PRAGMATIC TRIALS: DESIGNING AND DELIVERING LARGE SCALE TRIALS IN REAL-WORLD SETTINGS

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On behalf of the REEACT collaborative
Pragmatic trials: todays talk

- Routine care settings and real-world interventions: the need for pragmatic trials
- What are pragmatic trials?
- Depression in primary care as a case example
- Choosing a comparator
- A motivating example
  - REEACT – cCBT for depression
- Effectiveness vs Efficacy
Two questions…. 

Can it work under ideal conditions? 

Versus 

Does it work in the real world?
Efficacy vs effectiveness

EXPLANATORY AND PRAGMATIC ATTITUDES IN THERAPEUTICAL TRIALS

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(Received 6 January 1967; in revised form 24 March 1967)
6. SUMMARY AND CONCLUSIONS

The “comparison between two treatments” is a problem which is inadequately specified even in its over-all characteristics. It may imply one of at least two types of problem which are basically different.

1. The first type corresponds to an explanatory approach, aimed at understanding. It seeks to discover whether a difference exists between two treatments which are specified by strict and usually simple definitions. Their effects are assessed by biologically meaningful criteria, and they are applied to a class of patients which is rather arbitrarily defined, but which is as likely as possible to reveal any difference that may exist. Statistical procedures used in determining the number of subjects and in assessing the results are aimed at reducing the probabilities of errors of the first and second kind.

2. The second type corresponds to a pragmatic approach, aimed at decision. It seeks to answer the question—which of the two treatments should we prefer? The definition of the treatments is flexible and usually complex; it takes account of auxiliary treatments and of the possibility of withdrawals. The criteria by which the effects are assessed take into account the interests of the patients and the costs in the widest sense. The class of patients is predetermined as that to which the results of the trial are to be extrapolated. The statistical procedures are aimed at reducing the probability of errors of the third kind (that of preferring the inferior treatment); the probability of errors of the first kind is 1.0.

Most real problems contain both explanatory and pragmatic elements, for ethical reasons. Most trials done hitherto have adopted the explanatory approach without question; the pragmatic approach would often have been more justifiable.
# Explanatory vs Pragmatic

**Explanatory/efficacy trial**
- Can it work under ideal conditions?
- Tightly-defined participants
- Strenuous effort for protocol adherence
- Narrowly-defined symptom outcomes
- Shorter term follow up where gains expected

**Pragmatic/effectiveness trial**
- Does it work in the real world?
- Those who would receive it in routine care
- Measure real-world adherence as an outcome
- Broadly-defined outcomes incl. QoL
- Longer term impact (incl service use)
Design considerations

- Where do you recruit?
- What is the intervention?
- Should you enforce compliance or see what happens?
- What is the comparator?
- Should you rigidly control what happens in addition to the intervention?
- What choice of outcomes?
Depression as a motivating example
Common mental health problems

- Depression & anxiety
- 1:10 population
- Profound personal suffering
- Reduced function and quality of life
- Life adversity & long term health problems
- Costs to the UK economy £23 billion
- Absenteeism, presenteeism & reduced economic productivity
- Primary care problem
Limitations of depression trials

- More about efficacy than effectiveness
- Secondary rather than primary care
- Limited range of outcomes
- Short term follow up
- Comparator designed to ensure greatest benefit is demonstrated

- Struggle to answer questions that policy makers ask
- ‘what is the additional benefit we could expect if were to invest and add this treatment to routine care’
Computerised cognitive behaviour therapy (cCBT) as treatment for depression in primary care (REEACT trial): large scale pragmatic randomised controlled trial

Simon Gilbody,1 Elizabeth Littlewood,1 Catherine Hewitt,2 Gwen Brierley,3 Puvan Tharmanathan,2 Ricardo Araya,4 Michael Barkham,5 Peter Bower,6 Cindy Cooper,7 Linda Gask,6 David Kessler,8 Helen Lester,9 Karina Lovell,10 Glenys Parry,11 David A Richards,12 Phil Andersen,1 Sally Brabyn,1 Sarah Knowles,6 Charles Shepherd,13 Debbie Tallon,8 David White7 on behalf of the REEACT Team

ABSTRACT
STUDY QUESTION

How effective is supported computerised cognitive behaviour therapy (cCBT) as an adjunct to usual primary care for adults with depression?

METHODS

This was a pragmatic, multicentre, three arm, parallel randomised controlled trial with simple randomisation. Treatment allocation was not blinded.

Beating the Blues v usual GP care; 0.98 (0.62 to 1.56) for MoodGYM v usual GP care. There was no evidence of an overall difference between either programme compared with usual GP care (0.99 (0.57 to 1.70) and 0.68 (0.42 to 1.10), respectively) at any time point. Commercially provided cCBT conferred no additional benefit over free to use cCBT or usual GP care at any follow-up point. Uptake and use of cCBT was low, despite regular telephone support. Nearly a quarter of participants (24%) had made a call before the trial started.
CBT in the age of technology.....
Evidence for cCBT from systematic reviews

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Andersson & Cuijpers 2009
Some limitations of the literature

- Small n, underpowered
- Recruited by advertisement or conducted in academic centres
- Only one study conducted in primary care
- Short term follow-up, limited range of outcomes
- Actual use of programmes not measured
- Often intensively-supported cCBT – showed the largest effect
- Developer-led trials
- Efficacy rather than effectiveness
Computerised cognitive behaviour therapy for depression and anxiety update: a systematic review and economic evaluation

E Kaltenthaler, J Brazier, E De Nigris, I Tumur, M Ferriter, C Beverley, G Parry, G Rooney and P Sutcliffe

September 2006
HTA identified the need for a large scale trial of cCBT

- “Research needs to be carried out by independent researchers. It should be carried out by those who are not associated with commercial or product gains.”
- HTA Clinical Trials Board commissioned a trial in 2008

HTA report 2006
The NIHR HTA Programme supports research that is immediately useful to patients, clinical practice, and policy or decision makers. HTA research is undertaken when evidence exists to show that a technology can work (efficacy). The purpose of an HTA study is to establish the clinical and cost-effectiveness for the NHS in comparison with the current best alternative(s).
On behalf of the REEACT trial collaboration
History of react

- Began recruiting 2009
- End recruiting 2011
- Last follow up 2013
- Published in late 2015
Our research question

Is there any benefit from cCBT for people with depression when this is added to their usual primary care?
Overarching pragmatic design principles

REEACT had to:

- Be conducted in primary care
- Include representative patients
- Replicate how cCBT might be used and supported in the real world (not under ideal conditions or according to rigid protocols)
- Comparator of usual care, rather than ‘do nothing’
- Not constrain treatments, but measure what happens
- Monitor actual use of the technology
- Be well-powered with a long duration of follow up
- Analyse all participants according to randomised group (ITT rather than per-protocol analysis)
Overarching design principles

REEACT had to:

- Be conducted in primary care
- Include representative patients
- Replicate how cCBT might be used and supported in the real world (not under ideal conditions)
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- Monitor actual use of the technology
- Be well-powered with a long duration of follow up
Depression PHQ9 ≥10 (N=691)

R

Usual primary care

Usual primary care

Usual primary care

Plus MoodGYM

Plus Beating the Blues

4, 12 & 24 month follow up 4, 12 & 24 month follow up 4, 12 & 24 month follow up

PHQ9, GAD7, SF12, EQ5D, computer use, & resource use
What level of support?

- Entirely self guided
- Non-clinical technical support for cCBT
- Clinician-facilitated cCBT
What level of support?

- Entirely self guided
- Non-clinical technical support for cCBT
- Clinician-facilitated cCBT
Manualised non-clinical technical support

- Weekly telephone contact (8 – 10 weeks)
- Technical support, checking progress, problem solving & general motivation to engage
- No therapeutic content
- Avoid requests for advice about depression & problems
- Taped and quality assured
The tyranny of the recruitment graph

REEACT: Recruitment to a multi-centre primary care trial

- Target recruitment
The tyranny of the recruitment graph

REEACT: Recruitment to a multi-centre primary care trial

Cumulative number of recruits

Month

Actual recruitment

Target recruitment
Clinicians and patients like pragmatic trials!
What did we find?
REEACT1 results – depression severity

Beating the Blues

Mean PHQ-9 score by group

- Usual care
- Intervention care
REEACT1 results – depression severity
Poor uptake, despite technical support

MoodGym usage session by session
Our research question

Is there any benefit from cCBT for people with depression when this is added to their usual primary care?
Is there any benefit from cCBT for people with depression when this is added to their usual primary care?
REEACT1 not universally well-received!

Blood on the correspondence pages
Twitter lit up
Social media
Should have done an efficacy trial

Should have cranked-up the support

No surprise that such a poorly supported intervention had no impact
Comparison usual care = not fair!

Quite a lot happens in usual care
Sets the bar unfairly high
We don’t know the first thing about cCBT

No experience in developing cCBT products and technological innovation
Evaluating yesterday's technology

Beating the Blues and MoodGYM

Old and clunky
Randomised Evaluation of Effectiveness & Acceptability of Computerised Therapy
Our REEACT2 research question

Does cCBT become more effective if we add structured support and guidance?
Concluding comments
Concluding comments

- cCBT – efficacious, but can’t assume effectiveness
- Important to undertake large-scale pragmatic trials in real world settings
- Impact on practice and policy
- Minimally supported cCBT (as offered in the UK) is not effective
- Got some ideas about how we can support cCBT
- More research needed
Concluding comments

This is why we do trials
More on pragmatic trials

PRECIS-2 tool: designing trials that are fit for purpose

Kirsty Loudon, Shaun Treweek, Frank Sullivan, Peter Donovan, Kevin E Thorpe, Merrick Drummond

PRECIS is a tool to help trialists make design decisions consistent with the intended purpose of their trial. This paper gives guidance on how to use an improved, validated version, PRECIS-2, which has been developed with the help of over 80 international trialists, clinicians, and policymakers. Keeping the original simple wheel format, PRECIS-2 has nine dimensions: eligibility criteria, recruitment, setting, organisation, flexibility (delivery), flexibility (adherence), follow-up, primary outcome, and primary analysis—scored from 1 (very explanatory) to 5 (very pragmatic) to facilitate-domain discussion and consensus. It is hoped PRECIS-2 will be useful in supporting the explicit matching of design choices to the trial results intended to be used.
How pragmatic is my trial?

The PRagmatic-Explanatory Continuum Indicator Summary 2 (PRECIS-2) wheel.
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