Answering patient-centered questions efficiently in primary care through response-adaptive platform trials: the ALIC4E study.

Chris Butler
Theo Verheij

Reaching out: a meeting to advance clinical research preparedness for infectious disease outbreaks; Brussels 20.09.2018

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8
Disabled Access
Cardiff Road Surgery
WARNING
LIVE 24/7 CCTV

Public Health England

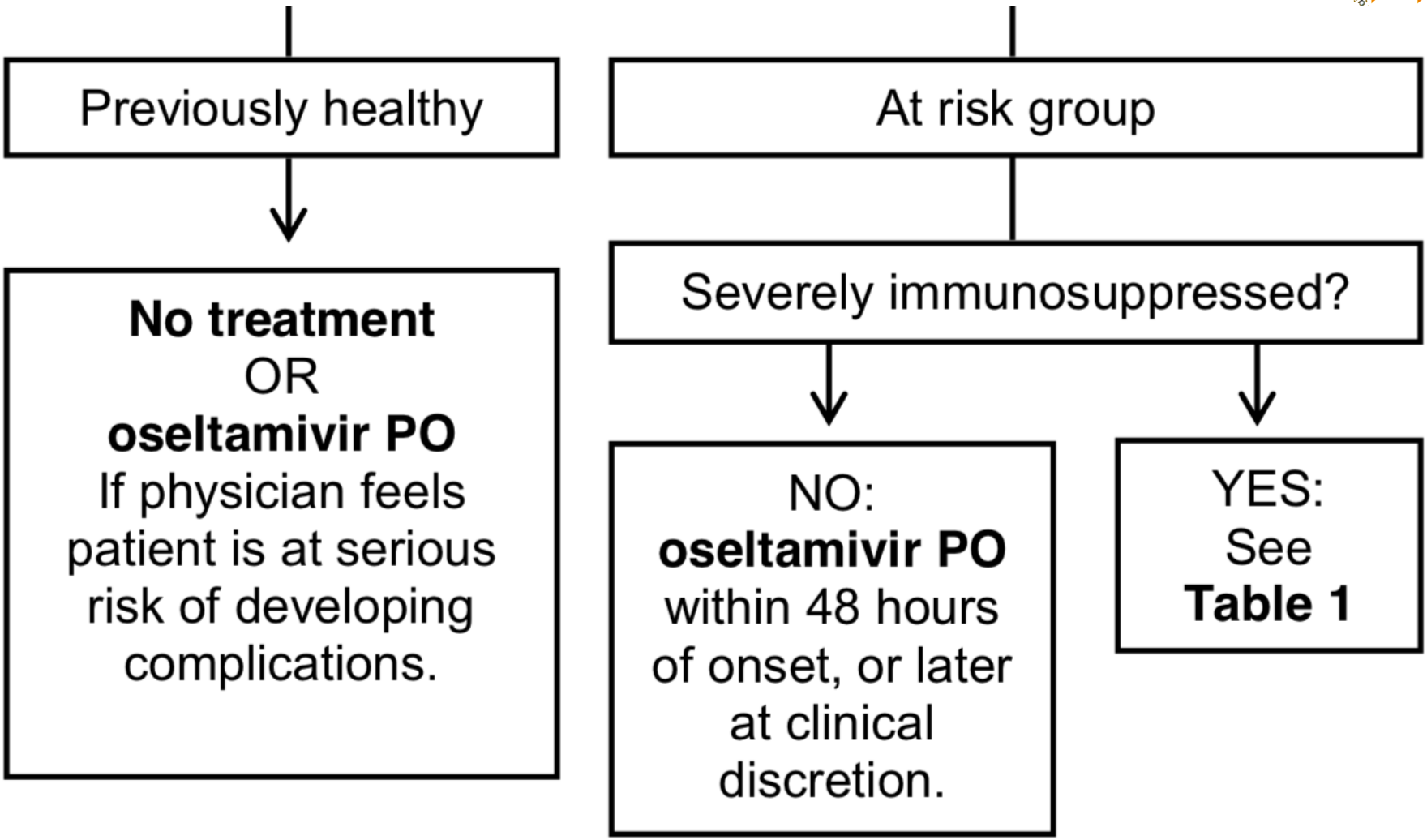
Protecting and improving the nation's health

PHE guidance on use of antiviral agents for the treatment and prophylaxis of seasonal influenza

Version 8.0, September 2017

3. Risk factors for complicated influenza:

a. Neurological, hepatic, renal, pulmonary and chronic cardiac disease.
b. Diabetes mellitus.
c. Severe immunosuppression.
d. Age over 65 years.
e. Pregnancy (including up to two weeks post partum).
f. Children under 6 months of age.
g. Morbid obesity (BMI ≥40).


Previously healthy
No treatment
OR
oseltamivir PO
If physician feels patient is at serious risk of developing complications.
At risk group
Severely immunosuppressed?
NO:
oseltamivir PO
within 48 hours of onset, or later at clinical discretion.
YES:
See
Table 1

BMJ

The truth about Tamiflu?

PLUS Hypothyroidism after pre-eclampsia
Managing hepatocellular carcinoma
Does weight loss improve sleep apnoea?

Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children (Review)

Jefferson T, Jones MA, Doshi P, Del Mar CB, Hama R, Thompson MJ, Spencer EA, Onakpoya I, Mahtani KR, Nunan D, Howick J, Heneghan CJ

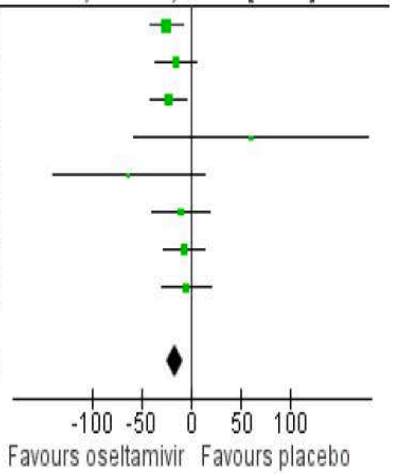
THE COCHRANE COLLABORATION®

Figure 4. Forest plot of comparison: 1 Oseltamivir versus placebo for treatment, outcome: 1.1 Time to first alleviation of symptoms in adult treatment (ITT population) [hours].

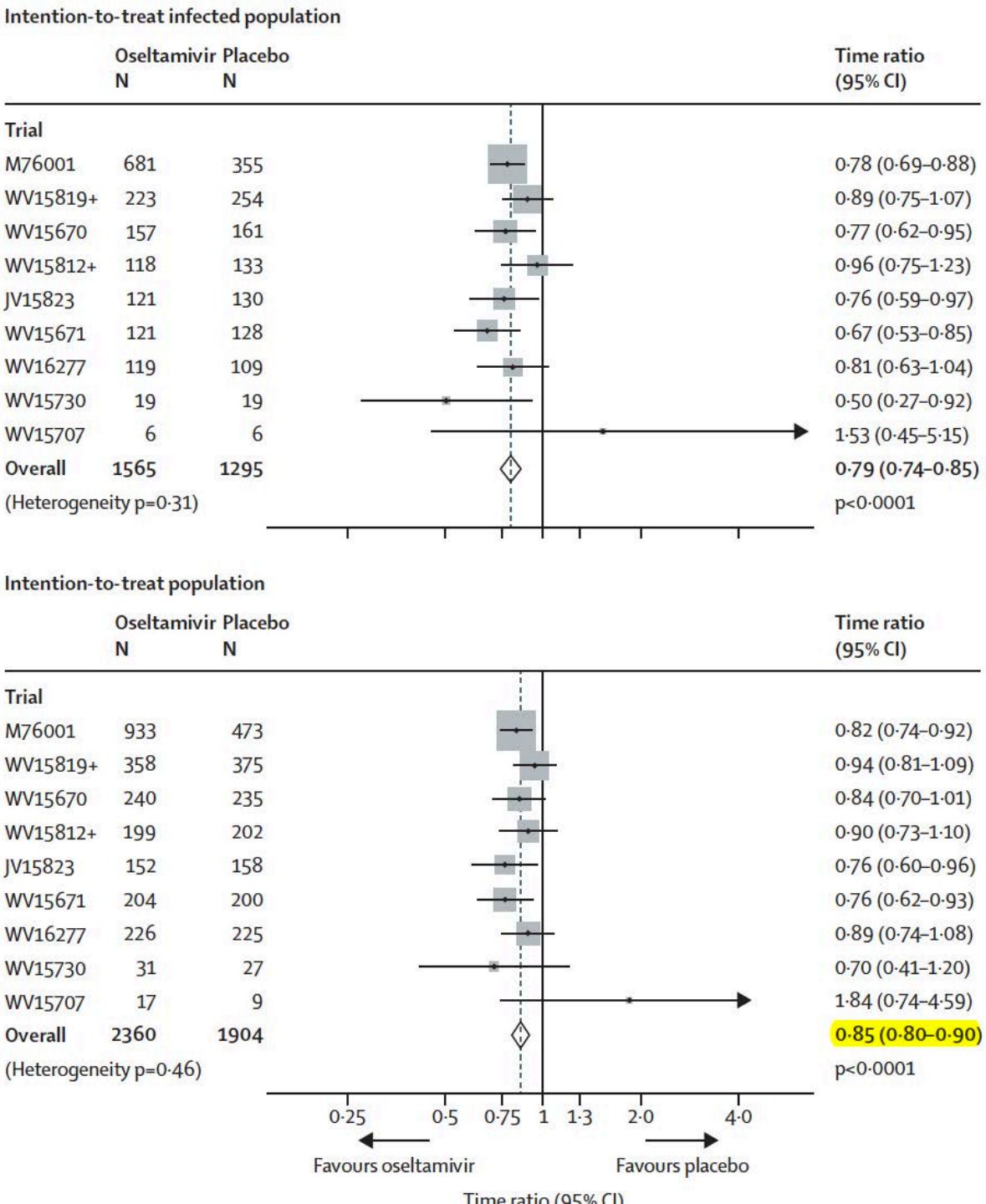
	Oseltamivir			Placebo				Mean Difference	Mean Difference
Study or Subgroup	Mean [hours]	SD [hours]	Total	Mean [hours]	SD [hours]	Total	Weight	IV, Random, 95% CI [hours]	IV, Random, 95% CI [hours]
M76001	140.6	125.2	933	165.5	156.5	473	26.4%	-24.90 [-41.13, -8.67]	
WV15670	129	114.6	240	144.5	118	235	15.9%	-15.50 [-36.42, 5.42]	
WV15671	102.4	89.9	204	125.3	98.9	200	20.5%	-22.90 [-41.34, -4.46]	
WV15707	154	166.5	17	93.6	134.4	9	0.5%	60.40 [-57.81, 178.61]	
WV15730	107.6	104.6	31	171	177.1	27	1.2%	-63.40 [-139.68, 12.88]	
WV15812/WV15872	193.7	152.3	199	203.9	146.3	202	8.1%	-10.20 [-39.44, 19.04]	
WV15819/WV15876/WV15978	185	145.6	358	192.4	145.2	375	15.7%	-7.40 [-28.46, 13.66]	
WV16277	138.7	138.4	226	143.7	125.4	225	11.7%	-5.00 [-29.37, 19.37]	
Total (95% CI)			**2208**			**1746**	**100.0%**	**-16.76 [-25.10, -8.42]**	

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 6.33$, df = 7 (P = 0.50); $I^2 = 0\%$

Test for overall effect: Z = 3.94 (P < 0.0001)



3954 in total



- Dobson et al. Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials. *Lancet*. 2015; **385**: 1729–1737

High risk?

BMJ 2013;347:f5061 doi: 10.1136/bmj.f5061 (Published 23 August 2013)

RESEARCH

Populations at risk for severe or complicated influenza illness: systematic review and meta-analysis

Dominik Mertz *assistant professor*[1 2], Tae Hyong Kim *researcher*[2], Jennie Johnstone *researcher*[2], Po-Po Lam *researcher*[3 4], Michelle Science *staff physician*[5], Stefan P Kuster *staff physician*[6], Shaza A Fadel *researcher*[4], Dat Tran *assistant professor*[5], Eduardo Fernandez *researcher*[2], Neera Bhatnagar *librarian*[7], Mark Loeb *professor*[2 8 9]

Not so clear…

- 234 studies
- 610782 participants
- The evidence supporting risk factors for severe outcomes of influenza ranged from being limited to being absent
- The level of evidence was low for any risk factor, obesity, CVS disease
- The evidence was very low for all other risk factors
- Some well accepted risk factors such as pregnancy and belonging to an ethnic group could not be identified as risk factors

H1N1… And indeed seasonal ‘flu’

- We gave out huge amounts of oseltamivir
- We did not test before issuing oseltamivir
- We did not randomise any patients in primary care
- GPs are urged to prescribe NAIs for ‘high risk people’ with ILI, but they hardly ever do

So…

- We don’t know if we did the right thing in H1N1
- And we still don’t know if we should routine use NAIs in primary care for seasonal flu
- Should we treat and treat?
- Are NAIs cost effective?

A trial design to answer real world questions…

BMJ Open

Antivirals for influenza-Like Illness? A randomised Controlled trial of Clinical and Cost effectiveness in primary CarE (ALIC^4 E): the ALIC^4 E protocol

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The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

THE CHANGING FACE OF CLINICAL TRIALS

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Pragmatic Trials

Ian Ford, Ph.D., and John Norrie, M.Sc.

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N Engl J Med 2016;375:454-63.
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PRAGMATISM IN CLINICAL TRIALS AROSE FROM CONCERNS THAT MANY trials did not adequately inform practice because they were optimized to determine efficacy.[1] Because such trials were performed with relatively small samples at sites with experienced investigators and highly selected participants, they could be overestimating benefits and underestimating harm. This led to the belief that more pragmatic trials, designed to show the real-world effectiveness of the intervention in broad patient groups, were required. Medical researchers, both academic and commercial, must deliver health care innovations (drugs, devices, or other interventions) that are safe, beneficial, and cost-effective, and they must identify the subgroups for whom the innovation will provide the greatest benefit relative to risk. A broad view of an intervention, including approaches to improve its effectiveness, is critical. An ideal trial includes a population that is relevant for the intervention, a control group treated with an acceptable standard of care, and outcomes that are meaningful, and it must be conducted and analyzed at a high standard of quality. Pragmatic trials frequently include complex interventions, sometimes consisting of several interacting components[2] and often involving the skills and experience of one or more health care professionals to deliver the intervention — for example, surgeons, physiotherapists, or cognitive behavioral therapists.

In this article, we do not provide a definitive exposition of the methods used for pragmatic trials. Rather, we explore the contexts in which a pragmatic design is most and least attractive and identify the strengths and limitations of — and challenges in implementing — pragmatic trials.

WHAT IS A PRAGMATIC TRIAL?

Schwartz and Lellouch[1] proposed a distinction between explanatory trials, which confirm a physiological or clinical hypothesis, and pragmatic trials, which inform a clinical or policy decision by providing evidence for adoption of the intervention into real-world clinical practice. The original PRECIS (Pragmatic–Explanatory Continuum Indicator Summary) tool[3] attempted to clarify the concept of pragmatism and provided a guide, scoring system, and graphical representation of the pragmatic features of a trial. Features included the recruitment of investigators and participants, the intervention and its delivery, follow-up, and the determination and analysis of outcomes. Many trials could be deemed to be pragmatic with regard to at least one of these dimensions, but few are truly pragmatic on all dimensions. Pragmatism has been discussed widely,[4-20] and a special issue of *Clinical Trials* had 12 articles focused on ethical and regulatory issues in pragmatic trials.[21] The requirements for pragmatism were loosened substantially in PRECIS-2,[22] and

Pragmatic trials: ”evidence for adoption of the intervention into real-world clinical practice”

- Pragmatism in clinical trials arose from concerns that many trials did not adequately inform practice because they were **optimized to determine efficacy**
- **Efficacy (explanatory) trials=overestimate benefits**, underestimate harms
  - Small samples
  - Highly selected participants: not similar to those seen in usual care
  - Outcomes not relevant to patients
- Academic and commercial, must deliver health care innovations (drugs, devices, or other interventions) **that are safe, beneficial, and cost-effective, and they must identify the subgroups for whom the innovation will provide the greatest benefit relative to risk**.
- An ideal trial **includes a population that is relevant for the intervention, a control group treated with an acceptable standard of care, and outcomes that are meaningful,** and it must be conducted and analysed at a high standard of quality.
- Primary outcome is relevant to participants (time to first alleviation of symptoms” vs “Back to usual function with headache and fever minimal)

Platform trial

- Master protocol
- Ongoing study
- Especially relevant to changing context such as resistance and virulence
- Suited to short term primary outcome
- Treatments may be added or dropped during course of trial

Sub groups

- Pre-specified
- Powered for each cell

Response adaptation

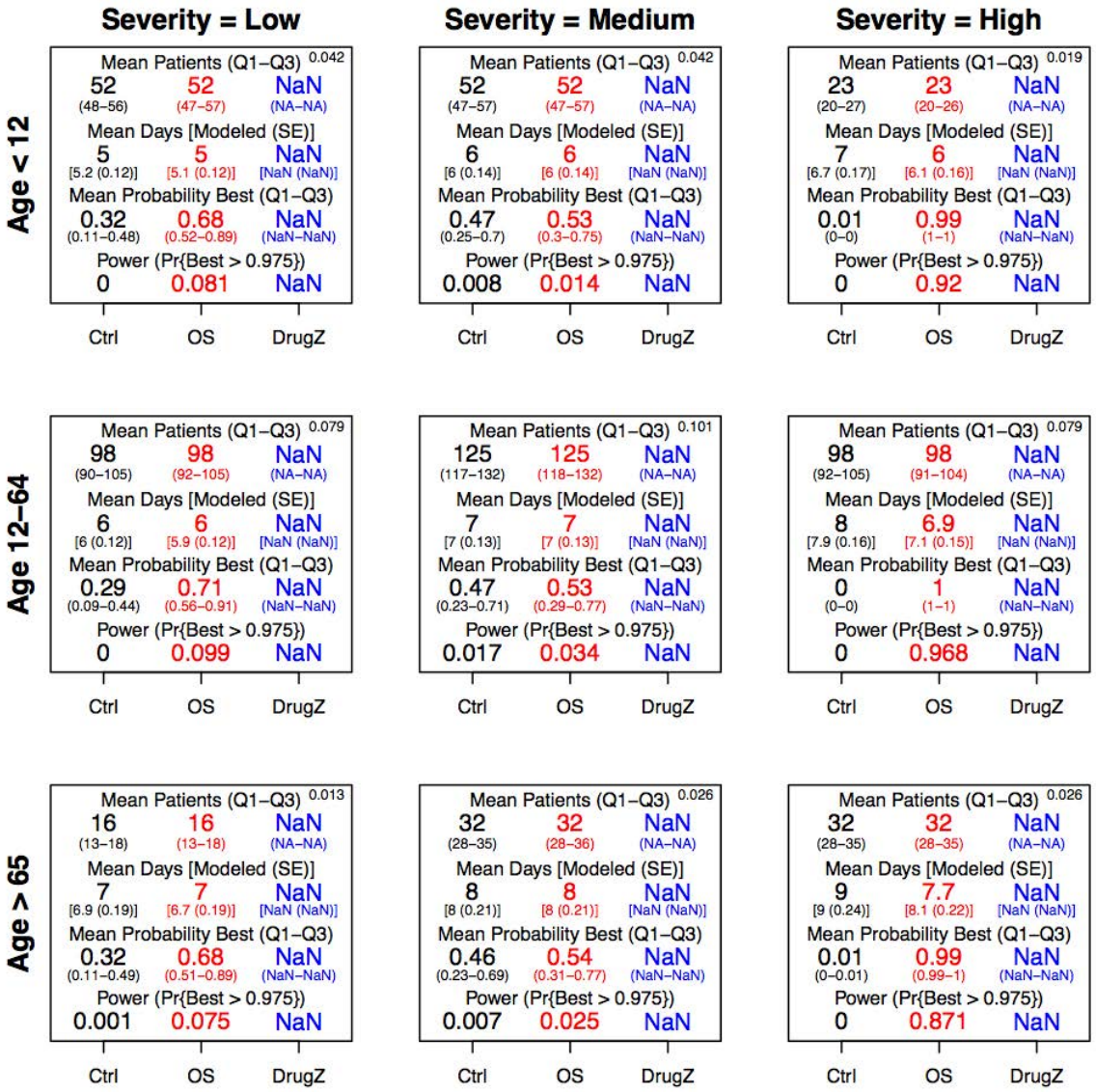
- Simulations determine possible power under a range of assumptions based on previous research
- Study is powered to some extent within each cell, although information is borrowed from other cells
- We don't stop allocating in each cell, but may change the proportions, with more receiving the more effective treatment
- The proportion of participants randomised to the intervention may be altered, according to prespecified thresholds, during the course of the trial itself.
- Arms added or dropped
- Information may be available sooner
- Answers with smaller numbers
- Seamless transition from phase2 to 3

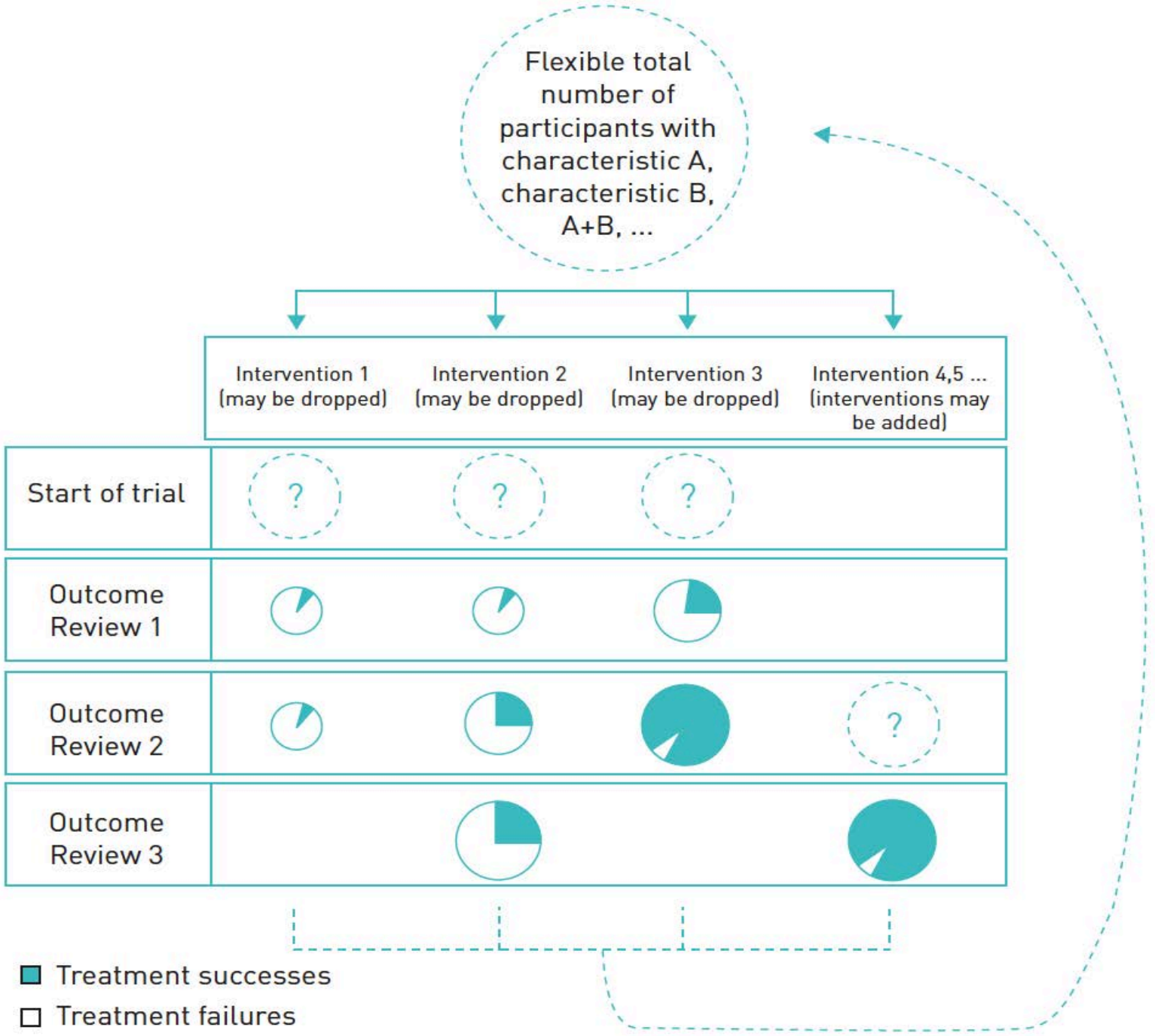
Response adaptation:

- “if only we had known that we had needed a slightly bigger sample size and could have carried on recruiting?”.

- “Did we really need to carry on recruiting when, had we analysed the data regularly during study, it would already have been obvious that one intervention was far better?”

Commorbidities=No, Duration=Short; Assumed Effect – 2 Days Better OS(Flu): High Severity




Flexible total number of participants with characteristic A, characteristic B, A+B, ...
Intervention 1 (may be dropped)
Intervention 2 (may be dropped)
Intervention 3 (may be dropped)
Intervention 4,5 ... (interventions may be added)
Start of trial
Outcome Review 1
Outcome Review 2
Outcome Review 3
?
Treatment successes
Treatment failures

Open trial

- Once efficacy is proven
- Placebos influence help seeking behaviour, and capturing this is critical to cost effectiveness
- Suited to issues of effectiveness
- Comparison: “Usual practice or the best available alternative management strategy, offering practitioners considerable leeway in deciding how to apply it”
- “GPs don’t prescribe placebos”: S. Webb
- Examples of open studies:

  - Antimicrobial catheters for reduction of symptomatic urinary tract infection (UTI) in adults requiring short-term catheterization in hospital
  - Initial Antidepressant Choice in Primary Care
  - Leukotriene Antagonists as First- Line or Add-on Asthma-Controller Therapy
  - High-Sensitivity Troponin in the Evaluation of Patients With Acute Coronary Syndrome (High-STEACS)

Open trial: consider the possible ALIC^{4}E trial results

The assumption is that taking a drug, even if possibly inert, is likely to enhance expectations for improved outcomes: i.e. no placebo increases the chance of a Type I error

Scenarios :

1. No difference between two arms/subgroups: don't use oseltamivir
2. Oseltamivir arm worse: don't use
3. Oseltamivir clearly better: would you really say this is just because there was no placebo, given the rational drugs design, known mechanism, challenge studies and efficacy trials?

ERJ open research

A trial like ALIC^{4}E: why design a platform, response-adaptive, open, randomised controlled trial of antivirals for influenza-like illness?

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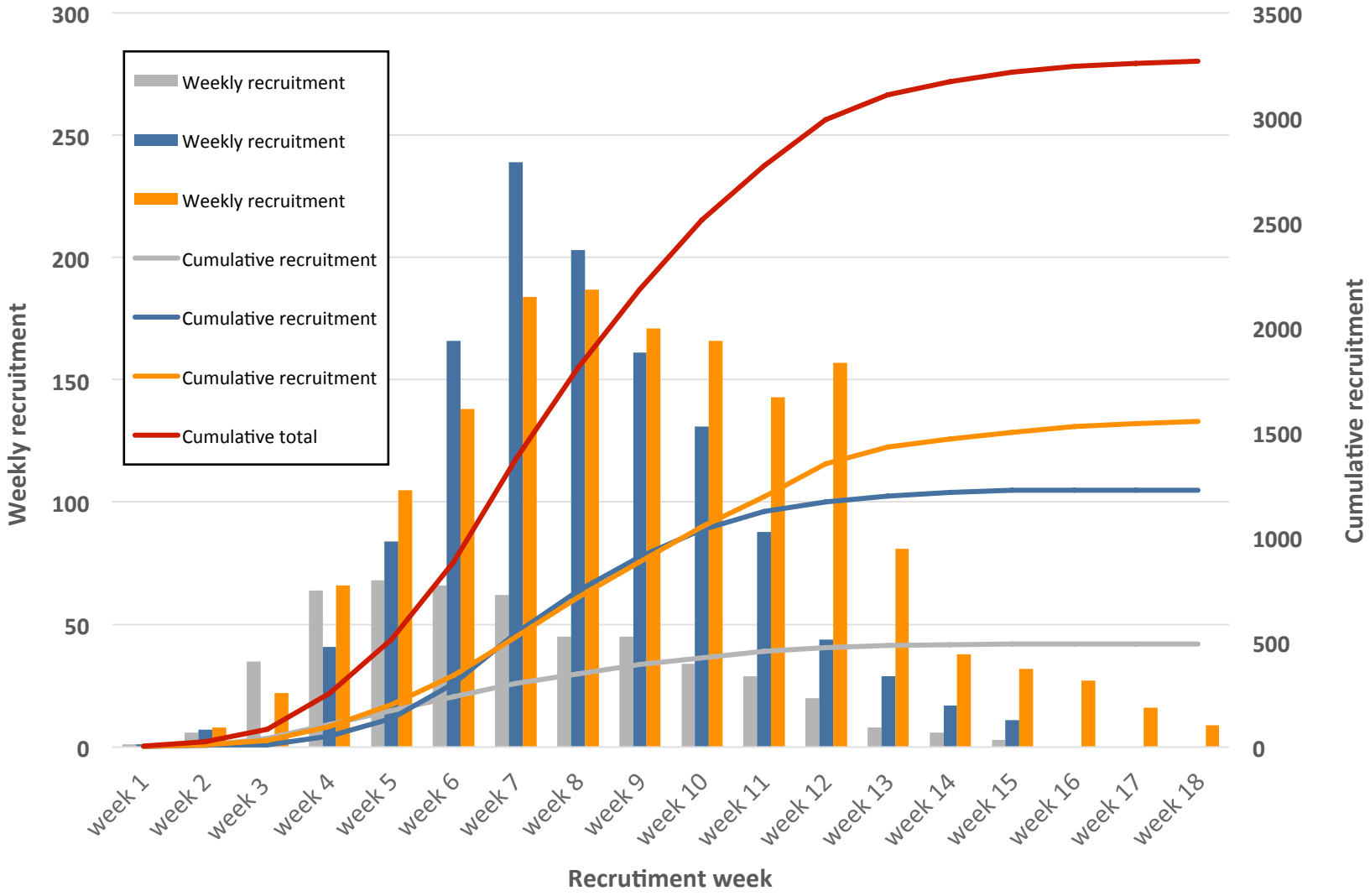
Alice

We aimed to randomise >3000 patients from f primary care settings:
Best usual care plus oseltamivir vs. best usual care

- 21 networks
- 15 countries
- 13 languages
- 207 primary care practices

✓ 3268 patients



ALICE: Closer to the vision of randomising patients within a week of the onset of a pandemic to multiple intervention algorithms to generate evidence that is useful for guiding clinical decisions within the pandemic itself