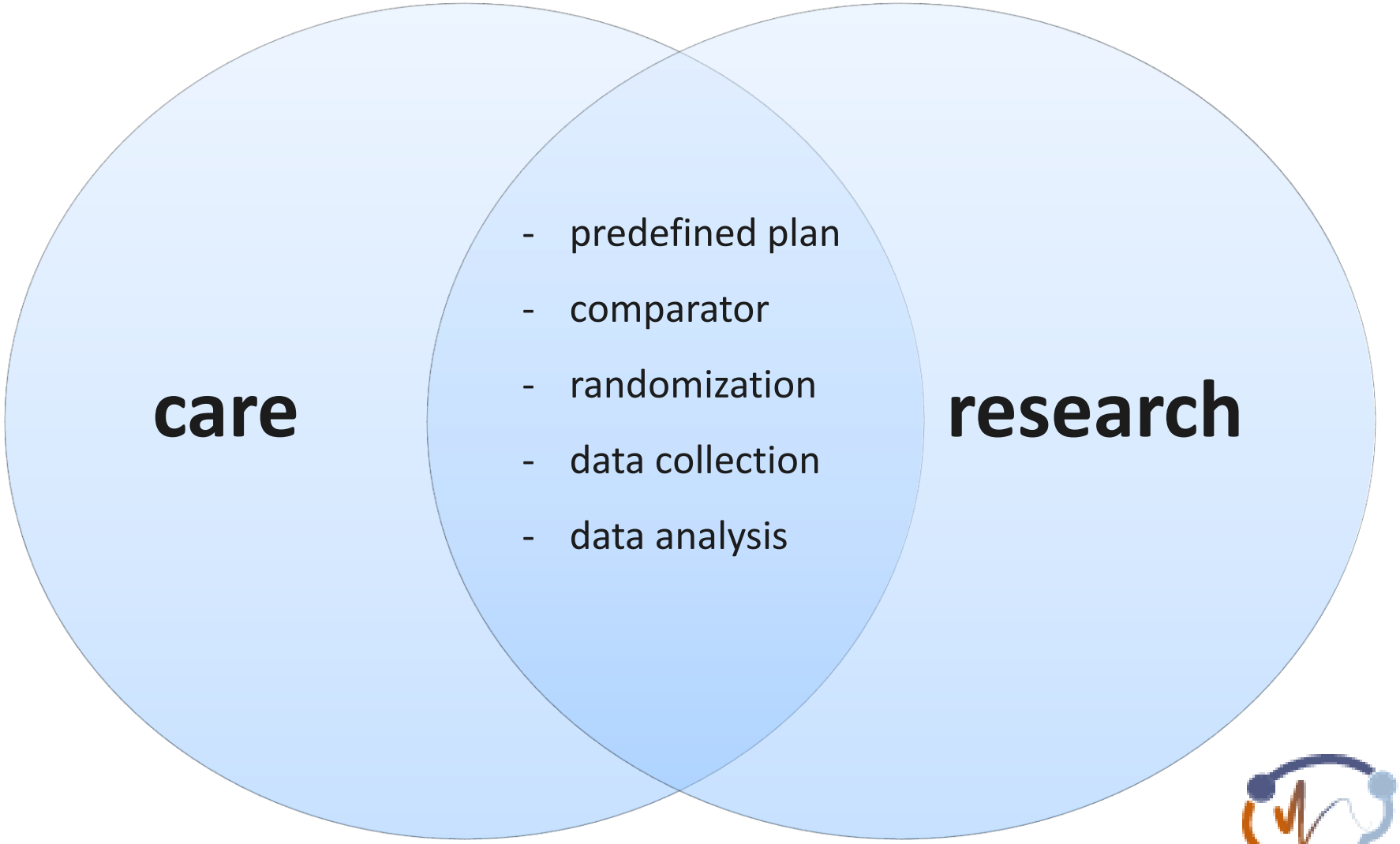
n-of-1 strategies at the intersection of research and care



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project setup

retrospective study

- explore:
  - dosages
  - clinical outcomes
  - adverse effects
- define patient populations that may benefit from precision treatment

tailored
N-of-1 approaches

- baseline monitoring
- outcomes
- phenotype
- treatment characteristics
- **ethical aspects**
- logistical support

N-of-1
methodological rigour

prospective
N-of-1 trials

ethical framework for n-of-1 strategies

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where are we now

registry

- 20 centers in EU participating in the retrospective study

methodology

- n-of-1 trial review on n-of-1 design in epilepsy
- simulation analysis using Bayesian inference

ethical

- model framework to be used to help ethical committees distinguish between research and care n-of-1 strategies

prospective

- use of multiaxial PCOMs for seizure severity and non-seizures aspects
- protocol for n-of-1 trials

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challenges

- ❑ administrative burden of rare disease registry

few patients per center
deep phenotyping / time consuming
delays with administration and contracts

- ❑ financial and logistical limitations in multicenter studies

cost to obtain placebo
several visits / follow protocol
need of expert and motivated staff

- ❑ statistical analysis of n-of-1 studies

Need of good quality data
User-friendly statistical software

- ❑ local ethical committee perspectives on n-of-1 trial

different countries laws

- ❑ patient and physician perspective

motivation!

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way forward

- analysis of retrospective data to inform methodology
- tailored n-of-1 methodology as toolkit for trial model for rare monogenic epilepsies
- select outcome measurements suitable for use in n-of-1 studies
- involve local ethical committees to map local procedures “care vs research”
- consult regulatory agencies when conducting research n-of-1 projects
- consider other small population clinical methodologies for different (rare) epilepsy phenotypes

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conclusion

- n-of-1 trials are one alternative design suitable for rare disease with complex phenotypes
- tailored n-of-1 methodology can be adjusted to different settings, phenotypes and treatments
- user-friendly methodology and analysis tools will aid use of n-of-1 design
- thanks to ERN- EpiCare and their members this projects will be realized

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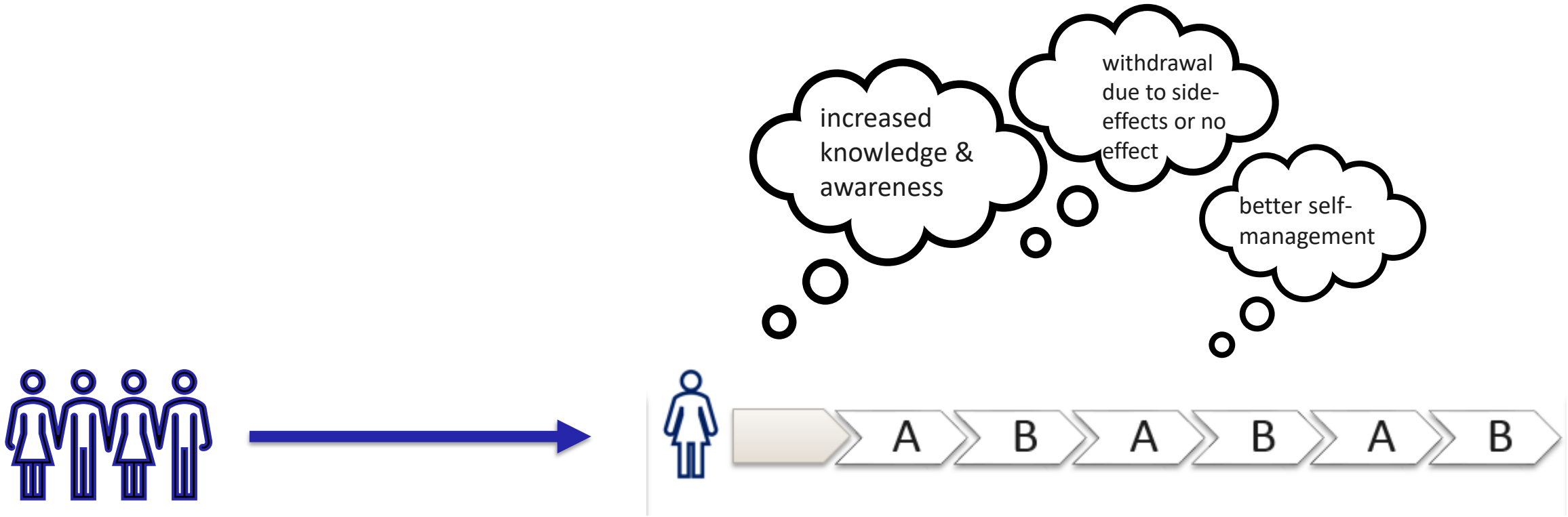
patient perspectives of n-of-1 trials

- **interest in participating in n-of-1 trials:**
  - personal gain outweighing potential risks
  - interest related to perception of low-risk
  - exhausted other possibilities

Nickles et al. 2006
Johnston et al. 2006
Brookes et al. 2007

patient perspectives of n-of-1 trials



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