Leiden University
Medical Center

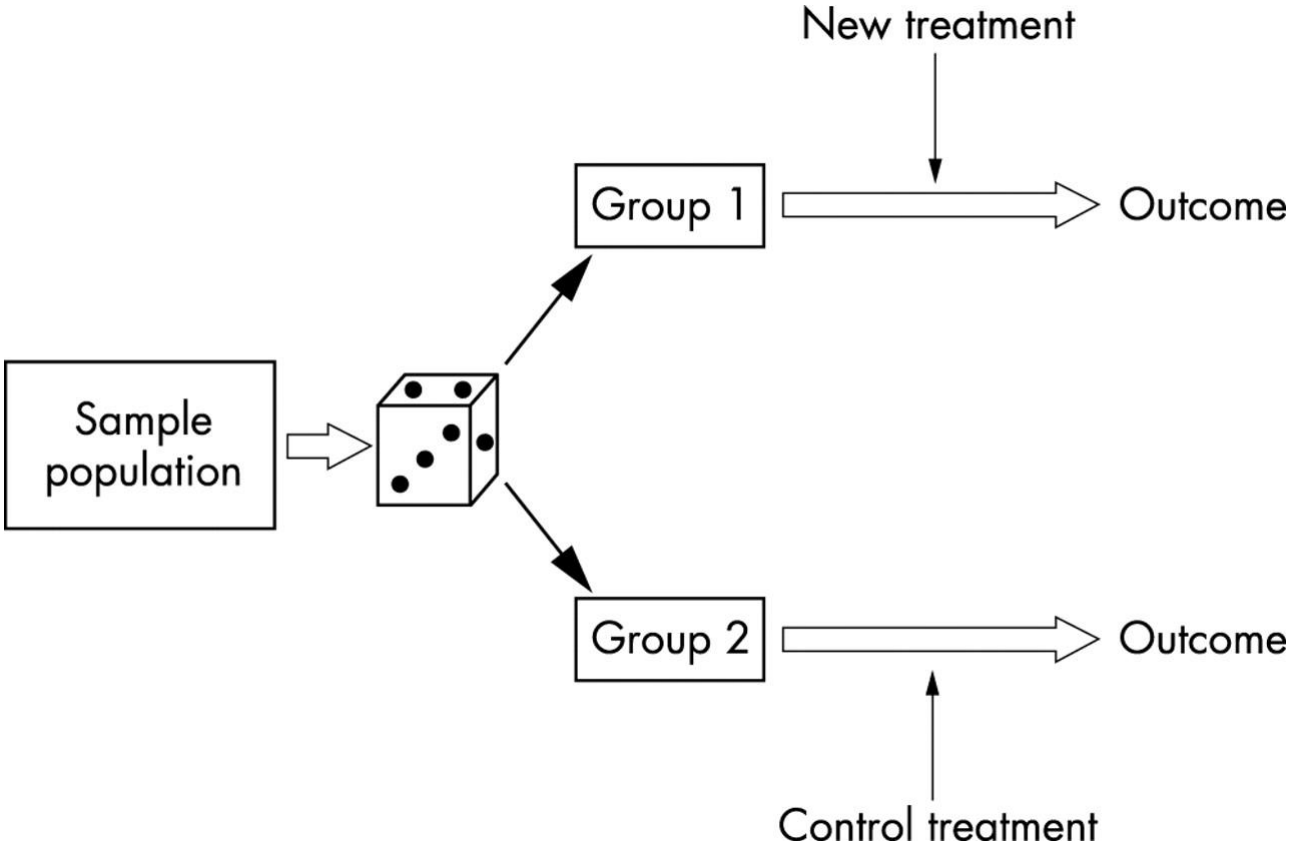
Developments in trial design

A methodological perspective

Rolf H.H. Groenwold

RSNN meeting, 17 April 2019

Trial design used to be ‘easy’



Challenges

- RWE
- Patient subgroups
- Small populations
- Rapid developments
- Costly infrastructure

Adaptations to conventional trial design
(not exhaustive)

Challenge	Adaptation
RWE	Pragmatism - ‘real-world’ populations - ‘real-world’ physicians - ‘real-world’ monitoring (wearables) - Trials within cohorts (Twics)
Patient subgroups / small populations	- N-of-1 studies - Single arm studies - Informed analysis - Co-enrolment
Rapid Developments	- Platform trial - Master protocol
Costs	- Learning healthcare system (LHS)

Pragmatic trials

Efficacy
Restricted patient group
Controlled environment
Value to regulators

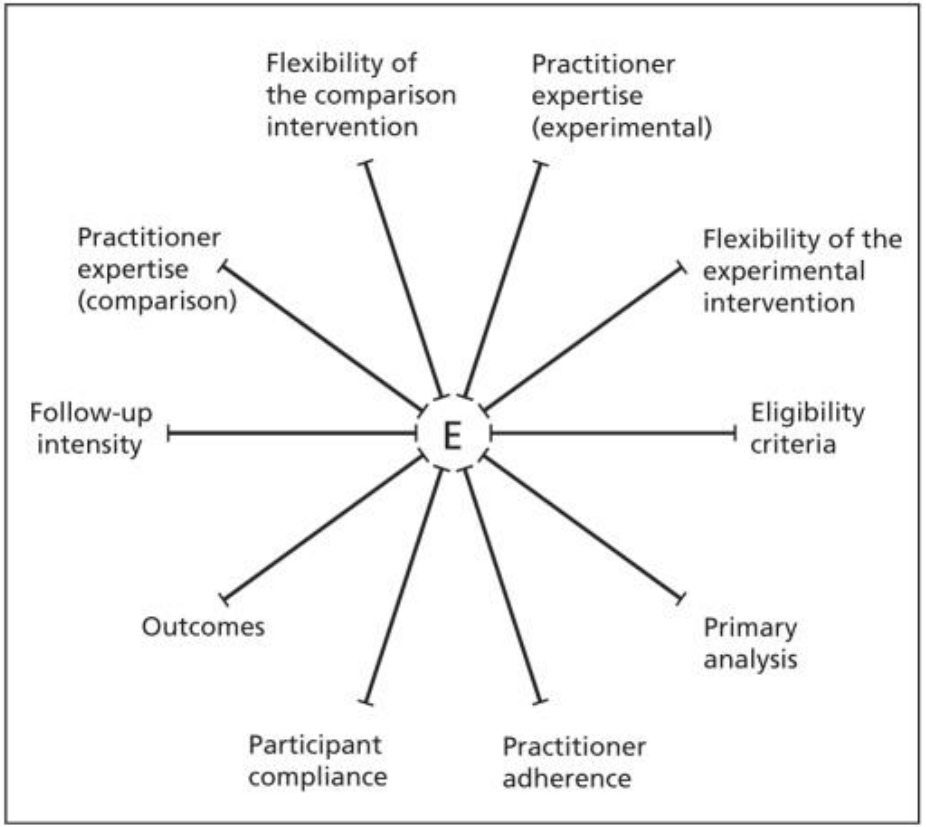
Effectiveness
All patients
Real life environment
Value to payers

Pragmatic trials

Example: EHR-based trials

- Recruitment
- Outcome assessment
- Safety monitoring(?)

GCP vs. pragmatism



Mentz e.a., Circulation 2016; Ford & Norrie, NEJM 2016; Thorpe e.a., CMAJ 2009

TABLE 7 Drop-out rates of practices at each step in the recruitment and approval procedure

Step in site recruitment	Retropro		eLung	
	n practices	%	*n* practices	%
Practices contacted	459	100	459	100
Practices returned letter of interest	377	82.1	377	82.1
Interested	270	58.8	270	58.8
Declined	107	23.3	107	23.3
Site agreement received	63	13.7	53	11.5
Site-specific submission	50	10.9	45	9.8
NHS permission granted	48	10.5	43	9.4
GCP and protocol training complete	35	7.6	32	7.0
Approved to recruit by study team	30	6.5	31	6.8
Practices remaining following subsequent withdrawals	25	5.4	24	5.2
Were seeking to recruit patients	17	3.7	8	1.7
Recruited patients	17	3.7	6	1.3

Van Staa e.a., Health Technol Assess 2014

Low risk pragmatic trials do not always require participants' informed consent

Clinical trial regulations should remove unnecessary obstacles for the conduct of pragmatic trials assessing the comparative effectiveness of medicines posing no or minimal risk to participants, say **Rafael Dal-Ré and colleagues**

Rafael Dal-Ré *senior investigator*[1], Cristina Avendaño-Solà *head*[2], Brigitte Bloechl-Daum *professor*[3], Anthonius de Boer *professor*[4], Stefan Eriksson *associate professor*[5], Uwe Fuhr *professor*[6], Søren Holm *professor*[7], Stefan K James *professor*[8], Robert J Mentz *investigator*[9], Emilio Perucca *professor*[10], Frits R Rosendaal *professor*[11], Shaun Treweek *professor*[12]

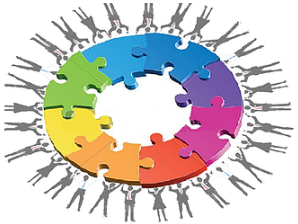
BMJ 2019;364:l1092

Trials within cohorts

Infrastructure for trials

- Staged recruitment
- Staged informed consent
- Consent to be randomized
- Control arm remains ignorant

Trials within Cohorts



Home | The design (TwiCs) | Use of the design | Events | Network

This section describes the rationale for the 'cohort multiple RCT' design, how the design is being used, the different types of published protocols relating to the design. The differences between standalone trials and trials within cohorts is also explained, including a description of the different approaches to informed consent.

Rationale for the cmRCT design

The theoretical article describing the design was published in 2010. Relton C, O'Cathain A, Nicholl J, Torgerson D. Rethinking pragmatic randomised controlled trials: Introducing the "cohort multiple randomised controlled trial" design. 2010 BMJ Online 340(7753):963-967. The cmRCT design was created in an attempt to overcome many of the problems associated with standard pragmatic randomised controlled trial (RCT) design (poor recruitment rates, unrepresentative trial populations, lack of long term outcomes etc.); problems which reduce the generalisability of results and a sub-optimal system for efficiently informing routine healthcare decision making.

Implementation of the cmRCT design

Since its publication, the theoretical article describing the design has been well cited, and the cmRCT design is now being used in a variety of settings and arenas.

The initial partial pilot of the design was conducted in 2005-2007 in a UK NHS community clinic and the trial results were published in 2012.

A hypothetical test of the acceptability of the design was conducted in primary care mental health in the UK.

In addition to conference presentations about the design, and symposiums of triallists interested in (or already using the design), triallists in a number of different fields have cited the design as a potential way forward for research in their field e.g. Verkooijen 2013. And some groups have held consensus building events e.g. stakeholders in prostate cancer surgery

Protocols using the cmRCT design

A growing number of protocols for studies using the cmRCT design are now being published in trial registries and/or in peer reviewed online journals – these include a four different types of protocols. Below are some examples of each different type.

- Protocols describing the methods used to create long term observational studies (cohorts) with the facility for multiple trials.
- *Examples*
  - the multi country SPIN study
  - the Canada based FORBOW study
  - the UK based regional Yorkshire Health Study
- Protocols describing the cohorts and one or more of the trials planned to be embedded within the cohort.

www.twics.global/the-design-twics

Pragmatic trials

Possible advantages:

- RWE

Possible limitations:

- RWE

N-of-1 Trials

JAMA | Original Investigation

Effect of Mexiletine on Muscle Stiffness in Patients With Nondystrophic Myotonia Evaluated Using Aggregated N-of-1 Trials

Bas C. Stunnenberg, MD; Joost Raaphorst, MD, PhD; Hans M. Groenewoud, MSc; Jeffrey M. Statland, MD; Robert C. Griggs, MD;
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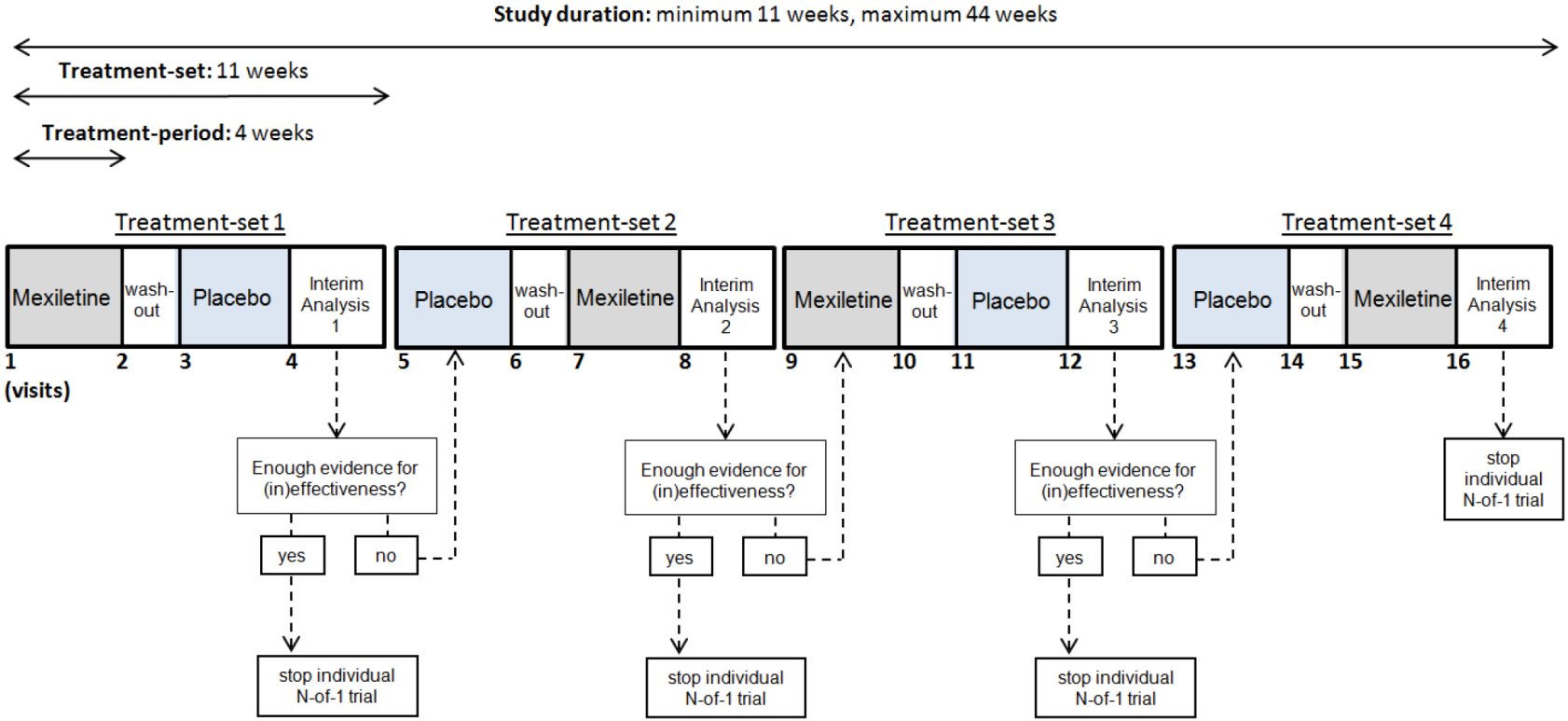
DESIGN, SETTING, AND PARTICIPANTS A series of aggregated, double-blind, randomized, placebo-controlled N-of-1-trials, performed in a single academic referral center. Thirty Dutch adult patients with genetically confirmed nondystrophic myotonia (38 patients screened) were enrolled between February 2014 and June 2015. Follow-up was completed in September 2016.

N-of-1 Trials



Stunnenberg e.a., JAMA 2017

N-of-1 Trials

Possible advantages:

- Small samples
- Adaptive

Possible limitations:

- Deblinding (gastrointestinal adverse reactions)
- Only for chronic/stable diseases and treatment with rapid response

Informed analysis

JAMA | Original Investigation

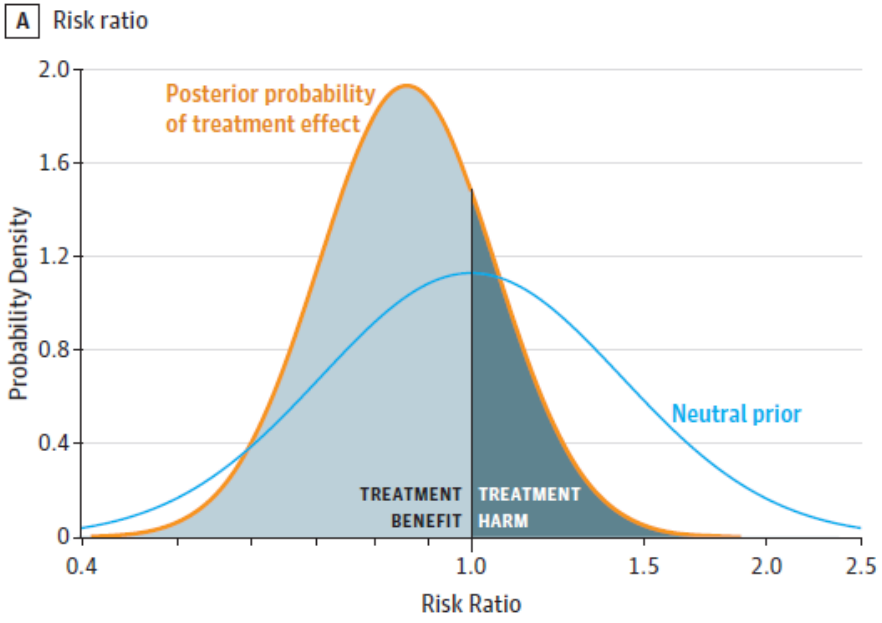
Effect of Therapeutic Hypothermia Initiated After 6 Hours of Age on Death or Disability Among Newborns With Hypoxic-Ischemic Encephalopathy

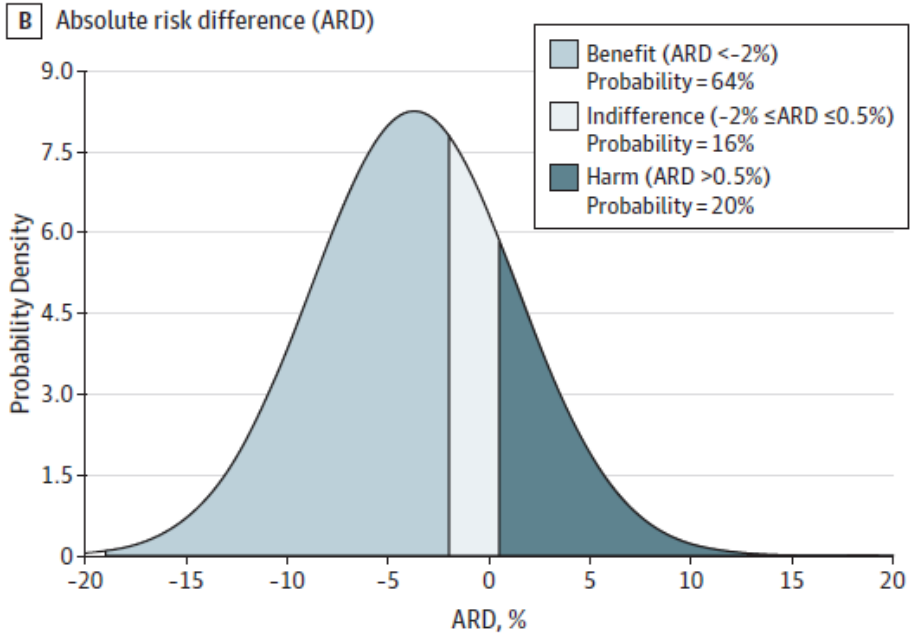
DESIGN, SETTING, AND PARTICIPANTS A randomized clinical trial was conducted between April 2008 and June 2016 among infants at 36 weeks' or later gestation with moderate or severe hypoxic-ischemic encephalopathy enrolled at 6 to 24 hours after birth. Twenty-one US Neonatal Research Network centers participated. Bayesian analyses were prespecified given the anticipated limited sample size.

INTERVENTIONS Targeted esophageal temperature was used in 168 infants. Eighty-three hypothermic infants were maintained at 33.5°C (acceptable range, 33°C-34°C) for 96 hours and then rewarmed. Eighty-five noncooled infants were maintained at 37.0°C (acceptable range, 36.5°C-37.3°C).

Informed analysis

Figure 2. Posterior Probability of Death or Disability With Hypothermia Initiated at 6 to 24 Hours After Birth vs Noncooling





Laptook e.a., JAMA 2017

Informed analysis

Table 3. Primary and Secondary Outcomes: aRRs and Posterior Probability of Treatment Effect[a]

Outcome	No. (%)		Enthusiastic Prior (RR, 0.72)		Neutral Prior (RR, 1.0)		Skeptical Prior (RR, 1.10)	
	Hypothermia (n = 78)	Noncooled (n = 79)	aRR (95% Credible Interval)	P-TB, %	aRR (95% Credible Interval)	P-TB, %	aRR (95% Credible Interval)	P-TB, %
Primary Outcome								
Death or moderate-severe disability	19 (24.4)	22 (27.9)	0.78 (0.52-1.15)	90	0.86 (0.58-1.29)	76	0.89 (0.60-1.32)	73

Laptook e.a., JAMA 2017

Informed analysis

Possible advantages:

- Small samples (statistical efficiency due to external information)

Possible limitations:

- Willingness to accept external information?

Clinical Therapeutics/Volume 39, Number 10, 2017

Enrollment of Neonates in More Than One Clinical Trial

Jonathan M. Davis, MD[1]; Gerri R. Baer, MD[2]; Ronald Portman, MD[3]; Robert Nelson, MD, PhD[2]; Linda Storari[4]; Jacob V. Aranda, MD, PhD[5]; Ralph Bax, MD[6]; Anne Zajicek, MD, PharmD[7]; Agnes Klein, MD, DPH[8]; Mark Turner, MD[9]; Simin Baygani[10]; Merran Thomson, MD[11]; Karel Allegaert, MD[12,13]; for the International Neonatal Consortium

Co-enrollment

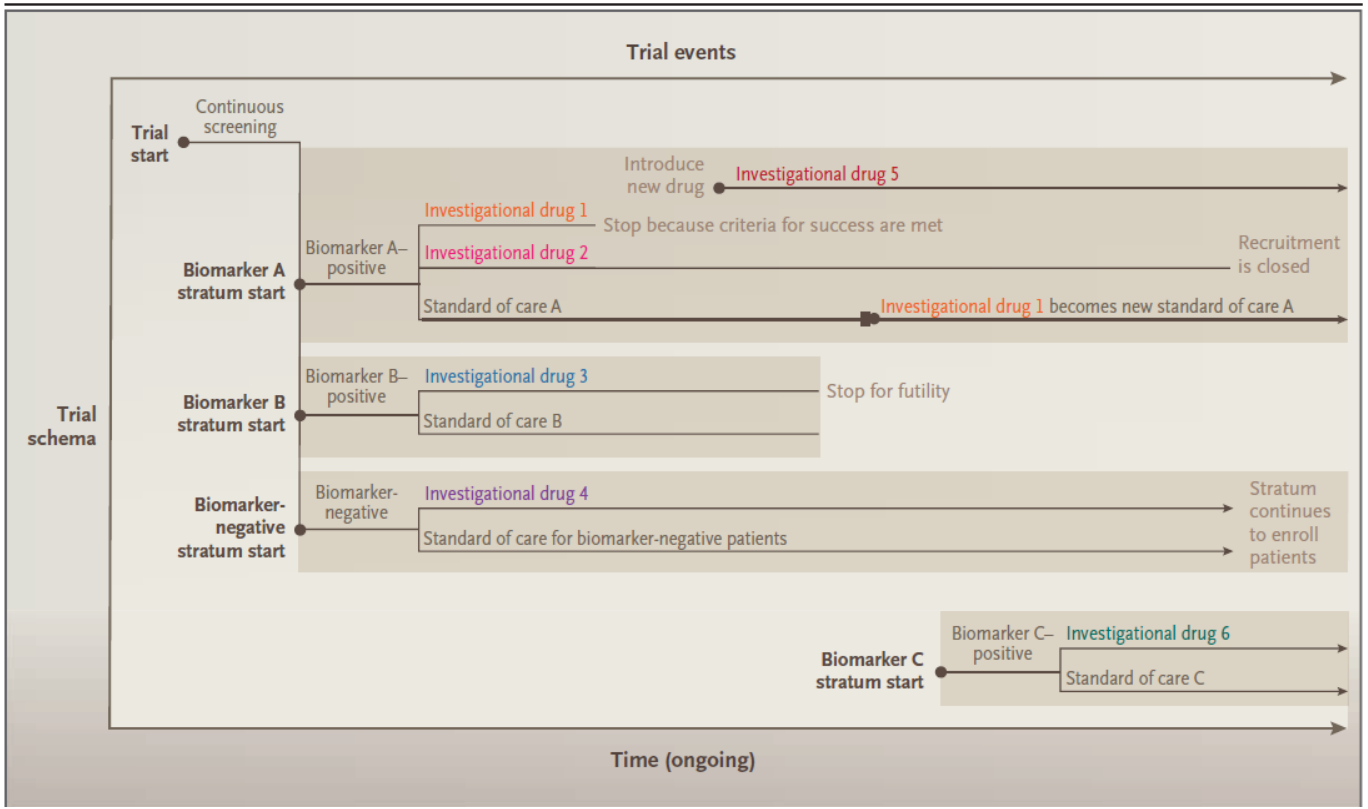
Possible advantages:

- Multiple studies in small populations

Possible limitations:

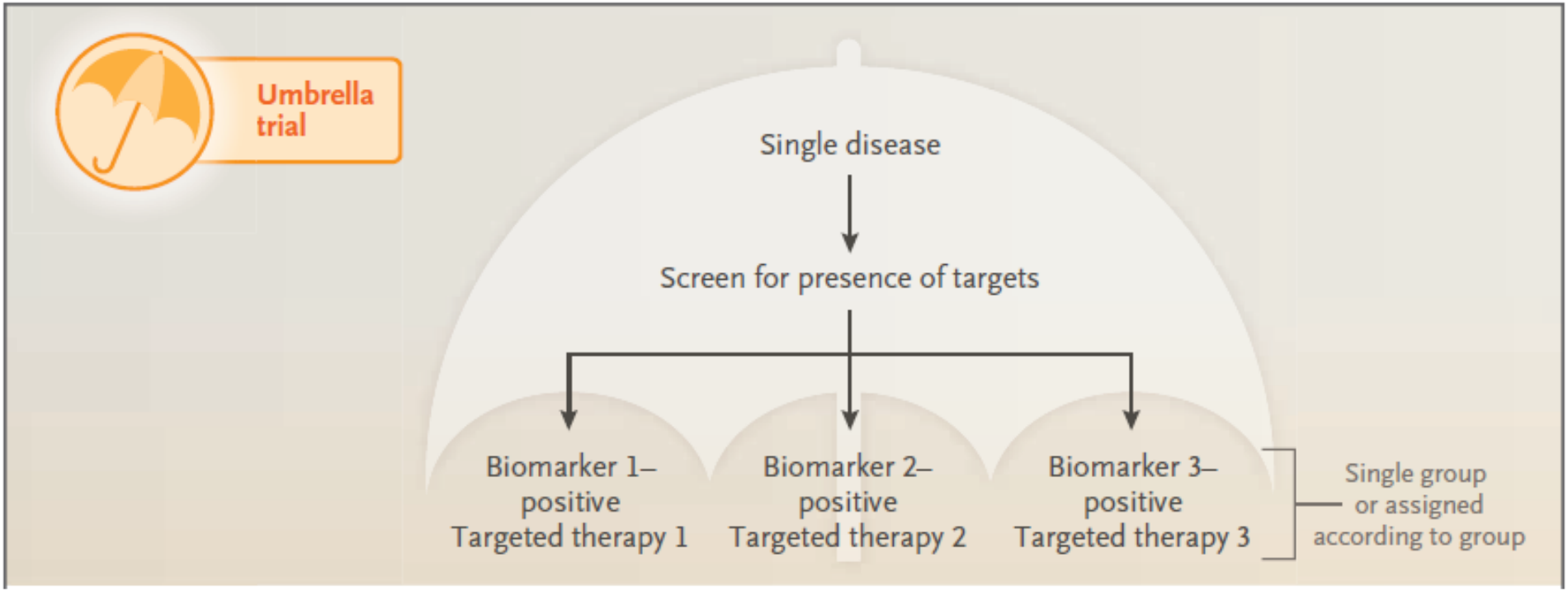
- Contamination
- Burden of participation

Platform trial



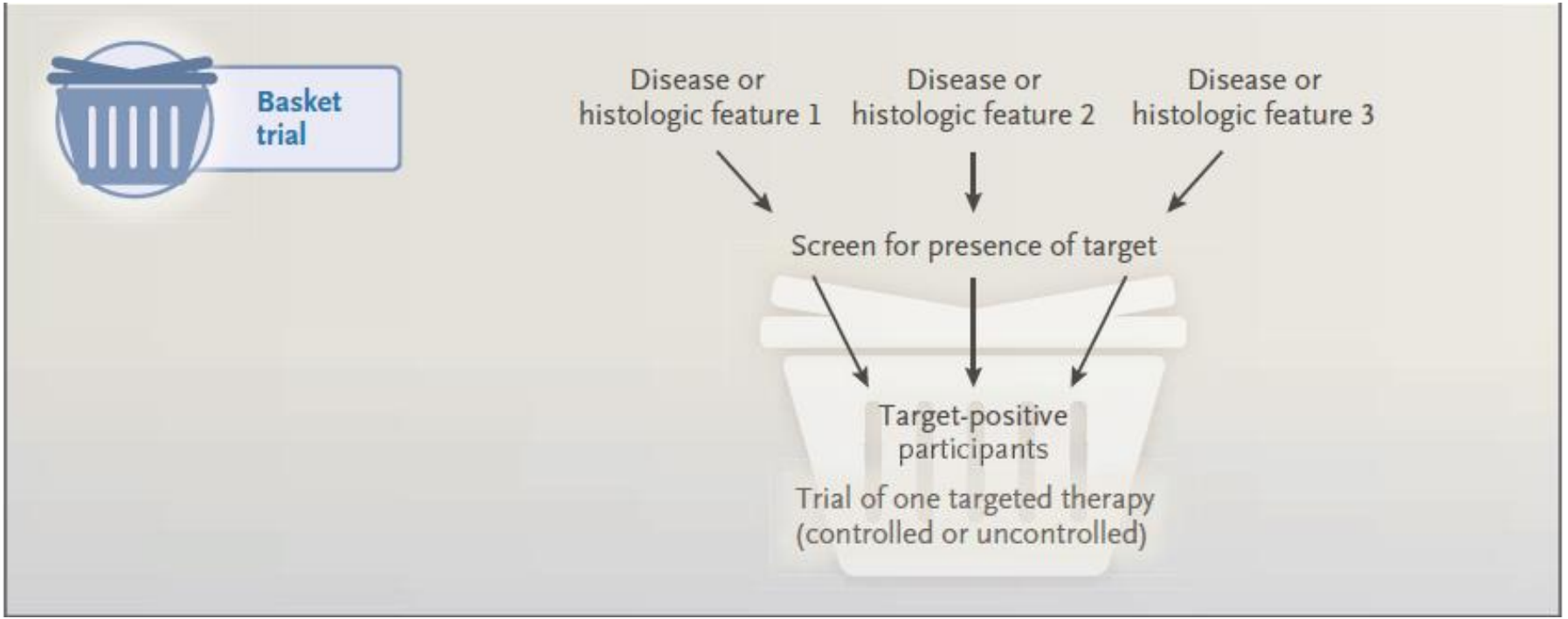
Woodcock e.a., NEJM 2017

Umbrella trial



Woodcock e.a., NEJM 2017

Basket trial



Woodcock e.a., NEJM 2017

Master protocols

Possible advantages:

- Trial infrastructure
- Improve recruitment
- Access to small populations (?)
- Respond quickly to new developments

Possible limitations:

- Institutional review process (?)
- Costs to maintain infrastructure (?)

Learning Healthcare system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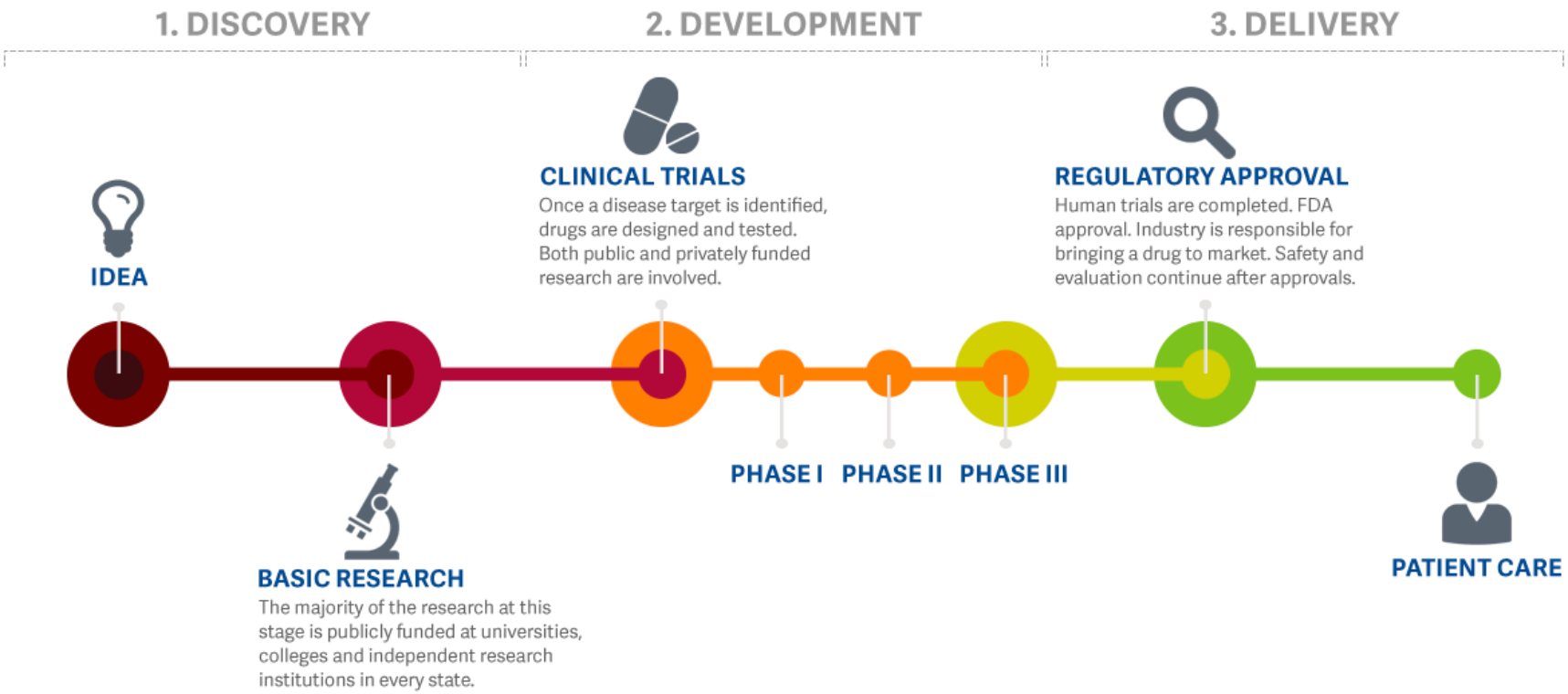
1. DISCOVERY
2. DEVELOPMENT
3. DELIVERY
IDEA
BASIC RESEARCH
The majority of the research at this stage is publicly funded at universities, colleges and independent research institutions in every state.
CLINICAL TRIALS
Once a disease target is identified, drugs are designed and tested. Both public and privately funded research are involved.
PHASE I
PHASE II
PHASE III
REGULATORY APPROVAL
Human trials are completed. FDA approval. Industry is responsible for bringing a drug to market. Safety and evaluation continue after approvals.
PATIENT CARE

Leiden University
Medical Center

r.h.h.groenwold@lumc.nl