Developing a research protocol: PICO–population, intervention, comparator, outcomes; setting, timing and feasibility issues in real life

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BREATHE WELL

Components of a question

Aims? Describe the following components in detail in the protocol

- **P** **population**
  - clear definition, consider two aspects
    - Inclusion criteria
    - Exclusions-limits should have a clear rationale; “generalisability”?
- **I** **intervention**
  - formulation, dose, intensity, delivery, timing, frequency, duration, equipment, personnel (qualifications, training), location
- **C** **comparison**
  - define specific active comparisons in as much detail as intervention
  - what do you mean by ‘no intervention’? , e.g. none, placebo, usual care, etc ??

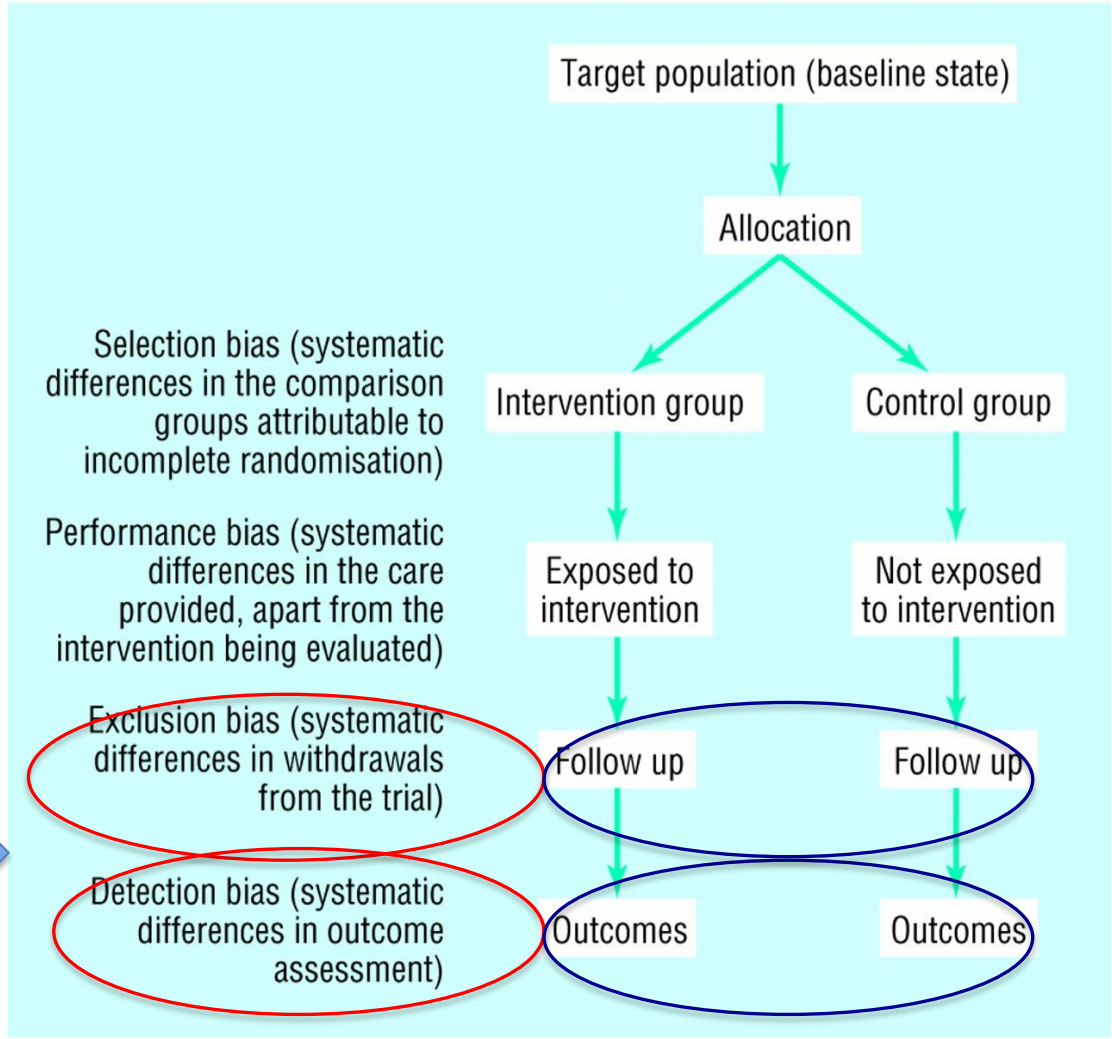
Randomisation & “concealment of allocation”

- **O** **outcomes** **(later slide)**

Study design: outcome measurement

randomised controlled trial (RCT)

(case control, cohort)



Avoid systematic biases

Greenhalgh T BMJ 1997;315:305-308

BMJ

Outcomes: what to measure and how

Consider:

- Objective outcomes
  - "Hard"…DEATH pretty good! …but even then!
  - Surrogate? e.g. blood level of stuff (biomarkers)
  - Need blinded validation (mortality: what/why/when from medical records; Smoking cessation: exhaled CO, urinary/salivary cotinine)

- Patient reported outcomes (PRO)
  - Relevance, importance, appropriate symptoms
  - Objectively validated reliable scales
  - Assessor and patient blinded

Follow up issues: feasibility, time points and losses

- Size of sample
  - Sample size (power calculation and its assumptions)
- Duration of follow up
  - Long enough for effects to be reflected in chosen outcome
- Completeness of follow up
  - Subjects who withdraw (“drop outs”) from studies may be “systematically different” :sicker, wrong diagnosis, adherence issues, adverse reaction (genetic?); controls: don`t like “no effect” etc
  - Outcome data on all randomised participants should be analysed (“intention to treat”), but sub-set analysis or per protocol may give ”correct’ answer!

An example: how does it work in practice?

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RESEARCH

Effect of high flow oxygen on mortality in chronic obstructive pulmonary disease patients in prehospital setting: randomised controlled trial

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ABSTRACT

Objectives To compare standard high flow oxygen treatment with titrated oxygen treatment for patients with an acute exacerbation of chronic obstructive pulmonary disease in the prehospital setting.

Design Cluster randomised controlled parallel group trial.

Setting Ambulance service in Hobart, Tasmania, Australia.

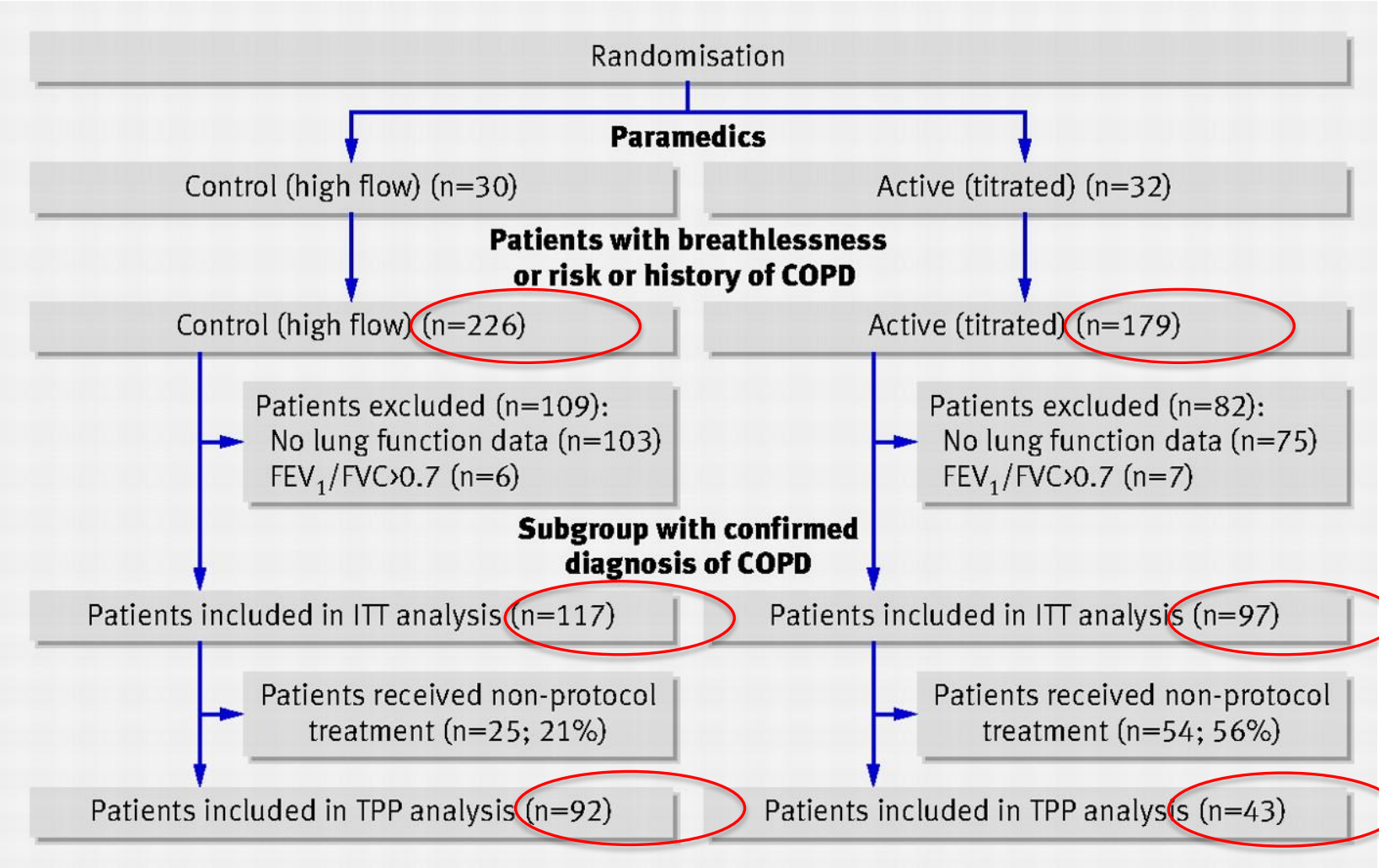
Participants 405 patients with a presumed acute exacerbation of chronic obstructive pulmonary disease who were treated by paramedics, transported, and admitted to the Royal Hobart Hospital during the trial period; 214 had a diagnosis of chronic obstructive pressure −33.6 (16.3) mm Hg; P=0.02; n=29) than were patients who received high flow oxygen.

Conclusions Titrated oxygen treatment significantly reduced mortality, hypercapnia, and respiratory acidosis compared with high flow oxygen in acute exacerbations of chronic obstructive pulmonary disease. These results provide strong evidence to recommend the routine use of titrated oxygen treatment in patients with breathlessness and a history or clinical likelihood of chronic obstructive pulmonary disease in the prehospital setting.

Trial registration Australian New Zealand Clinical Trials Register ACTRN12609000236291.

- **“Cluster randomised”** controlled parallel group trial.
- **Setting:** Ambulance service in Hobart, Tasmania, **Participants**
  - 405 patients with presumed acute exacerbation of COPD, diagnosed and acutely treated by paramedics
  - transported and admitted to Royal Hobart Hospital
- **Interventions prehospital (ambulance/paramedic)** High flow (HF) oxygen standard treatment
  - compared with titrated oxygen treatment
- **Main outcome measures**
  - Prim: Acute/sub-acute mortality; Second:ICU / biomarkers
- **Sample size** -200 participants (100/ group) would provide 83% power to detect a 12**% reduction in mortality**, (reckoned to be 10% due to HF O2)

Flow of participants through study.



Austin M A et al. BMJ 2010;341:bmj.c5462

Assumptions about Power

- Over 400 ED admission per year for acute exacerbation COPD
- 50% would have “validated” COPD
- All paramedics in southern Tassie would join in
- Paramedics would follow protocol

Table 1 Baseline characteristics of treating paramedics. Values are numbers (percentages) unless stated otherwise

Characteristic	Control (high flow oxygen) (n=30)	Active (titrated oxygen) (n=32)
Location:		
Urban	23 (77)	23 (72)
Rural	7 (23)	9 (28)
Qualification:		
Paramedic	10 (33)	8 (25)
Intensive care paramedic	20 (67)	24 (75)
Mean (SD) years of experience	15.5 (8.3)	16.7 (12.1)

Table 2 Baseline characteristics for all patients and subgroup with confirmed diagnosis of chronic obstructive pulmonary disease (COPD). Values are mean (SD) unless stated otherwise

Characteristic	Control (high flow oxygen)	Active (titrated oxygen)
All patients (n=405)		
No (%) male	114/226 (50)	83/179 (46)
Age (years)	69 (10.9) (n=202)	69 (11.8) (n=152)
Prehospital treatment time (minutes)	47 (19) (n=156)	47 (18) (n=144)
Pretreatment oxygen saturation (%)	86 (13.6) (n=189)	88 (9.8) (n=160)
Confirmed diagnosis of COPD (n=214)		
No (%) male	57/117 (49)	45/97 (46)
Age (years)	68.0 (10.2) (n=117)	67.9 (10.3) (n=97)
Per cent predicted FEV1	42.1 (16.4) (n=117)	43.3 (16.5) (n=97)
Smoking history (pack years)	45.5 (26.0) (n=87)	46.3 (22.1) (n=83)
Prehospital treatment time (minutes)	47 (17) (n=87)	50 (19) (n=80)
Pretreatment oxygen saturation (%)	84 (14) (n=101)	87 (10) (n=87)

FEV1=forced expiratory volume in one second.

Table 3 Intention to treat analysis. Values are numbers (percentages) unless stated otherwise

	Control (high flow oxygen)	Active (titrated oxygen)	Treatment effect	P value
Mortality				
All patients	21/226 (9)	7/179 (4)	0.42 (0.20 to 0.89)*	0.02
Confirmed COPD	11/117 (9)	2/97 (2)	0.22 (0.05 to 0.91)*	0.04
Incidence of ventilation				
All patients	19/213 (9)	13/166 (8)	0.88 (0.45 to 1.72)*	0.70
Non-invasive ventilation	7	8		
Invasive ventilation	12	5		
Confirmed COPD	15/105 (14)	8/84 (10)	0.67 (0.29 to 1.54)*	0.34
Non-invasive ventilation	6	5		
Invasive ventilation	9	3		
Length of hospital stay (mean (SD) days)				
All patients	5.9 (5.6) (n=226)	5.5 (5.9) (n=179)	−0.45 (0.57)†	0.19
Confirmed COPD	6.3 (5.8) (n=117)	5.4 (4.1) (n=97)	−0.88 (0.70)†	0.37
Arterial blood gases (<30 min) (confirmed COPD patients)				
Mean (SD) pH	7.29 (0.14) (n=19)	7.35 (0.16) (n=19)	0.06 (0.05)†	0.11
Mean (SD) carbon dioxide (mm Hg)	77.8 (49.2) (n=20)	54.7 (31.1) (n=20)	−23.1 (13.0)†	0.06
Mean (SD) bicarbonate (mmol/l)	32.3 (10.1) (n=19)	26.8 (6.5) (n=19)	−5.5 (2.76)†	0.07
Mean (SD) oxygen (mm Hg) (arterial only)	98.4 (46.1) (n=14)	79.3 (24.9) (n=9)	−19.1 (16.8)†	0.34

Table 4 Treatment per protocol. Values are numbers (percentages) unless stated otherwise

	Control (high flow oxygen)	Active (titrated oxygen)	Treatment effect	P value
Mortality				
All patients	16/177 (9)	3/66 (5)	0.50 (0.16 to 1.54)*	0.23
Confirmed COPD	9/92 (10)	1/43 (2)	0.24 (0.04 to 1.57)*	0.14
Incidence of ventilation				
All patients	19/167 (11)	5/63 (8)	0.70 (0.25 to 1.97)*	0.50
Non-invasive ventilation	7	4		
Invasive ventilation	12	1		
Confirmed COPD	15/83 (18)	3/40 (8)	0.42 (0.14 to 1.20)*	0.11
Non-invasive ventilation	6	2		
Invasive ventilation	9	1		
Length of hospital stay (mean (SD) days)				
All patients	5.9 (5.5) (n=177)	6.0 (5.3) (n=66)	0.09 (0.78)†	0.87
Confirmed COPD	6.5 (6.0) (n=92)	6.2 (4.6) (n=43)	−0.29 (1.04)†	0.96
Arterial blood gases (<30 min) (confirmed COPD patients)				
Mean (SD) pH	7.29 (0.15) (n=18)	7.41 (0.09) (n=10)	0.12 (0.05)†	0.01
Mean (SD) carbon dioxide (mm Hg)	76.5 (50.2) (n=19)	42.9 (14.2) (n=10)	−33.6 (16.3)†	0.02
Mean (SD) bicarbonate (mmol/l)	31.5 (9.9) (n=18)	26.0 (4.2) (n=10)	−5.5 (3.30)†	0.15
Mean (SD) oxygen (mm Hg) (arterial only)	98.4 (46.1) (n=14)	81.5 (30.9) (n=6)	−16.9 (20.7)†	0.46

Summary

- Clearly defined research question and hypothesis
- Define PICO in protocol
- Ensure concealment of allocation to groups
- Ensure adequate randomisation procedure
- Beware and avoid systematic bias in study design

Not covered but….

- Don’t forget to register your trial prospectively
- Obtain ethical clearance
- In research you cannot trust anyone! (but yourself?)
- Oxygen is quite dangerous!!!