

# Pragmatic Trials – An overview

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# Background

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- Features & goals of “traditional” clinical trials:
  - Very controlled protocol: Population (inex), environment, ...
  - Demonstrate efficacy and safety of a new treatment
  - Designed to show that treatment “works”

⇒ High internal validity
- What about external validity?
  - Often important to establish **clinical effectiveness**
  - Generalizability of results? Setting too artificial?

⇒ Demonstrate treatment effect in heterogeneous setting, assumed to reflect the “real world” with regard to population, environment, ...

# Background

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Ideas to run trials in a “real-world” setting:

- Data sources (health records, registries, social media, ...)
- Collection of data (home monitoring, e-devices, apps, ...)
- Design of trials (prospective/retrospective, randomized or not, ...)

⇒ Increase external validity (!?)

“Real-world” trials and randomization – a contradiction?

*“Real world evidence and randomisation are two fully compatible concepts”*

– Sherman et al. (2016) [1]

*“Statisticians can also perform a valuable service by continually reminding people about what a powerful tool randomization is.”*

– Robert M Califf (2016) [2]

# Pragmatic Trials

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- Pragmatic **randomised** trials (PrCTs) are a way to estimate a treatment's effectiveness
- First paper to discuss pragmatic approaches in clinical trials goes back to the 1960s (Schwartz and Lellouch (1967) [3])

*“[...] there is a continuum between pragmatic and explanatory trials [...]”*

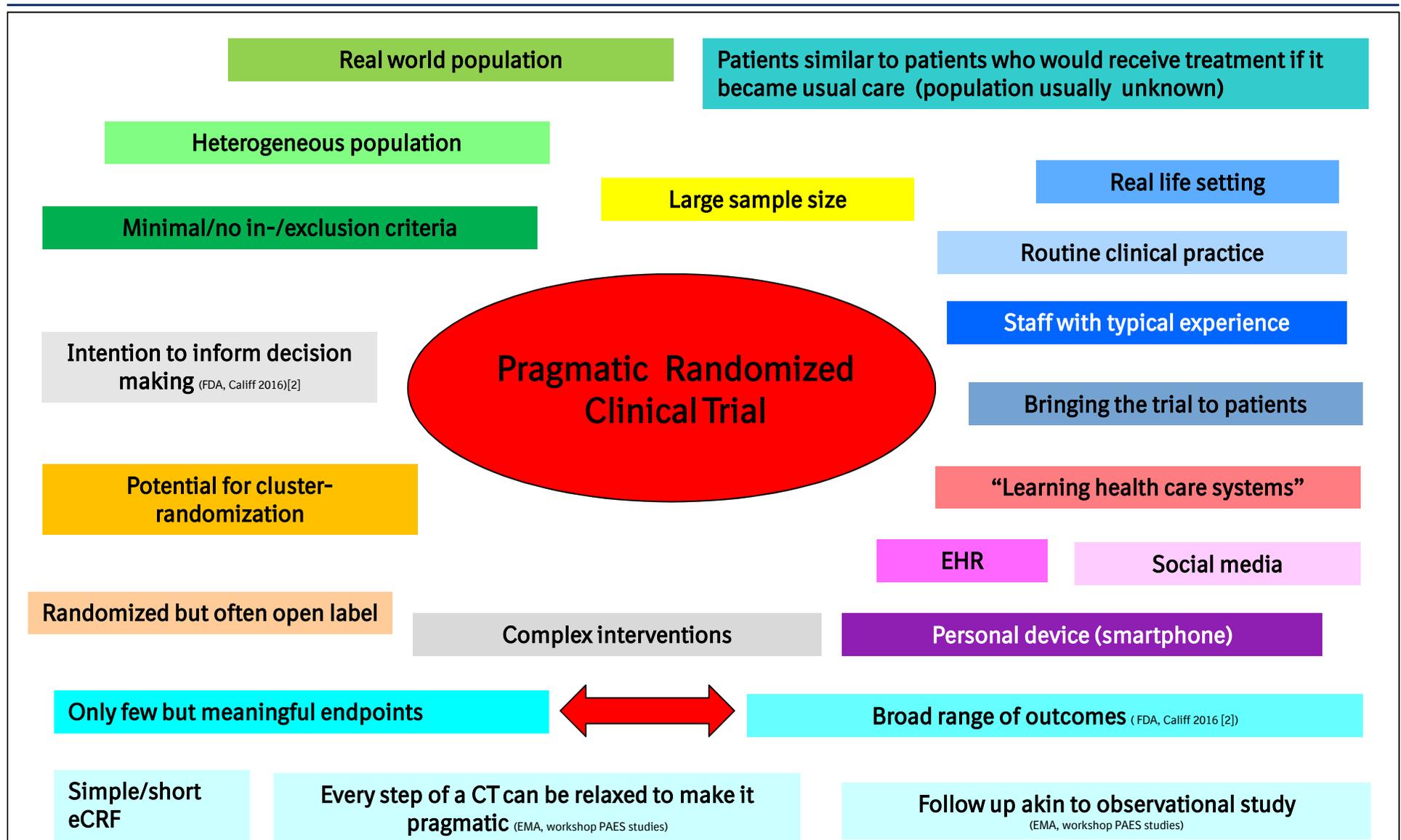
*– Patsopoulos N. (2011) [4]*

*“Very few trials can be fully pragmatic.”*

*– Ford and Norrie (2016) [5]*

Note: By *explanatory trials* the “classical” confirmatory randomized trials are meant

# Pragmatic Trials - Definition



# Pragmatic Trials - Definition

Not a single, generally accepted definition (yet) ⇒ some (common and overlapping ) ideas of a definition in:

- Zuidgeest MGP, Goetz I, Growenwold RHH, et al. (2017). *Series: Pragmatic trials and real world evidence: Paper 1. Introduction*; Journal of Clinical Epidemiology; 88, 7-13 [6]
- Califf RM (2016). *Pragmatic clinical trials: Emerging challenges and new roles for statisticians*. Clinical Trials; 13(5):471-477 [2]
- Ford I and Norrie J (2016). *Pragmatic Trials*. N Engl J Med; 375:454-463 [5]

A definition from IMI GetReal [7]:

“A study comparing several health interventions among a randomised, diverse population representing clinical practice, and measuring a broad range of health outcomes.”

Sim  
eCRF

pragmatic (EMA, workshop PAES studies)

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# Pragmatic Trials - Definition

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Internal WG on PrCT within BI ⇒ White Paper and identification of the following **key pragmatic design elements**

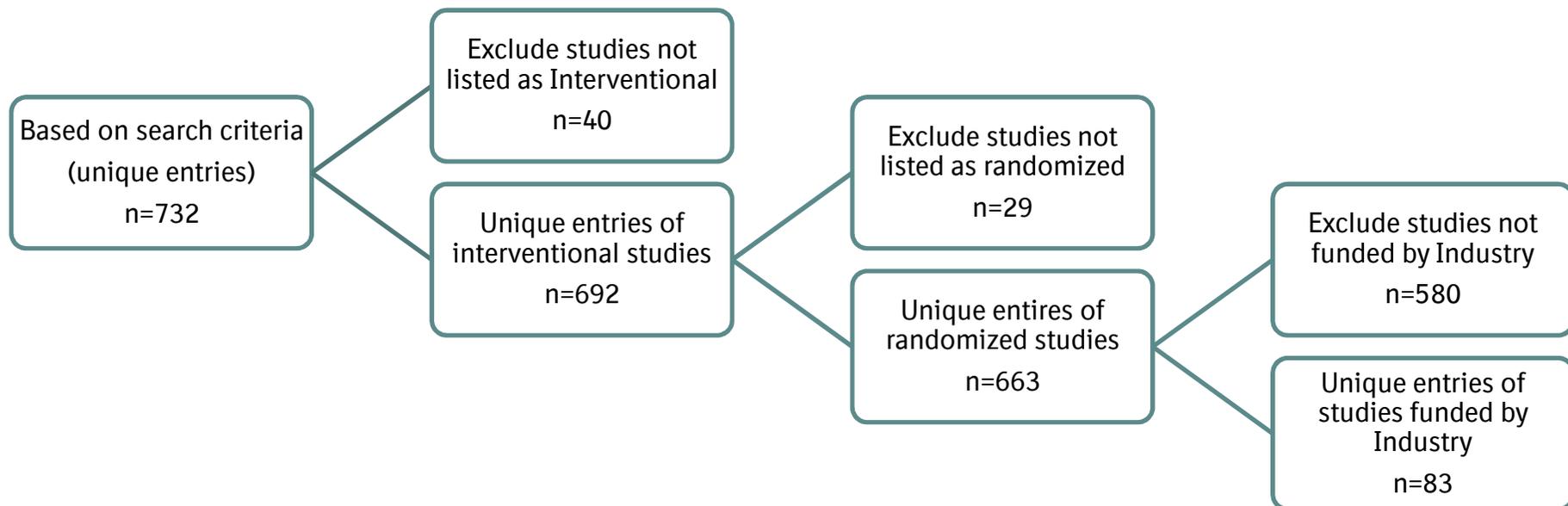
PrCT is a randomized clinical trial, which

- enrolls a **real-world population**, i.e. a population close to the patient population that would receive the treatment in practice
- is conducted in a **real-world setting** (e.g. rather GPs, community sites than professional study sites)
- captures the **relevant outcomes** to inform optimal healthcare treatment decisions
- includes an **appropriate comparison arm** depending on the question of interest

# Pragmatic Trials - CT.gov Search Results for PrCT

Search terms	n
pragmatic AND randomized	450
pragmatic AND randomised	94
real world AND randomized	271
real world AND randomised	15
<b>total</b>	<b>830</b>

Conducted in Sep 2017



Victoria Gamerman, Tianxi Cai, Amelie Elsässer (2018). *Pragmatic randomized clinical trials: best practices and statistical guidance*. Health Services and Outcomes Research Methodology, under review

# Pragmatic Trials - CT.gov Search Results for PrCT

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- Review of industry funded studies titles  $\Rightarrow$  20 titles allow for identification as clearly PrCT (or included 'effectiveness' or 'real world')

<u>Phase</u>	<u>Results (n=20)</u>	<u>Therapeutic area</u>	<u>Results (n=20)</u>
II/III	1	CNS	2
III	2	Metabolic disease	5
IV	11	Respiratory	5
not listed	6	Cardiovascular	3
		Oncology	0
		Other	5

- Limitation: Very few trials identified as pragmatic**  
Not all pragmatic trials are easily identifiable through a database search if relevant terms like 'pragmatic' or 'real world' were not used e.g. in the title

Victoria Gamerman, Tianxi Cai, Amelie Elsässer (2018). *Pragmatic randomized clinical trials: best practices and statistical guidance*. Health Services and Outcomes Research Methodology, under review

# Pragmatic Trials - EudraCT Search Results for PrCT

<u>Search terms</u>	<u>n</u>
pragmatic AND randomized	15
pragmatic AND randomised	21
real world AND randomized	6
real world AND randomised	5
<b>Total in EudraCT</b>	<b>47</b>
<b>PrCT after title review</b>	<b>26</b>

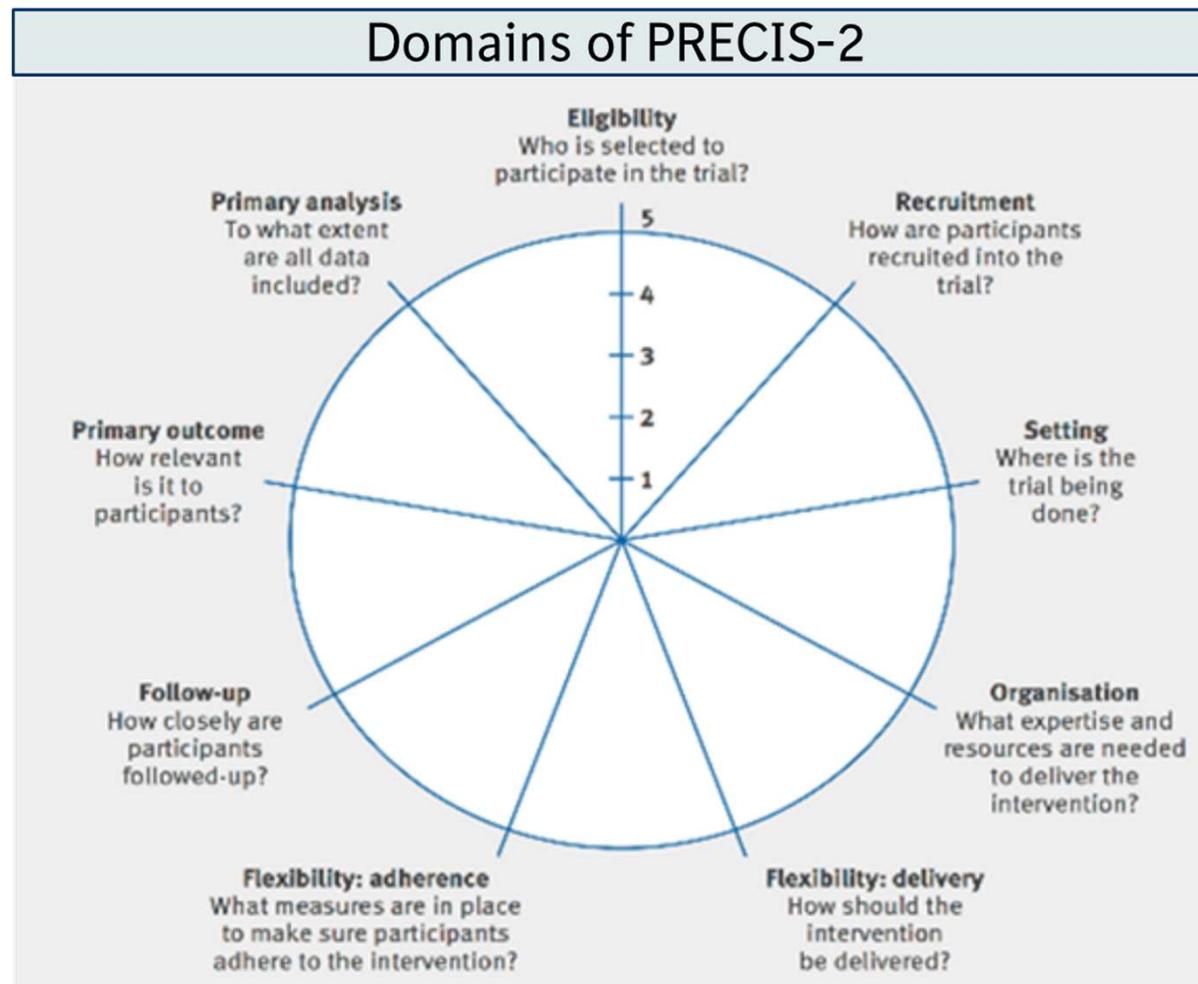
<u>Therapeutic area</u>	
CNS	10
Metabolic disease	5
Respiratory	2
Cardiovascular	1
Oncology	0
Other	8
<b>Total</b>	<b>26</b>

<u>Type of sponsor</u>	<u>n</u>
Pharmaceutical company	8
University / University hospital	13
Other	5
<b>total</b>	<b>26</b>

- 18 out of 26 trials conducted in Great Britain
- Only 3 trials marked as completed
- Same limitations of search as with CT.gov

# Pragmatic Trials – Assessing degree of pragmatism

- <https://www.precis-2.org/> [8]
- <https://www.pragmamic.eu>



# Examples - Salford Lung Study & AIRWISE

GSK, 2 trials: one for COPD, and one for asthma, pragmatic randomised open label Phase III trials) [9, 10]

- “World’s first pragmatic randomized controlled trial of an investigational medication”[9]
- Fluticasone furoate/vilanterol vs. existing COPD/existing asthma maintenance therapy
- Study conducted around Salford, high COPD prevalence, single hospital, established **electronic medical record, GPs and pharmacies** collaborated
- **Minimal exclusion criteria**
- Primary outcome:
  - for COPD: mean annual rate of COPD exacerbations
  - for asthma: asthma control test at week 24

*Randomized Pragmatic Clinical Trial in a Community-Based Setting  
Comparing STIOLTO® RESPIMAT® vs. ICS-LABA plus LAMA in Patients  
with COPD*

- “[...] phase 4 clinical trial aiming to assess how commonly prescribed medicines may decrease the worsening of symptoms in [...] COPD [...]” ([www.copdnews.com](http://www.copdnews.com), OCT 6, 2017)
- “The AIRWISE trial (NCT03265145) is described as the **world’s largest ever pragmatic clinical trial**, meaning it is designed to test a medication’s effectiveness in routine clinical practice settings.” ([www.copdnews.com](http://www.copdnews.com), OCT 6, 2017)
- **3200 participants randomized parallel assessment**
- Started September 2017, estimated completion in June 2020
- Primary outcome: Time to first moderate or severe COPD) exacerbation over 12 months

# Example - Ebola Ça Suffit!

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WHO sponsored, vaccine from Merck Sharp & Dohme, ring vaccination cluster randomized open-label clinical trial in Guinea/Sierra Leone during Ebola outbreak in 2015 [11]

- Vaccine for Zaire Ebola Virus
- **Ring/cluster** i.e. all contacts and contacts of contacts of confirmed Ebola case
- 1:1 rand. to immediate or **delayed vaccination**, i.e. 21 days later, of all people in the cluster
- Immediate vaccination: 51 cluster with n=4539 contacts and contacts of & delayed vaccination: 47 clusters with n=4557 contacts and contacts of contacts identified
- Primary outcome: laboratory confirmed case of Ebola virus disease with onset 10 days or more until 31 days from randomisation

# Thank you

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“[...] access to **statistical support and collaboration** is among the **most critical needs** identified by clinical and translational investigators [...]”

“[...] it is imperative that we work to **expand the pipeline of well-trained statisticians** [...]”

*-- Robert M Califf (2016) [2]*

# References

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- [1] Sherman RE, et al.: *Real-World Evidence – What Is It and What Can It Tell Us?* N Engl J Med 2016; 75(23):2293-2297
- [2] Califf RM: *Pragmatic clinical trials: Emerging challenges and new roles for statisticians.* Clinical Trials 2016; 13(5):471-477.
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- [5] Ford I and Norrie J: *Pragmatic Trials.* N Engl J Med 2016; 375:454-463.
- [6] Zuidgeest MGP., Goetz I, Growenwold RHH, et al. Series: Pragmatic trials and real world evidence: Paper 1. Introduction; Journal of Clinical Epidemiology 2017, 88:7-13.
- [7] [https://www.imi-getreal.eu/Portals/1/Documents/01%20deliverables/D1.3%20-%20Revised%20GetReal%20glossary%20-%20FINAL%20updated%20version\\_25Oct16\\_webversion.pdf](https://www.imi-getreal.eu/Portals/1/Documents/01%20deliverables/D1.3%20-%20Revised%20GetReal%20glossary%20-%20FINAL%20updated%20version_25Oct16_webversion.pdf) (last accessed 8 JUL 2018)
- [8] Loudon K, et al., The PRECIS-2 tool: designing trials that are fit for purpose; *BMJ* 2015; 350:h2147

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- [9] Bakerly et al. : *The Salford Lung Study protocol: a pragmatic, randomised phase III real-world effectiveness trial in chronic obstructive pulmonary disease*; Respiratory Research 2015;16:101
- [10] Woodcock et al. : *The Salford Lung Study protocol: a pragmatic, randomised phase III real-world effectiveness trial in asthma*; BMC Pulmonary Medicine 2015;15:160
- [11] Restrepo et al. : *Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial*; Lancet 2017; 389:505–18