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Clinical Trials in Breathlessness

Clinical trials: definition

A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis, or treatment of a disease. Also called a clinical study.

National Cancer Institute website.

Clinical Trials in Breathlessness

Why?

- Common, multifaceted, poorly managed symptom

What?

- Multi-site clinical trials

Who?

- You: we all need to participate

How?

- Systematically, carefully, persistently

Researching breathlessness in palliative care: consensus statement of the NCRI Palliative Care Breathlessness Subgroup

***Dorman et al* , 2008 (under review)**

Clinical trials: fundamentals

- Effect size of intervention

‘How well does it work in a range of contexts?’

- Outcome measures

‘Do they assess what is needed accurately, reliably, consistently enabling sample size calculation?’

- Characterising population

‘Are the intervention and control groups the same at baseline?’

- What are you trying to prove?

‘Well defined hypothesis.’

A systematic review of the use of opioids in the management of dyspnoea

- 18 studies fulfilled criteria – all crossover
- largest O/P trial only had 19 pts, largest nebulised trial 79
- total numbers of patients in trials = 293
- meta-analysis gave the evidence for effectiveness opioids

Jennings A L, Davies AN, Higgins, J P, Gibbs, J S, Broadley K.E

2002 Thorax **57**(11): 939-44.

Clinical Trials: systematic review & meta-analysis

What did we learn?

- There is some good evidence for opioids
- Methodologies inconsistent
- Total numbers in studies small
- No evidence for nebulised opioids
- Larger, well-designed studies needed

Clinical Trials: RCT

The **R**andomised **C**ontrolled **T**rial ***minimises bias***

- Start with 2+ similar groups
- Randomly assign treatments
- Conceal treatment from patient & clinician
- Analyse on ‘intention to treat’ basis

Clinical trials: the crossover RCT

- Patients act as their own controls & receive both treatments
- Only possible with short-acting interventions
- Short trials = more completions
- Reduces sample size: breathless patients very heterogeneous population

Clinical Trials: *crossover* RCT

1. **Randomised, double blind, placebo controlled crossover trial of sustained release morphine for the management of refractory dyspnoea**, *Abernethy et al, BMJ 2003;327:523-528*
2. **Does oxygen help dyspnoea in cancer patients?** *Booth et al, The AJRCCM 1996;153:1515 -1518.*
3. A randomised double blind crossover trial of the effect of oxygen on dyspnea in patients with advanced cancer. *Philip J et al, J PSM,* 2006 **32**: 541 - 50.
4. Does the use of a handheld fan improve chronic dyspnoea: a randomised controlled crossover trial. *Galbraith et al, 2008 (under review)*

Cross-over trial: plan of interventions

	Intervention 1	Wash out period	Intervention 2
Order A	Air	15 minutes	Oxygen
Order B	Oxygen	15 minutes	Air

Clinical Trials: the multi-site RCT

A multi-centre randomised double-blind controlled trial of oxygen versus medical air for the relief of breathlessness in patients with intractable dyspnoea and PaO2>7.0 kPa.

Careful standardisation of procedures across different sites

Abernethy et al, data collection completed

Clinical trials: non-inferiority RCT

The effect of a new treatment is *not worse* than that of an active control by more than a specified margin

Limitations:

- Difficult to use conservative analysis approach
- Lack of protection from bias by blinding
- Difficult to specify non-inferiority margin

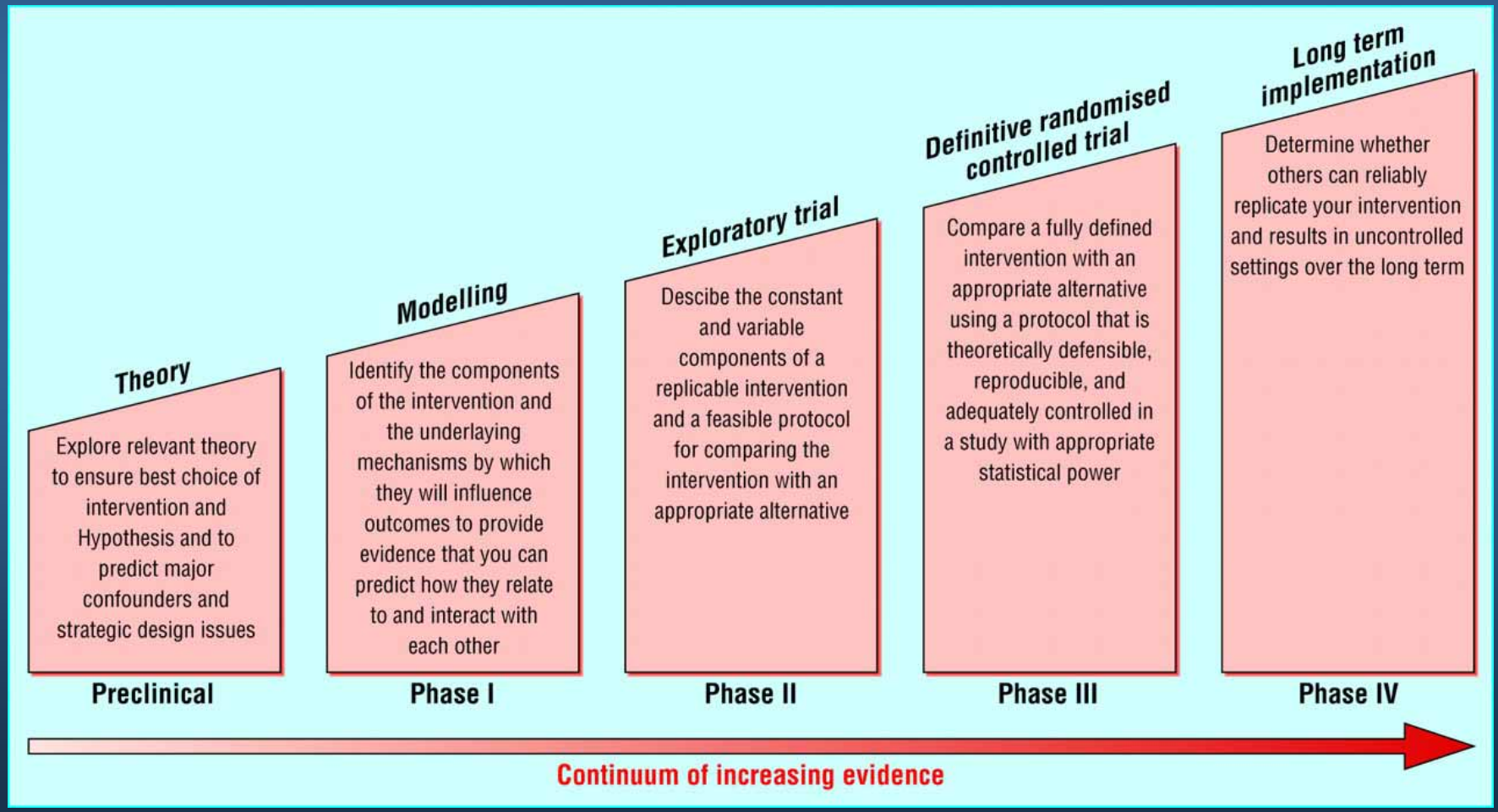
Snappin, *Curr Control Trials in Cardiovasc Medicine 2000, 1;19-21*

Clinical Trials: will the method answer the question?

- RCT is probably the best method for assessing single interventions scientifically
- Mixed methods better for complex questions such as impact on QOL in longer term

Mixed methods = qualitative + quantitative

Clinical trials: MRC framework



Clinical Trials: MRC methodology

- Breathlessness in Cancer and Chronic Obstructive Pulmonary Disease: using a Qualitative Approach to Describe the Experience of Patients and Carers. *Booth S. et al Palliative and Supportive Care 2003: **1**: 337 – 344.*

- The Impact of a Breathlessness Intervention Service (BIS) on the Lives of Patients with Intractable Dyspnoea: a Qualitative Phase 1 Study *Booth S. et al, Palliative and Supportive Care 2006; **4**: 287 - 293.*

Takes years

Does the use of a handheld fan improve chronic dyspnoea: a randomised controlled crossover trial

Now a multi-site trial is being planned.

Galbraith PS, Fagan P, Perkins P, Lynch AG, Booth S, under review 2008

Clinical Trials: starting out

- Is the question worth answering?
- Have you done a literature review/searched trial registers?
- Have you formed a team, including a statistician?
- What is the best methodology to answer this question?
- Is a feasibility/pilot study needed?

Clinical Trials in Breathlessness: Needs

- Adequately characterised populations
- Adequately described interventions
- Adequately powered trials

Multi-site trials and collaboration answer these needs

Clinical Trials: Summary

- Many clinical interventions are still based on ‘best practice.’
- Most remaining questions on clinical interventions need to be evaluated by multi-site trials to be answered definitively.
- Multi-site trials need to be planned using available evidence or feasibility work.

As a specialty we all need to participate if we are to give patients the best care

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Clinical Trials: NCRI methodology

Recommendation 8

For longer term studies, a scale such as the Chronic Respiratory Questionnaire (which includes a “mastery” subscale) should be used.

Clinical Trials: characteristics of success

- Planning
- Phasing
- Persistence
- Patience
- *Active* participation

Clinical Trials: NCRI methodology

Recommendation 5

Populations should be accurately defined; co-morbidity indices such as the Charlson co-morbidity scale and performance status measures such as the modified Karnofsky scale are recommended.

Clinical trials: NCRI methodology

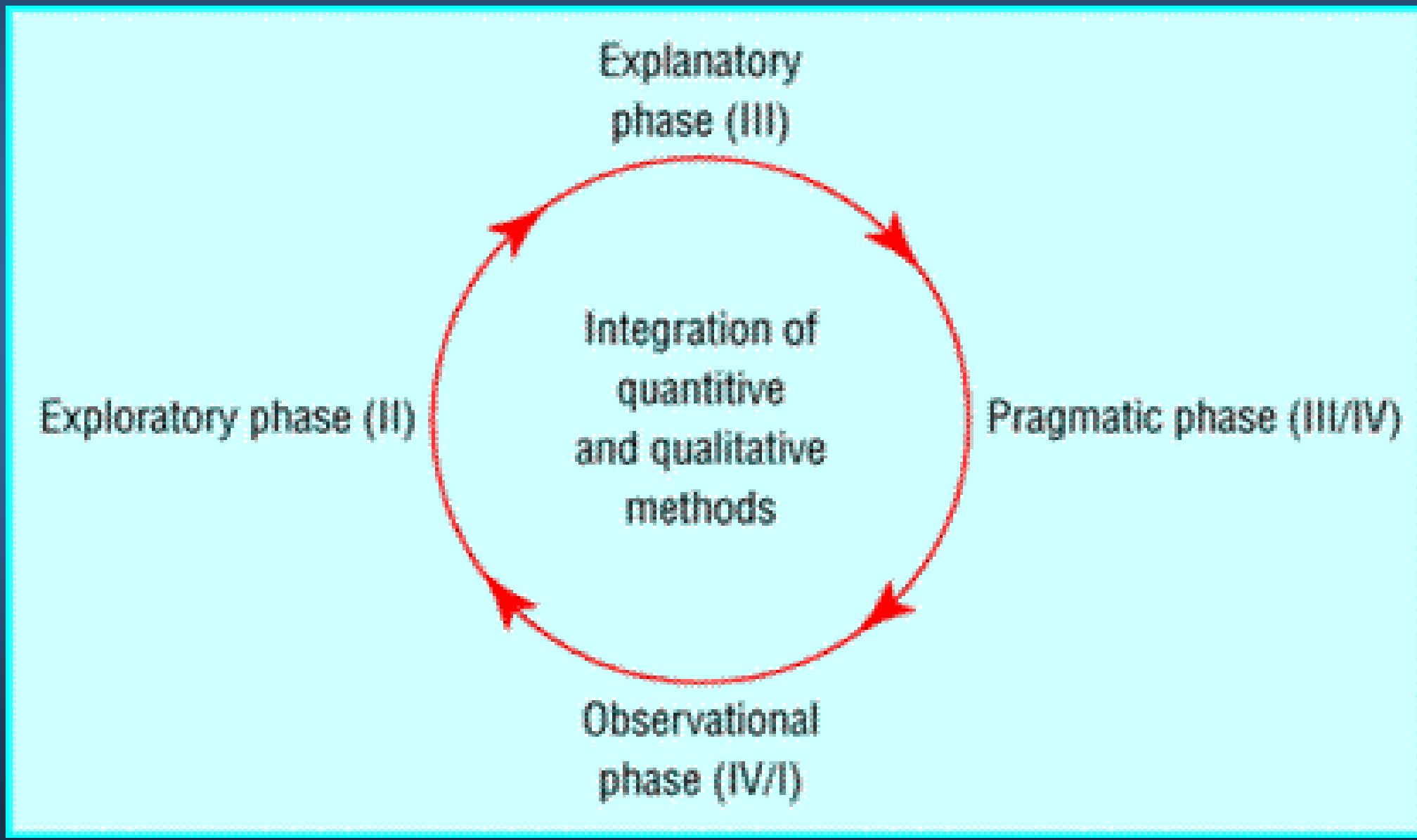
Recommendation 6

Interventions should be described clearly to allow replication of studies in different settings, sites and patient groups.

Clinical Trials: NCRI methodology

Recommendation 7.

Validated outcome measures (e.g. numeric rating scale or modified Borg scale) should be used to assess the severity of breathlessness “right now”, “on average over the last 24 hour”, at worst over the last 24 hours”; the degree of relief from breathlessness should also be assessed.

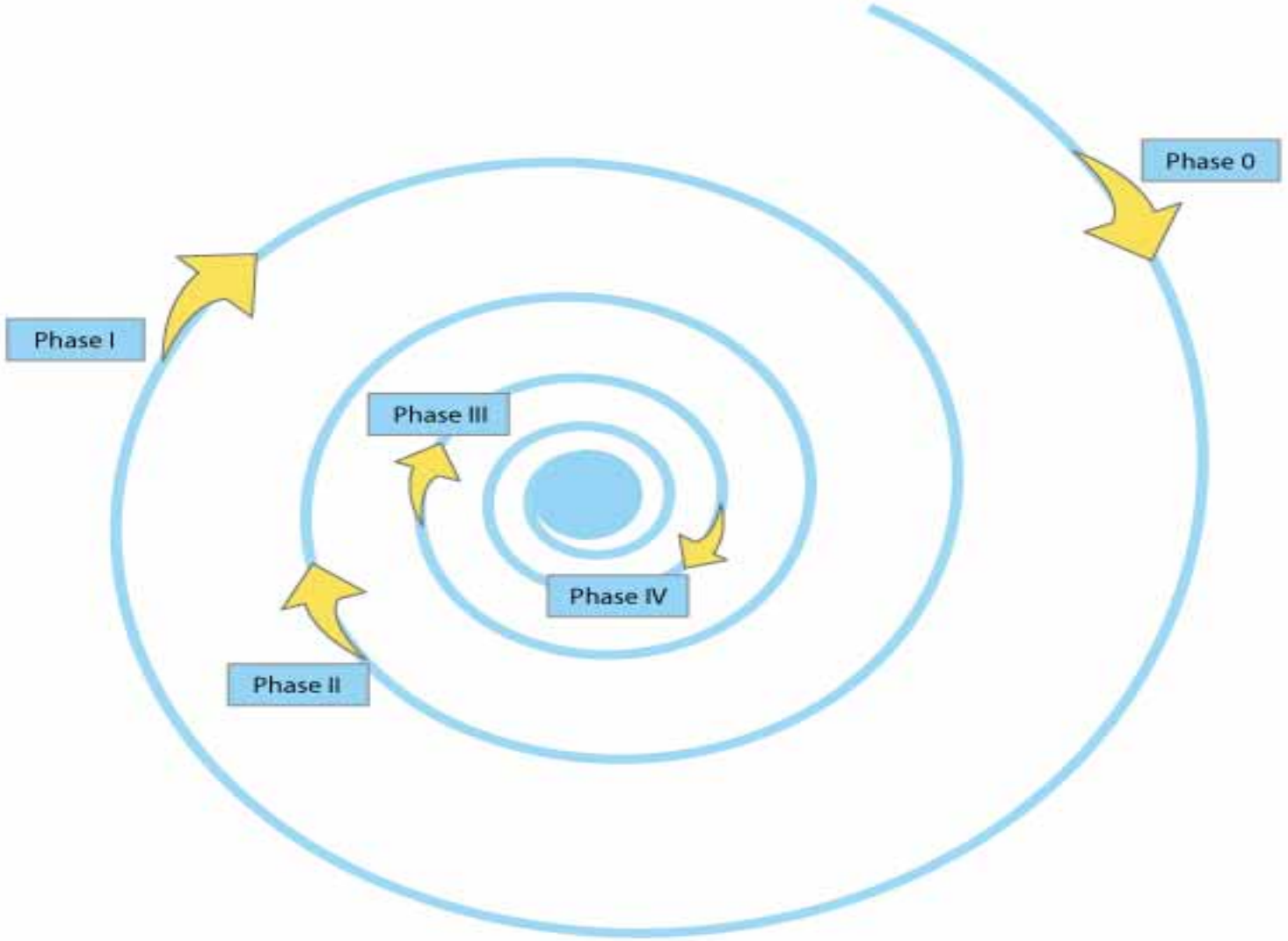

Explanatory phase (III)
Exploratory phase (II)
Integration of quantitive and qualitative methods
Pragmatic phase (III/IV)
Observational phase (IV/I)

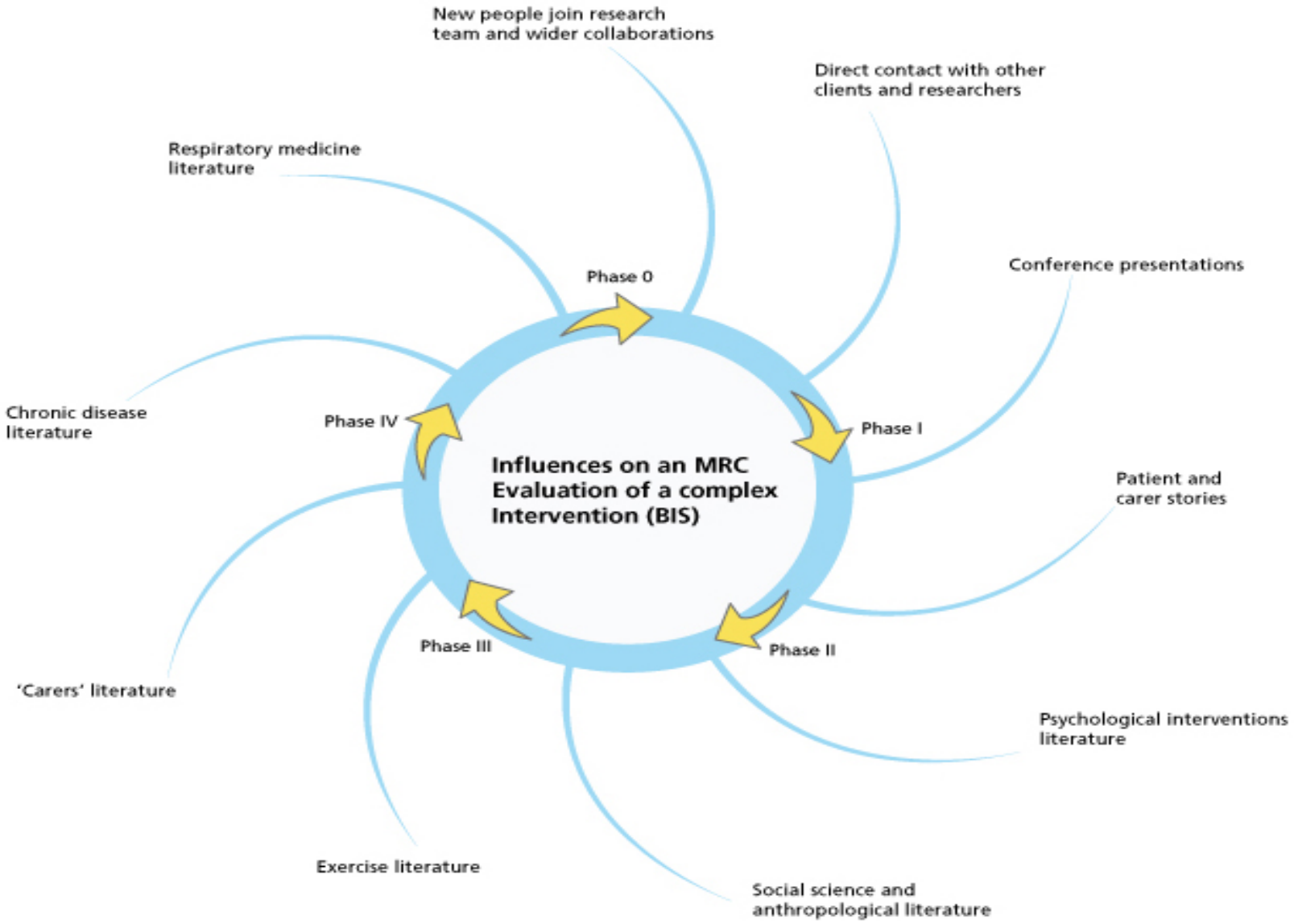
Clinical Trials: NCRI methodology

1. Multi site trials are needed to answer the key clinical questions. International collaboration is now feasible; web-based entry can facilitate this.

2. Statisticians expert in the design and conduct of palliative care studies should be involved at an early stage of trial planning.

3. Feasibility studies and a calculation of anticipated recruitment (assuming attrition rates of 40%) are important in the planning stages.


Phase 0
Phase I
Phase III
Phase IV
Phase II


New people join research team and wider collaborations
Direct contact with other clients and researchers
Respiratory medicine literature
Conference presentations
Phase 0
Chronic disease literature
Phase IV
Phase I
Influences on an MRC Evaluation of a complex Intervention (BIS)
Patient and carer stories
Phase III
Phase II
'Carers' literature
Psychological interventions literature
Exercise literature
Social science and anthropological literature

Clinical Trials: NCRI methodology

Recommendation 9

Research is urgently needed to explore the validity of outcome measures in the palliative care population, as there is not yet a gold standard outcome measure in this setting.