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How to make trials efficient: adaptive designs

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Hot topics on methods for clinical research in infectious diseases
ECCMID, Madrid, 24 April 2018

Disclaimer

I have no conflicts of interest to report

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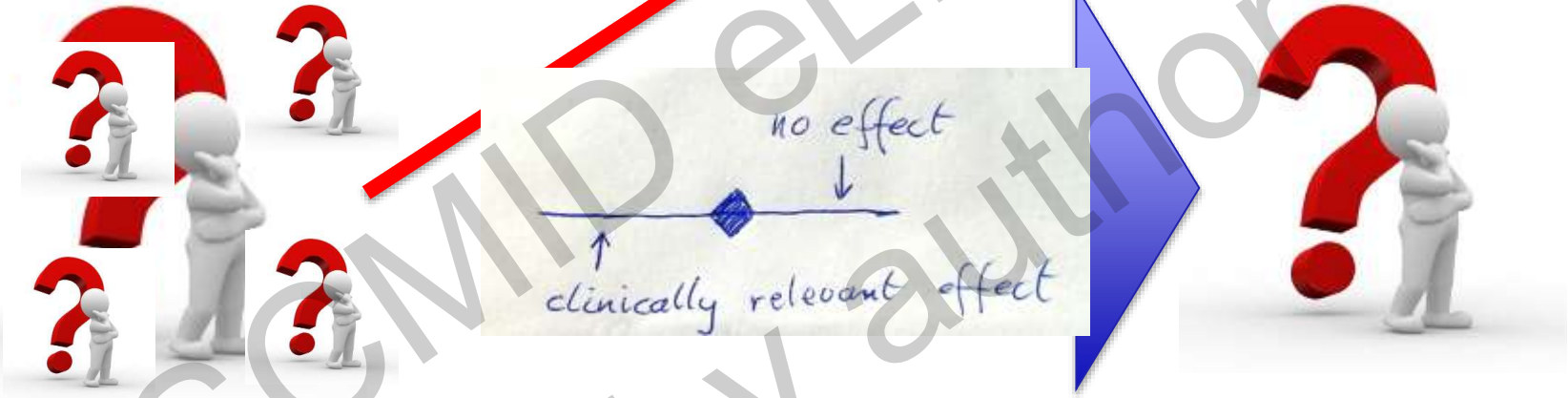
The most efficient way to a reliable answer



Adaptive trials promise to provide the answer to therapeutic questions as efficiently as possible without compromising reliability

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Learning objectives

- What are adaptive trials
- Possibilities, benefits, opportunities
- Risks / potential biases

What is your experience with (adaptive) trials?

1. I have never been involved in any randomised trial
2. I was involved in one or more non-adaptive trials
3. I was involved in one or more adaptive trials
4. I don't know, what is an adaptive trial anyway?

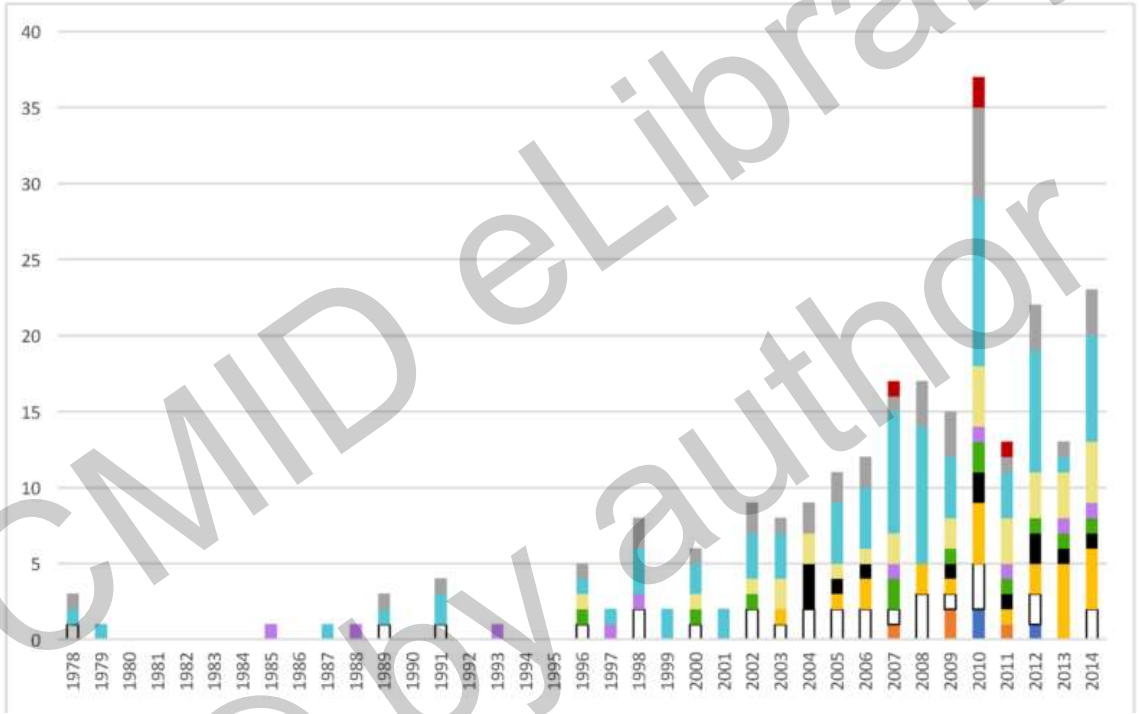
Definition adaptive trial

A trial design that includes decision rules based on which key design elements of the trial are changed during the course of a trial based on accumulating data

- Predefined criteria
- Predefined changes
- Key design elements
- Based on data in or outside the study

Berry DA. Nat Rev Clin Oncol. 2012 Apr;9(4):199–207.

Adaptive trials are increasingly popular



Bothwell LE et al. BMJ Open 2018

Adaptive trials are heterogeneous

Types of adaptive design - systematic review of 142 trials *

Adaptive dose-finding	Adaptive hypothesis
Adaptive group sequential	Adaptive randomisation
Seamless phase II/III	Adaptive treatment-switching
Biomarker-adaptive	Pick-the-winner/drop-the-loser
Sample size re-estimation	Multiple adaptive

* phase I trials and seamless phase I/II trials were excluded

Bothwell LE et al. BMJ Open 2018

Key design elements

- Sample size
- Interventions
- Study population
- Randomisation ratio

Berry DA. Nat Rev Clin Oncol. 2012 Apr;9(4):199–207.

Example research question

- Sepsis in critically ill patients

- Aminoglycosides in addition to a beta-lactam regimen
  - Dosage? Gentamycin 5 or 10 mg/kg OD
  - Duration? Single dose or 3 days
  - Therapeutic drug monitoring? (if >1 dose)
  - Subgroup effects? E.g. sepsis severity

= 6 regimens
+ standard care

- Outcome: alive without dialysis within 28 days

Example fixed trial design

- 7 arms
  - 21 comparisons

+ 2 subgroups
42 subgroup comparisons

- Sample size calculation
  - Baseline mortality: 20%
  - Relevant effect size: 5%
  - Power: 80%
  - Alpha: 0.0024
  - 1,737 * 7 → **12,159**

Alpha 0.0012
1,924 * 7 * 2 → **26,936**

Adaptive sample size

- Multiple interim analyses
- Predefined stopping rules
  - Safety
  - Superiority
  - Futility
- Sample size recalculation
  - Conditional power
- Typical interim analysis not considered adaptive

Adaptive sample size

Advantage:

- Larger effect → smaller sample size
- Smaller incidence → larger sample size → conclusive

Statistics adaptive sample size

- Frequentist
  - Statistical tests
    - Reject null hypothesis?
    - Futility?

p-value < 0.01
Test statistic

- Bayesian
  - Posterior probability of hypothesis being true
    - A > B & C & …
    - B > A & C & …, etc.
    - A = B = C = … (within equivalence margin)

Pr(H=true) > 0.99

Example adaptive sample size

	Outcome rates			Posterior probability			
N	Arm A	Arm B	Arm C	A sup	B sup	C sup	Eq
1000	25%	25%	20%	10%	10%	70%	20%
1500	25%	25%	20%	5%	5%	85%	10%
2000	25%	25%	20%	2%	2%	94%	5%
2500	25%	25%	20%	<1%	<1%	>99%	1%

Arm C superior, randomisation stops

Adaptive interventions

- Multi-arm trial
- Drop least promising based on response or toxicity
  - Drop-the-loser
- E.g. dose finding in phase I/II trials

Example adaptive interventions

	Outcome rates			Posterior probability			
N	Arm A	Arm B	Arm C	A sup	B sup	C sup	Eq
1000	25%	30%	20%	12%	5%	71%	15%
1500	25%	30%	20%	7%	<1%	85%	8%
2000	25%	-	20%	<1%	-	>99%	<1%

Arm B dropped because of inferiority

Study population

- Population enrichment
  - Continue trial with subset in which greatest benefit is observed
  - Stop recruiting subjects with unlikely clinically relevant benefit

- Clinically relevant factors
  - Rationale for effect modification
  - Identifiable in a clinical setting

- E.g. sepsis severity

Example adaptive study population

No septic shock

	Outcome rates			Posterior probability			
N	Arm A	Arm B	Arm C	A sup	B sup	C sup	Eq
1000	20%	20%	20%	33%	33%	33%	75%
1500	20%	20%	20%	33%	33%	33%	>99%

Equivalent: stop randomising septic shock patients

Septic shock

	Outcome rates			Posterior probability			
N	Arm A	Arm B	Arm C	A sup	B sup	C sup	Eq
1000	25%	25%	20%	10%	10%	70%	15%
1500	25%	25%	20%	5%	5%	85%	10%

Randomisation ratio

- Change treatment allocation ratio during trial
  - Response Adaptive Randomisation
  - Based on treatment success

Example response adaptive randomisation

Start with 1:1:1:1 randomisation

	Outcome rates				Posterior probability				
N	Arm A	Arm B	Arm C	Arm D	A sup	B sup	C sup	D sup	Eq
1000	25%	25%	30%	20%	12%	12%	5%	71%	15%

New allocation ratio 2:2:1:5

Response adaptive randomisation

- More patients treated with best treatment

- Statistical efficiency
  - Worse treatment drops off early
  - More data for treatments with smaller effect size

During a planned interim analysis the DSMB recommends to increase the sample size because the observed effect size was smaller than expected but still clinically relevant. The investigator follows the advise.

Is this an adaptive trial?

1. Yes
2. No

Putting all adaptations together: REMAP

Randomised

Embedded

Multifactorial

Adaptive

Platform

Putting all adaptations together: REMAP

Randomised
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- Randomisation for multiple treatment domains
- E.g. therapy A vs. B *and* rapid test vs. conventional test

Putting all adaptations together: REMAP

Randomised
Embedded
Multifactorial
Adaptive
Platform

→

- Embedded in clinical care
- Clinical moment
- Available treatment options

→

- Focus on disease
- Seamless transition to next therapeutic question

Putting all adaptations together: REMAP

Randomised
Embedded
Multifactorial
Adaptive
Platform

- Response Adaptive Randomisation
- Dropping inferior treatments
- Dropping subgroups
- Randomisation within domain until conclusion drawn
- Add new domains or treatments

I-SPY 2: adaptive platform trial

- Phase II trial stage II or III breast cancer
- Eight biomarker subtypes
- Multiple experimental regimens added to standard neoadjuvant chemotherapy
- Objective platform trial: reduce nr. patients needed
- Publication: veliparib and carboplatin in patients with HER2-positive, hormone-receptor–negative signature
- Trial goes on!

Rugo HS et al. N Engl J Med. 2016 Jul 7;375(1):23-34.

Advantages of adaptive trials

- Ethical
  - Better treatment
- Efficient
  - Costs
  - Time
- Conclusive result
- Epidemics preparedness

REMAP CAP

Platform for European Preparedness Against (Re-)emerging Epidemics

- Community-acquired pneumonia in ICU

- 2 antibiotic regimens
- 2 immune modulation arms
- 3 ventilation arms
- 4 subgroups

} 12 treatment modalities

- Pre-planned pandemic treatment arms

ClinicalTrials.gov: NCT02735707 (currently recruiting)

Are adaptive trials always smaller than RCTs?

1. Yes
2. No, it depends on the decision rules
3. No, it depends on the treatment effect size
4. No, it depends on the number of treatment arms
5. It's a lottery

Example trial – expected sample size

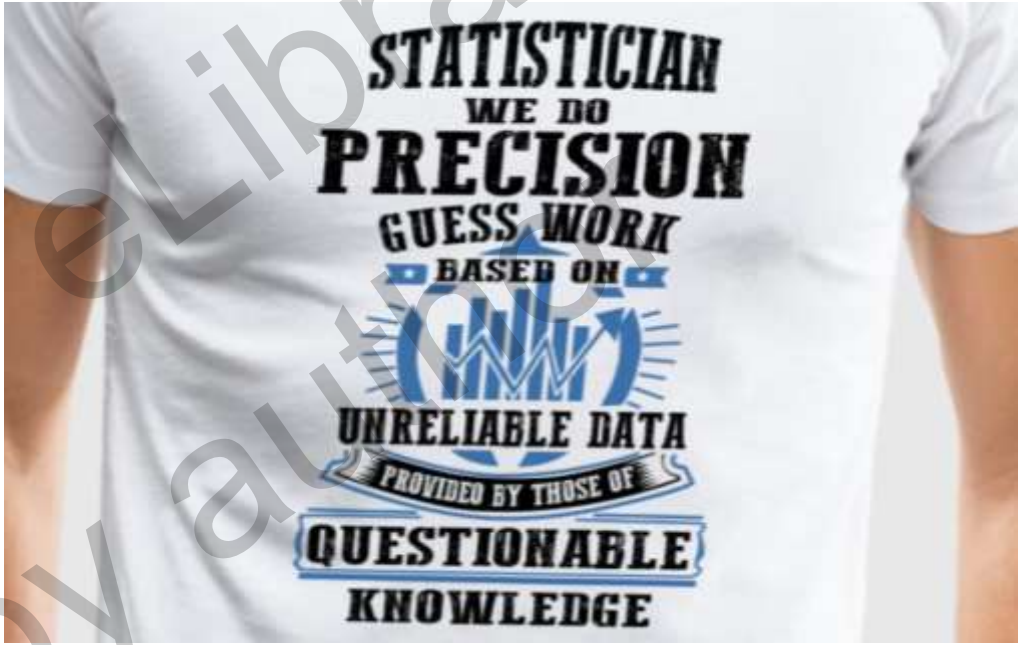
- Trial with 7 interventions
- Ignoring the subgroups
- Fixed trial: **N=12,159**
- REMAP trial: **N=~7,000** if 1-3 arms are superior
  N=~11,000 if all 7 arms are equivalent

No trial is the average trial

- Efficiency gain is average under assumed effects
  - Random process, actual sample size will differ
  - Small true effect might inflate required sample size
- Study budget
- But: fixed sample size in these cases inconclusive

Risks / potential biases

- Multiple testing
- Covariate imbalance
- Time trends



Summary adaptive trials

- Predefined decision rules to change key design elements
  - Sample size
  - Interventions
  - Randomisation ratio
  - Study population
- Advantages:
  - Ethics, costs, time, conclusive
  - Epidemics preparedness
- Risks: biases, budget

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REMAP CAP

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Back-up

Table 3 Leading areas of investigation, endpoints and intervention types in adaptive trials

Area of investigation	Number of trials
Oncology	28/142 (20%)
Infectious diseases	18/142 (13%)
Circulatory system disorders	14/142 (10%)
Nervous system diseases	14/142 (10%)
Other diseases/disorders	68/142 (48%)
Endpoints	**Number of trials**
Surrogate measures	25/142 (18%)
Clinical endpoints	38/142 (27%)
Surrogate measures and clinical endpoints	79/142 (56%)
Type of intervention	**Number of trials**
Drugs	121/142 (85%)
Other therapies	13/142 (9%)
Medical devices	9/142 (6%)

Bothwell LE et al. BMJ Open 2018

Adaptive trials are heterogeneous

Types of adaptive design in systematic review of 142 trials *

Adaptive dose-finding: **16%**	Adaptive hypothesis: **2%**
Adaptive group sequential: **21%**	Adaptive randomisation: **7%**
Seamless phase II/III: **57%**	Adaptive treatment-switching: **3%**
Biomarker-adaptive: **20%**	Pick-the-winner/drop-the-loser: **9%**
Sample size re-estimation: **8%**	Multiple adaptive

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Experimentwise error rate

- Multiple testing problem
  - False-positivity rate should be <0.05 (type-I error)
  - Power should be adequate (type-II error)

- Error rate control

Frequentist	Bayesian
Given type-I and type-II error rates	Given decision rules
Given clinically relevant effect	Given realistic scenarios
Calculation of decision rules	Simulations to determine error rate

Covariate imbalance

- Particularly for small trials
- But also relevant for small subgroups
- Solutions:
  - Stratified randomisation
  - Covariate adaptive randomisation
  - Adjustment

Ning & Huang. Statistics in medicine 2010

Time trends

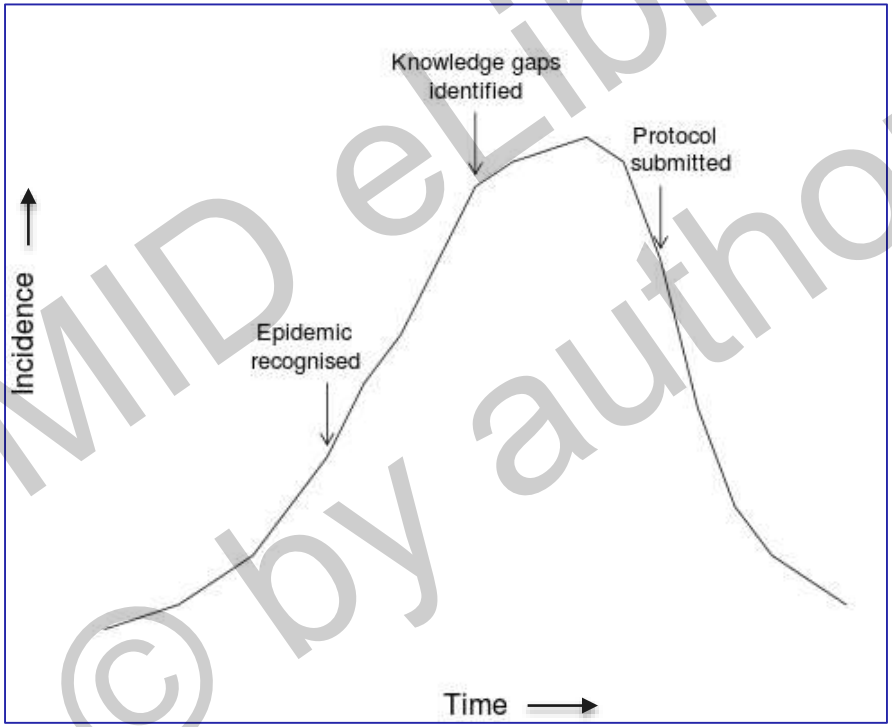
- Case mix & allocation ratio may change over time

- Needs to be solved in data analysis
  - Stratification by allocation time
  - Allocation time as trend
  - Inverse probability of treatment weighting
  - Hierarchical regression

Lipsky Clinical trials 2011

Opportunities for infectious diseases

Relation between trials and epidemics



Have adaptive platform trial up & running

- Domain of interest
  - e.g. acute respiratory infections
- Pre-planned rules to adapt treatment domains
  - e.g. upon start of influenza pandemic
- Efficiently spend waiting time
  - Answer relevant questions
  - Keep machinery running