A look on Best Practices in Pragmatic Trials

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Disclaimer

Opinions expressed in this presentation are my personal ones and must not be construed as representing the opinion of Boehringer Ingelheim or any other institution with which I have been affiliated in my professional life.

Prepared with material from Amelie Elsäßer and Victoria Gamerman

Background

The POET-COPD trial - a pragmatic trial?

- 1-year, randomized, parallel group (Tiotropium vs. Salmeterol), double-blind, global phase IV trial
- Set of In/Ex-criteria
- Primary endpoint: Time to first COPD exacerbation
- Supportive secondary endpoints with regard to exacerbations
- Safety monitoring concentrated on SAEs and mortality

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Tiotropium versus Salmeterol for the Prevention of Exacerbations of COPD

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ABSTRACT

BACKGROUND

Treatment guidelines recommend the use of inhaled long-acting bronchodilators to alleviate symptoms and reduce the risk of exacerbations in patients with moderate-to-very-severe chronic obstructive pulmonary disease (COPD) but do not specify whether a long-acting anticholinergic drug or a β_2-agonist is the preferred agent. We investigated whether the anticholinergic drug tiotropium is superior to the β_2-agonist salmeterol in preventing exacerbations of COPD.

METHODS

In a 1-year, randomized, double-blind, double-dummy, parallel-group trial, we compared the effect of treatment with 18 μg of tiotropium once daily with that of 50 μg of salmeterol twice daily on the incidence of moderate or severe exacerbations in patients with moderate-to-very-severe COPD and a history of exacerbations in the preceding year.

RESULTS

A total of 7376 patients were randomly assigned to and treated with tiotropium (3707 patients) or salmeterol (3669 patients). Tiotropium, as compared with salmeterol, increased the time to the first exacerbation (187 days vs. 145 days), with a 17% reduction in risk (hazard ratio, 0.83; 95% confidence interval [CI], 0.77 to 0.90; P<0.001). Tiotropium also increased the time to the first severe exacerbation (hazard ratio, 0.72; 95% CI, 0.61 to 0.85; P<0.001), reduced the annual number of moderate or severe exacerbations (0.64 vs. 0.72; rate ratio, 0.89; 95% CI, 0.83 to 0.96; P=0.002), and reduced the annual number of severe exacerbations (0.09 vs. 0.13; rate ratio, 0.73; 95% CI, 0.66 to 0.82; P<0.001). Overall, the incidence of serious adverse events and of adverse events leading to the discontinuation of treatment was similar in the two study groups. There were 64 deaths (1.7%) in the tiotropium group and 78 (2.1%) in the salmeterol group.

CONCLUSIONS

These results show that, in patients with moderate-to-very-severe COPD, tiotropium is more effective than salmeterol in preventing exacerbations. (Funded by Boehringer Ingelheim and Pfizer; ClinicalTrials.gov number, NCT00563381.)

From the Hospital of the Universities of Giessen and Marburg, Marburg (C.V.); Boehringer Ingelheim, Ingelheim (B.H., T.G., H.S.); and insaf Respiratory Research Institute, Wiesbaden (K.M.B.) — all in Germany; the Institute for Medical Technology Assessment (IMTA), Erasmus University, Rotterdam (M.P.M.H.R.-M.); and Leiden University Medical Center, Leiden (K.F.R.) — both in the Netherlands; and the University of Modena and Reggio Emilia, Modena, Italy (L.M.F.). Address reprint requests to Dr. Fabbri at the Section of Respiratory Diseases, Department of Oncology, Hematology, and Pulmonary Diseases, University of Modena and Reggio Emilia, Policlinico di Modena, Largo del Pozzo 71, I-41124 Modena, Italy, or at leonardo.fabbri@unimore.it.

*The investigators in the Prevention of Exacerbations with Tiotropium in COPD (POET-COPD) trial are listed in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2011;364:1093-103.

Background

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

  ⇨ High internal validity

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

  ⇨ Demonstrate a treatment effect in a more heterogeneous population – assumed to reflect a “real world” setting

Background

- Abundance of 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, …)

  ⇨ High 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

- 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

Real world population

Patients similar to patients who would receive treatment if it became usual care (population usually unknown)

Heterogeneous population

Large sample size

Real life setting

Minimal/no in-/exclusion criteria

Routine clinical practice

Staff with typical experience

Intention to inform decision making (FDA, Califf 2016)[2]

Pragmatic Randomized Clinical Trial

Bringing the trial to patients

Potential for cluster-randomization

"Learning health care systems"

EHR

Social media

Randomized but often open label

Complex interventions

Personal device (smartphone)

Only few but meaningful endpoints

Broad range of outcomes (FDA, Califf 2016 [2])

Simple/short eCRF

Every step of a CT can be relaxed to make it pragmatic (EMA, workshop PAES studies)

Follow up akin to observational study (EMA, workshop PAES studies)

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."

Pragmatic Trials - Definition

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 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

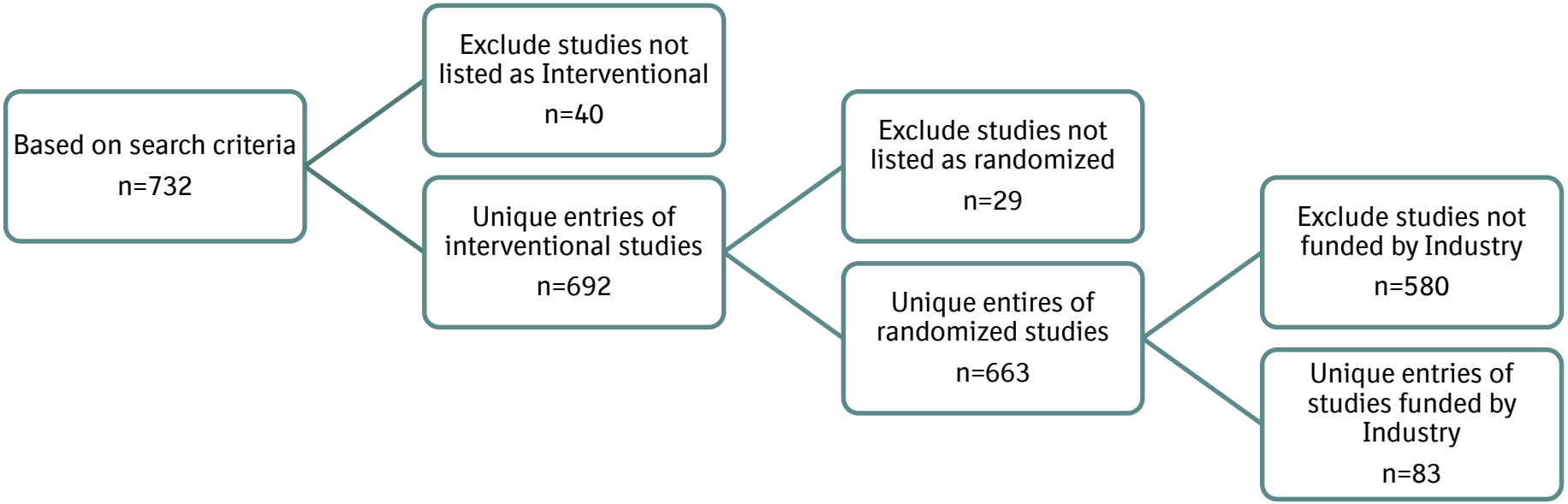
*Amelie Elsässer and Victoria Gamerman

Pragmatic Trials - CT.gov Search Results for PrCT

- Conducted in Sep 2017

  n=830 data base entries identified
  n=732 unique entries (excl. duplicates)

Search terms	n
pragmatic AND randomized	450
pragmatic AND randomised	94
real world AND randomized	271
real world AND randomised	15
total	**830**



Victoria Gamerman, Tianxi Cai, Amelie Elsäßer (2019). *Pragmatic randomized clinical trials: best practices and statistical guidance*. Health Services and Outcomes Research Methodology. Health Serv Outcomes Res Method 19: 23, https://doi.org/10.1007/s10742-018-0192-5

Pragmatic Trials - CT.gov Search Results for PrCT

- Industry sponsored entries ⇨ 20 titles came to the top of the list as being clearly pragmatic randomized trials, or included the term ‘effectiveness’ or ‘real world’

Phase	Results (n=20)
II/III	1
III	2
IV	11
not listed	6

Therapeutic area	Results (n=20)
CNS	2
Metabolic disease	5
Respiratory	5
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 (2019). *Pragmatic randomized clinical trials: best practices and statistical guidance*. Health Services and Outcomes Research Methodology. Health Serv Outcomes Res Method 19: 23, https://doi.org/10.1007/s10742-018-0192-5

Pragmatic Trials - EudraCT Search Results for PrCT

- Conducted March 2017
  - Overall n=47 trial entries in EudraCT identified
  - Out of n=47, n=26 remained to be classifiable as PrCT after title review

Search terms	n
pragmatic AND randomized	15
pragmatic AND randomised	21
real world AND randomized	6
real world AND randomised	5
total	**47**

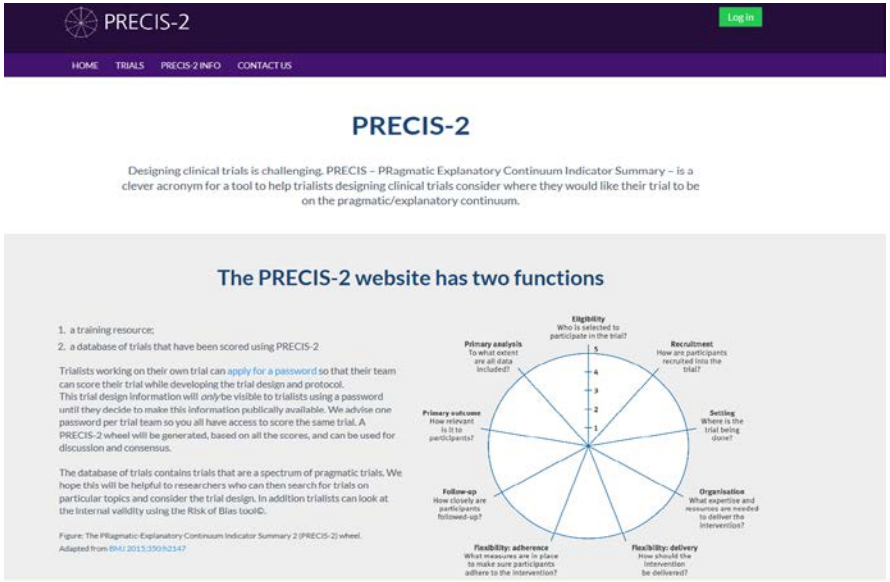
Type of sponsor	n
Pharmaceutical company	8
University / University hospital	13
Other	5
total	**26**

Therapeutic area	Results (n=26)
CNS	10
Metabolic disease	5
Respiratory	2
Cardiovascular	1
Oncology	0
Other	8

- Trials often conducted in Great Britain (n=18 list GB as country)
- Only **3 trials marked as completed**
- **Same limitations** of search as with CT.gov

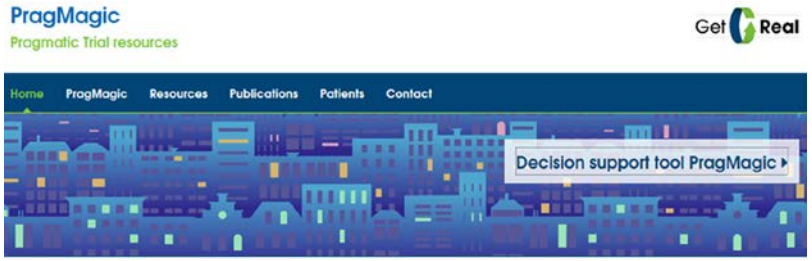
Pragmatic Trials - Tools

- https://www.precis-2.org/ [8]



- Developed by scientific experts with experience in pragmatic trials
- Provides 9 different domains
- Can be used in trial planning phase for discussions within trial team
- Can help to make trial design more pragmatic within the different domains

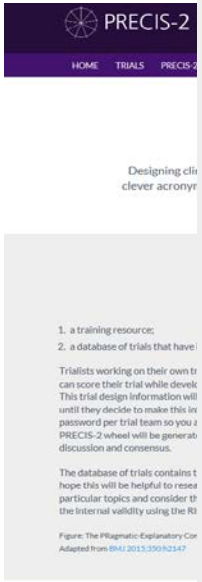
- https://www.pragmagic.eu



- Can be used like PRECIS-2 during trial planning phase
- Takes into account operational challenges and consequences of design choices
- Based on a decision tree – questionnaire with different answers to be ticked
- Includes some gamification elements – the more pragmatic your design choice the more lights are switched on in the city

Pragmatic Trials - Tools

- https:/ ic.eu



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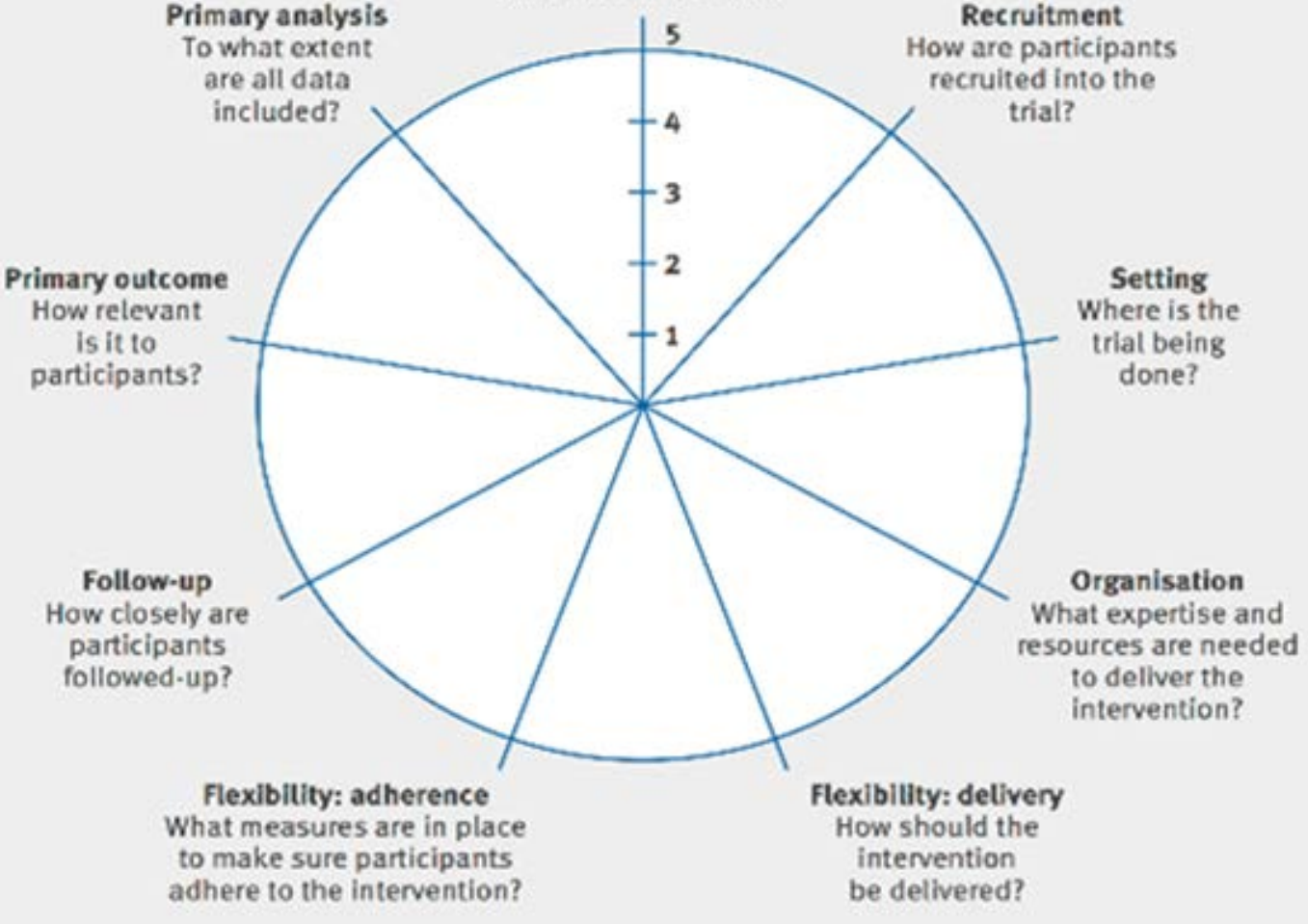
Domains of PRECIS-2



Example #1 – Salford Lung Study

2 trials (one for COPD, 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 /asthma maintenance therapy
- Study conducted around Salford (UK), high COPD prevalence, single hospital, established electronic medical record, GPs and pharmacies collaborated
- Minimal exclusion criteria
- Primary endpoints:
  - For COPD: Mean annual rate of COPD exacerbations
  - For asthma: Asthma control test at week 24

Example #2 - Ebola Ça Suffit!

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

References

[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.

[3] Schwartz D and Lellouch J: *Explanatory and pragmatic attitudes in therapeutical trials*. J Chronic Dis. 1967: 20(8):637-48. (re-printed 2009 in Journal of Clinical Epidemiology)

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[5] Ford I and Norrie J: *Pragmatic Trials*. N Engl J Med 2016; 375:454-463.

[6] Zuidgeest, M.G.P., Goetz, I., Growenwold, R.H.H., 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 (last accessed 22 Sep 2019)

[8] Loudon K. et al.: The PRECIS-2 tool: designing trials that are fit for purpose; *BMJ* 2015;350:h2147

[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