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Complex Intervention Trials and Studies

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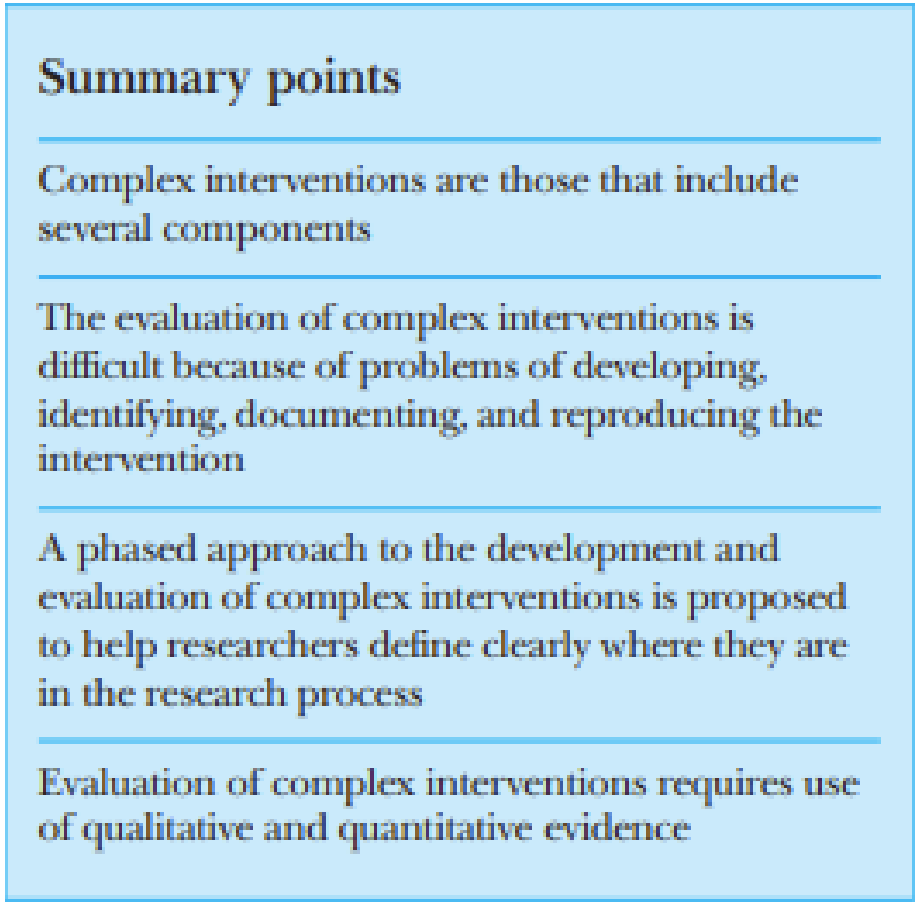
CaHRU Research Seminar: 10 November 2020

What are Complex Interventions?

- Widely used in the health service, in public health practice, and in areas of social policy such as education, transport and housing that **have important health consequences**.
- Conventionally defined as interventions with several interacting components which may present **special problems that must be overcome**.

- Framework for design and evaluation of complex interventions to improve health. BMJ 2000; 321: 694-6



Summary points

Complex interventions are those that include several components

The evaluation of complex interventions is difficult because of problems of developing, identifying, documenting, and reproducing the intervention

A phased approach to the development and evaluation of complex interventions is proposed to help researchers define clearly where they are in the research process

Evaluation of complex interventions requires use of qualitative and quantitative evidence

Generic examples:

Taken from:
Framework for design and evaluation of complex interventions to improve health. BMJ 2000; 321: 694-6

Examples of complex interventions

Service delivery and organisation:
- Stroke units
- Hospital at home

Interventions directed at health professionals' behaviour:
- Strategies for implementing guidelines
- Computerised decision support

Community interventions:
- Community based programmes to prevent heart disease
- Community development approaches to improve health

Group interventions:
- Group psychotherapies or behavioural change strategies
- School based interventions—for example, to reduce smoking or teenage pregnancy

Interventions directed at individual patients:
- Cognitive behavioural therapy for depression
- Health promotion interventions to reduce alcohol consumption or support dietary change

Dimensions of complexity

- Interactions between components within control and experimental interventions. *Risk factors such as age, disease severity etc.*
- Difficulties of behaviours required by those delivering/receiving interventions. *Practical considerations*.
- Number of groups/organisation levels targeted by intervention.
- Number/variability of outcomes.
- Any flexibility/tailoring of intervention? *Non-flexible -e.g. taking a tablet/vaccine of fixed dose vs flexible –e.g. CBT for phobias, personally tailored therapies.*

A trial intervention example that is *relatively* simple….

RIGHT-2

Lancet 2019; 393: 1009–20

- Stroke trial
- Transdermal GTN vs sham
- Can early GTN lower BP and improve outcome?
- Is it feasible to do large scale ambulance study?

BUT……most interventions turn out to be complex rather than simple once we start considering the DESIGN and IMPLEMENTATION details!

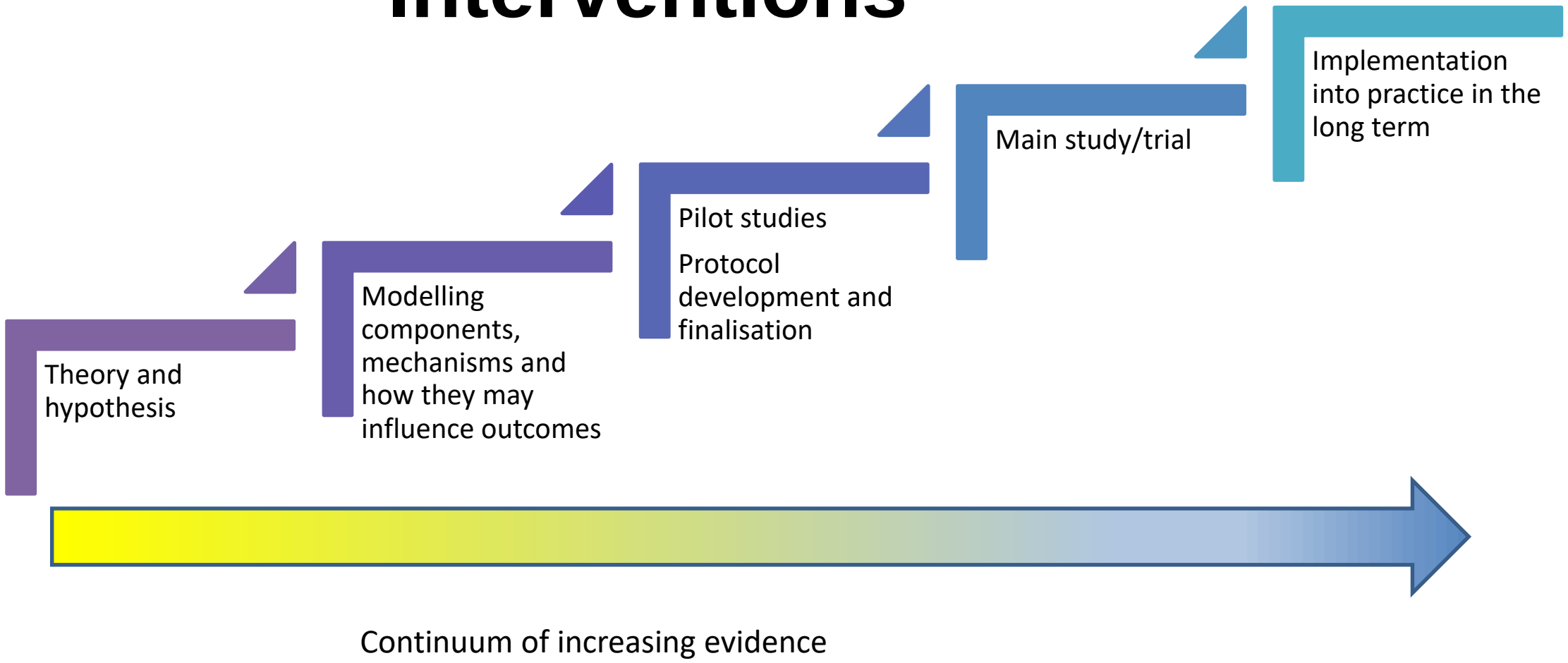
"RIGHT-2 was a pragmatic, multicentre, paramedic delivered, ambulance-based, prospective, randomised, sham-controlled, participant-blinded and outcome blinded, phase 3 trial in adult participants with ultra-acute presumed stroke within 4 h of onset in the UK."

- 8 ambulance services –training
- Diversity within patient population led to a need for 2 different analyses –primary outcome evaluated on a select sub-group and ITT (all participants)
- Meta-analyses informed study design and further review of post-study outcome

Complex interventions are NOT just clinical trials……
2 current examples from CaHRU

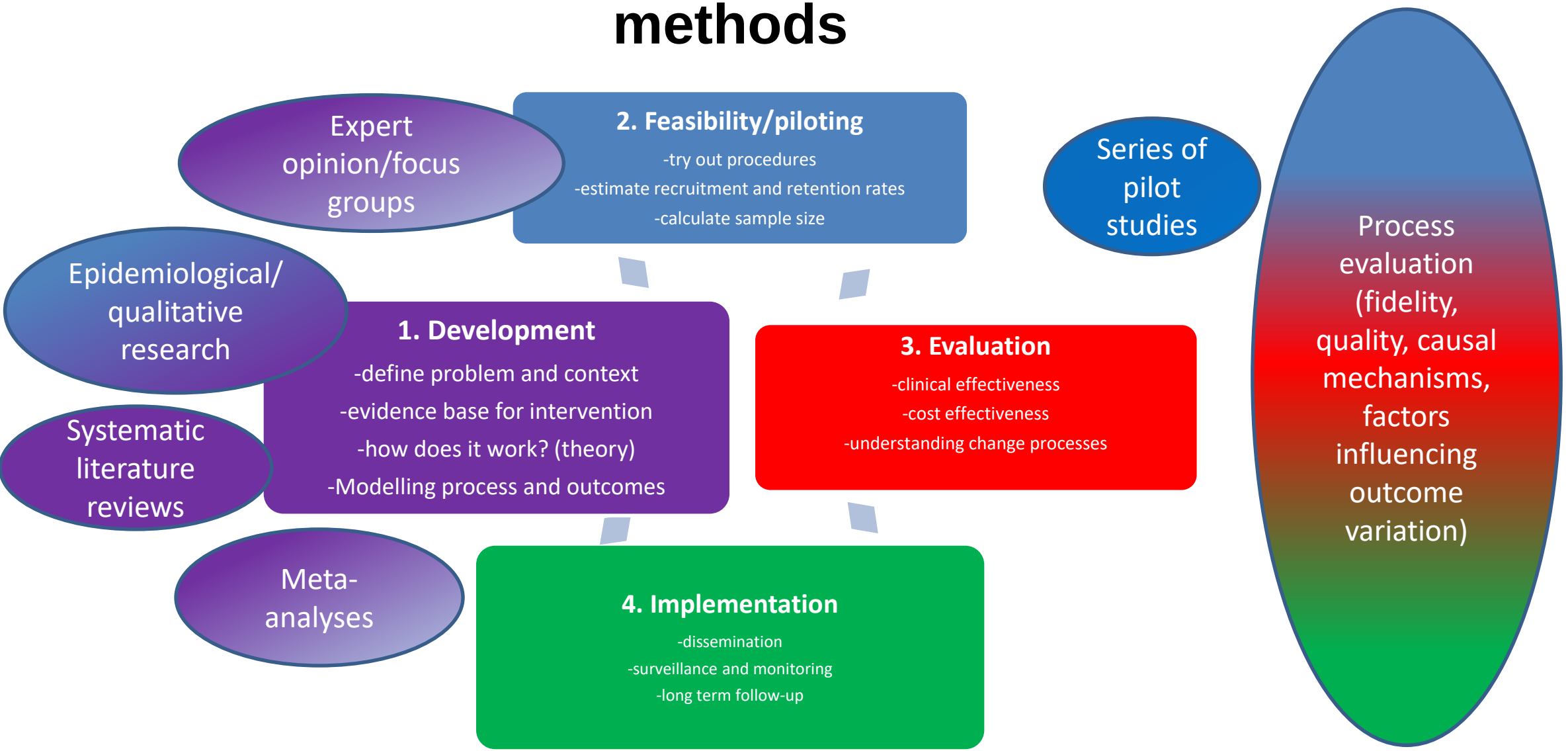
- A complex trial example:
  - HABIT
  - SRT vs sleep hygiene
  - Which is best?
  - Randomised
  - Process evaluation
- A complex study example:
  - Hypos Can Strike Twice
  - Leaflet intervention
  - Step-wedge
  - Interviews –post-study process evaluation

Sequential Development Phases for Interventions

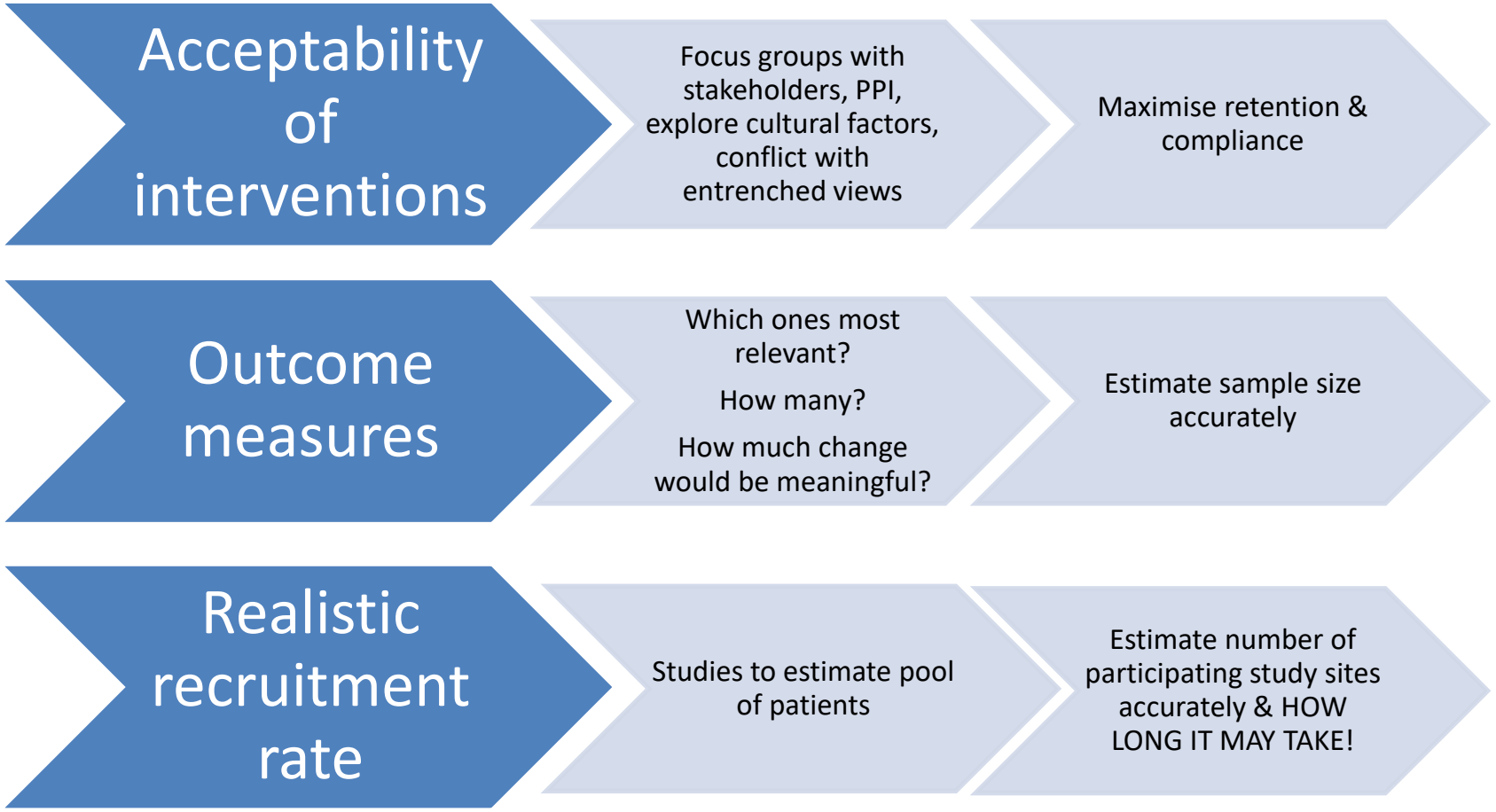


Stages to consider……..

Stages to consider…… **plus supporting research methods**



Feasibility considerations for complex interventions



Study Designs

-Defining control arms-options

- Alternative care package
- Standard care
- Placebo
- No treatment (is this really acceptable/ethical?)
- Randomised waiting list study*

*A wait list control group, also called a wait list comparison, is a group of participants included in an outcome study that is assigned to a waiting list and receives intervention after the active treatment group.

This control group serves as an untreated comparison group during the study, but eventually goes on to receive treatment at a later date. Wait list control groups are often **used when it would be unethical to deny participants access to treatment,** provided the wait is still shorter than that for routine services.

Design Name	Advantage	Notes
Individually randomised	Gold standard experimental design	e.g. HABIT trial, CHROMED, RIGHT-2

ORIGINAL ARTICLE

Telemonitoring in Chronic Obstructive Pulmonary Disease (CHROMED)

A Randomized Clinical Trial

Paul P. Walker[1,2*], Pasquale P. Pompilio[3*], Paolo Zanaboni[4], Trine S. Bergmo[4], Kaiu Prikk[5], Andrei Malinovschi[6], Josep M. Montserrat[7,8], Jo Middlemass[9], Silvana Šonc[10], Giulia Munaro[11], Dorjan Marušič[10], Ruth Sepper[5], Roberto Rosso[11], A. Niroshan Siriwardena[9], Christer Janson[12], Ramon Farré[8,13], Peter M. A. Calverley[2‡], and Raffaele L. Dellaca'[3,14‡]

American Journal of Respiratory and Critical Care Medicine Volume 198 Number 5 | September 1 2018

Abstract

Rationale: Early detection of chronic obstructive pulmonary disease (COPD) exacerbations using telemonitoring of physiological variables might reduce the frequency of hospitalization.

Objectives: To evaluate the efficacy of home monitoring of lung mechanics by the forced oscillation technique and cardiac parameters in older patients with COPD and comorbidities.

Methods: This multicenter, randomized clinical trial recruited 312 patients with Global Initiative for Chronic Obstructive Lung Disease grades II to IV COPD (median age, 71 yr [interquartile range, 66–76 yr]; 49.6% grade II, 50.4% grades III–IV), with a history of exacerbation in the previous year and at least one nonpulmonary comorbidity. Patients were randomized to usual care ($n = 158$) or telemonitoring ($n = 154$) and followed for 9 months. All telemonitoring patients self-assessed lung mechanics daily, and in a subgroup with congestive heart failure ($n = 37$) cardiac parameters were also monitored. An algorithm identified deterioration, triggering a telephone contact to determine appropriate interventions.

Measurements and Main Results: Primary outcomes were time to first hospitalization (TTFH) and change in the EuroQoL EQ-5D utility index score. Secondary outcomes included: rate of antibiotic/corticosteroid prescription; hospitalization; the COPD Assessment Tool, Patient Health Questionnaire-9, and Minnesota Living with Heart Failure questionnaire scores; quality-adjusted life years; and healthcare costs. Telemonitoring did not affect TTFH, EQ-5D utility index score, antibiotic prescriptions, hospitalization rate, or questionnaire scores. In an exploratory analysis, telemedicine was associated with fewer repeat hospitalizations (−54%; $P = 0.017$).

Conclusions: In older patients with COPD and comorbidities, remote monitoring of lung function by forced oscillation technique and cardiac parameters did not change TTFH and EQ-5D.

Clinical trial registered with www.clinicaltrials.gov (NCT 01960907).

Keywords: forced oscillation technique (FOT); COPD exacerbation; chronic obstructive pulmonary disease; home monitoring

COMPLEX BECAUSE…

- 6 sites in 5 countries
- Training of patients
- Different healthcare systems
- Different costs

Design Name	Advantage	Notes
Cluster randomised –patients randomised in groups (clusters).	Can reduce contamination of control arm. Used when individual randomisation to treatment arms is not possible or the intervention is naturally applied to a whole cluster.	Often used in health services research -SAFER 2 -educational outreach for immunisation rate improvement

Cluster randomised example –SAFER 2

Paramedic Assessment of Older Adults After Falls, Including Community Care Referral Pathway: Cluster Randomized Trial

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*Corresponding Author. E-mail: h.a.snooks@swansea.ac.uk, Twitter: @HSRSwansea.

Study objective: We aim to determine clinical and cost-effectiveness of a paramedic protocol for the care of older people who fall.

Methods: We undertook a cluster randomized trial in 3 UK ambulance services between March 2011 and June 2012. We included patients aged 65 years or older after an emergency call for a fall, attended by paramedics based at trial stations. Intervention paramedics could refer the patient to a community-based falls service instead of transporting the patient to the emergency department. Control paramedics provided care as usual. The primary outcome was subsequent emergency contacts or death.

Results: One hundred five paramedics based at 14 intervention stations attended 3,073 eligible patients; 110 paramedics based at 11 control stations attended 2,841 eligible patients. We analyzed primary outcomes for 2,391 intervention and 2,264 control patients. One third of patients made further emergency contacts or died within 1 month, and two thirds within 6 months, with no difference between groups. Subsequent 999 call rates within 6 months were lower in the intervention arm (0.0125 versus 0.0172; adjusted difference −0.0045; 95% confidence interval −0.0073 to −0.0017). Intervention paramedics referred 8% of patients (204/2,420) to falls services and left fewer patients at the scene without any ongoing care. Intervention patients reported higher satisfaction with interpersonal aspects of care. There were no other differences between groups. Mean intervention cost was $23 per patient, with no difference in overall resource use between groups at 1 or 6 months.

Conclusion: A clinical protocol for paramedics reduced emergency ambulance calls for patients attended for a fall safely and at modest cost. [Ann Emerg Med. 2017;■:1-11.]

Intervention= education + clinical protocol + care pathway + falls assessment

"We randomly allocated ambulance stations, not patients, because the intervention included training for ambulance paramedics that they could not later suppress. We chose to allocate stations so that ambulance services could support paramedics based at intervention stations while minimizing contamination of practice of those based at control stations."

Affected by changing landscape –lost stations due to introduction of competing intervention

Cluster randomised example

Cluster randomised controlled trial of an educational outreach visit to improve influenza and pneumococcal immunisation rates in primary care

A Niroshan Siriwardena, Aly Rashid, Mark R D Johnson and Michael E Dewey

"Because the target of the intervention …the **unit of randomisation was the practice**, cluster-randomized methodology was used. …..There is evidence that the capacity for a practice to increase immunisation rate depends on its baseline rate, i.e. it is easier to increase from a low baseline than a high one. Because of this ceiling effect, it was agreed to use **stratified randomisation** based on initial rate."

Intervention = educational visit by study GP (information, dialogue about barriers, practice specific review against targets, discussion about potential improvement).

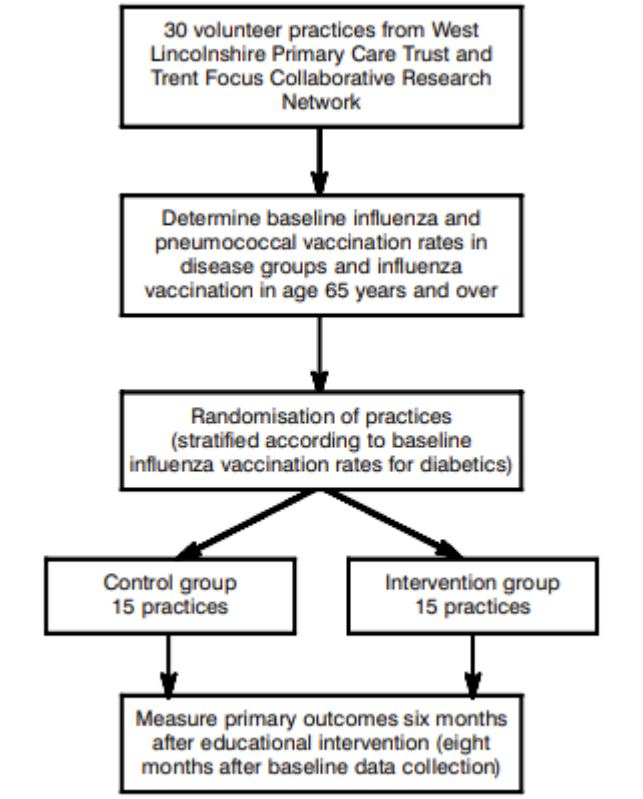
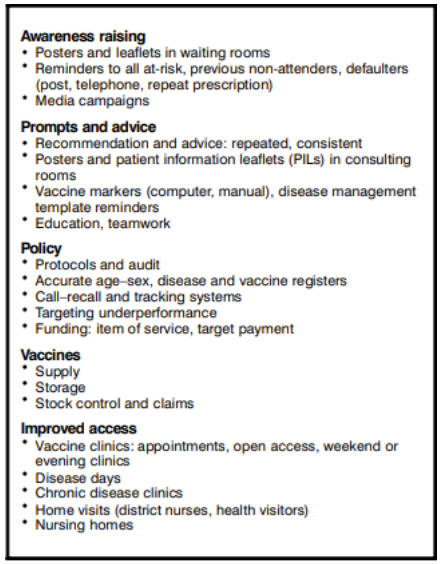


Figure 1. Flow chart summarising involvement of practices in trial.

Conclusion: *Practices where primary care teams received an educational outreach visit demonstrated a significantly greater improvement in uptake in high-risk groups for pneumococcal but not influenza vaccine.*

Semi-structured questionnaire captured how they achieved improvement in vaccination up-take:



Awareness raising
- Posters and leaflets in waiting rooms
- Reminders to all at-risk, previous non-attenders, defaulters (post, telephone, repeat prescription)
- Media campaigns

Prompts and advice
- Recommendation and advice: repeated, consistent
- Posters and patient information leaflets (PILs) in consulting rooms
- Vaccine markers (computer, manual), disease management template reminders
- Education, teamwork

Policy
- Protocols and audit
- Accurate age–sex, disease and vaccine registers
- Call–recall and tracking systems
- Targeting underperformance
- Funding: item of service, target payment

Vaccines
- Supply
- Storage
- Stock control and claims

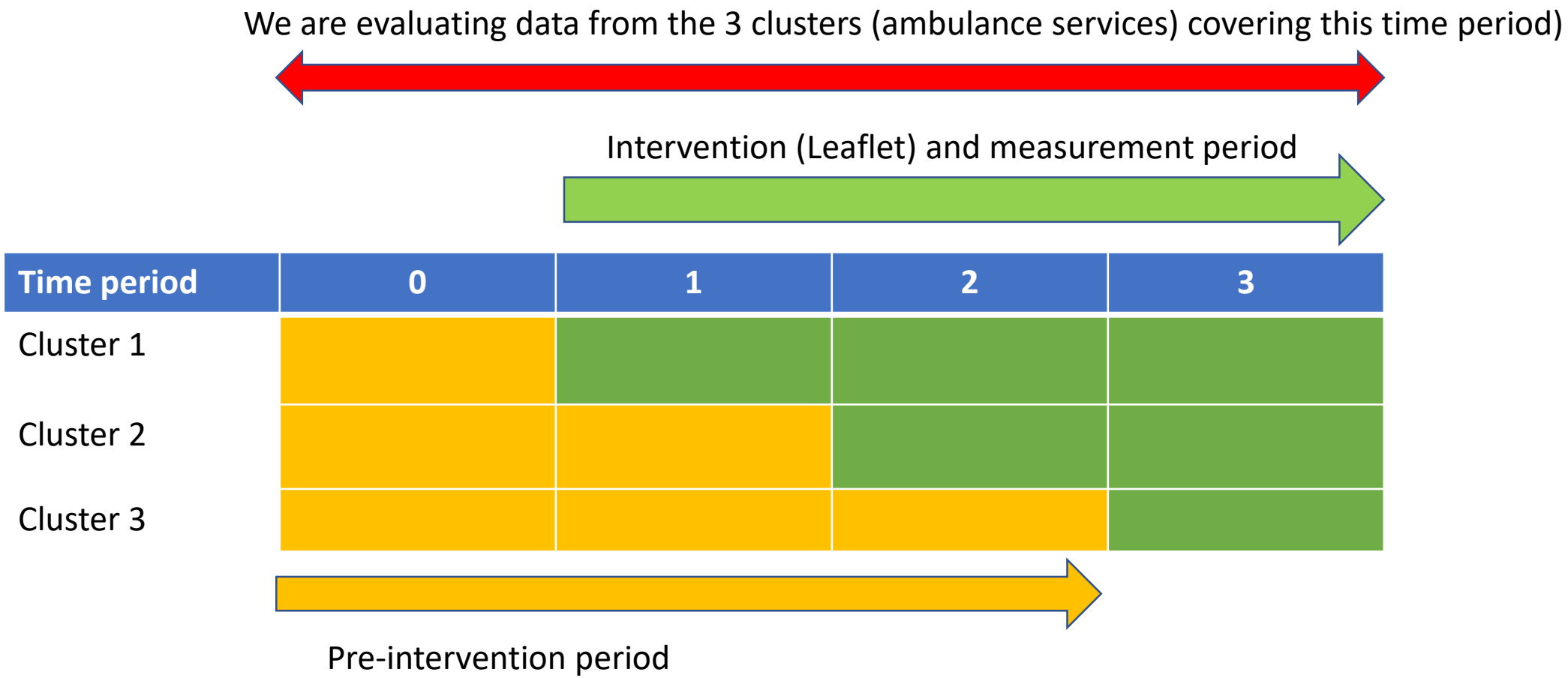
Improved access
- Vaccine clinics: appointments, open access, weekend or evening clinics
- Disease days
- Chronic disease clinics
- Home visits (district nurses, health visitors)
- Nursing homes

Figure 2. Techniques employed by practices to improve influenza and pneumococcal vaccination rates.

Design Name	Advantage	Notes
Stepped-wedge	Used where we can’t roll out the intervention to the whole study population at once and where there are practical or ethical constraints.	e.g. Hypos can strike twice (HS2) study

Stepped-wedge example –HS2

Did a leaflet provided by the ambulance service decrease the number of call outs by diabetic patients for hypoglycaemia?



Design Name	Advantage	Notes
Preference and randomised consent designs	Treatment allocation can be based on patient preference or patients are randomised before giving consent.	Non-standard design –can help where patients have strong preferences for treatments (could help avoid cross-overs)
N of 1 designs	Used to assess between and within person change. Estimating the effect of a treatment on the individual.	Crossover trials, usually randomized and often blinded, conducted in a single patient. Widely used in psychology, education, and social work.

Developing and evaluating complex interventions: the new Medical Research Council guidance

BMJ 2008:337:a1655 doi: 10.1136/bmj.a1655

- Updated MRC recommendations:
- More emphasis on:
- Piloting and development (establishing feasibility)
- Process and outcome evaluation
- Tailoring complex interventions to local contexts (as opposed to standardisation)

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Piloting and Development – Feasibility Experiences with HABIT

Dr Julie Pattinson

Feasibility & Piloting

- Feasibility considers the tasks and the activities outlined E.g. HABIT Groundwork
  - Practice recruitment - Site selection (SIV)
    - Patients: Estimating recruitment/retention
    - Resources: Staff/Nurses, delivery of intervention/searches
    - Availability of rooms for baseline assessments
    - Research Initiative Sites

Piloting: Internal pilot phase and Stop-Go Criteria

HABIT Pilot – Explore key uncertainties in the design (Craig et al; 2008)

Recruitment Criteria (% of Target n) Proposed Action

- >80% progress to main trial phase
- 70-80% progress to main trial phase, implementing strategies (e.g., recruitment of additional practices and nurses)
-
- 50-69% Urgent measures required, discuss with TSC and HTA

- <50% Consider stopping trial, discuss with Trial Steering Committee/Health Technology Assessment

Treatment Fidelity – Stop/Go [appraisal of sample of recorded nurse-patient consultations]

Treatment Fidelity Criteria (On average…) & ***Proposed Action***

- >70% of SRT elements are covered during sampled sessions progress to main trial phase
- 60-69% of SRT elements are covered during sampled sessions progress to main trial phase, implementing strategies (e.g., retrain certain nurses)
- <60% of SRT elements are covered during sampled sessions Consider stopping trial, discuss with TSC and HTA

Contamination – Stop/Go [e.g. based on questionnaire response and follow-up phone call with control group]

Contamination criteria & Proposed Action

- ≤5% of control participants receive SRT through their practice. Progress to main trial

- 6-15% of control participants receive SRT through their practice. Progress to main trial phase, consider implementing strategies (e.g., drop specific practices if disproportionately affected)
  - conduct review of sample size and statistical methods - ascertain need for adjustment

- >15% of control participants receive SRT through their practice. Consider stopping trial, discuss with TSC and HTA

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Process Evaluation of Complex Interventions and Experiences with HABIT

Dr Julie Pattinson

Why do we need process evaluations of complex interventions?

Aim: understand the functioning of an intervention delivery

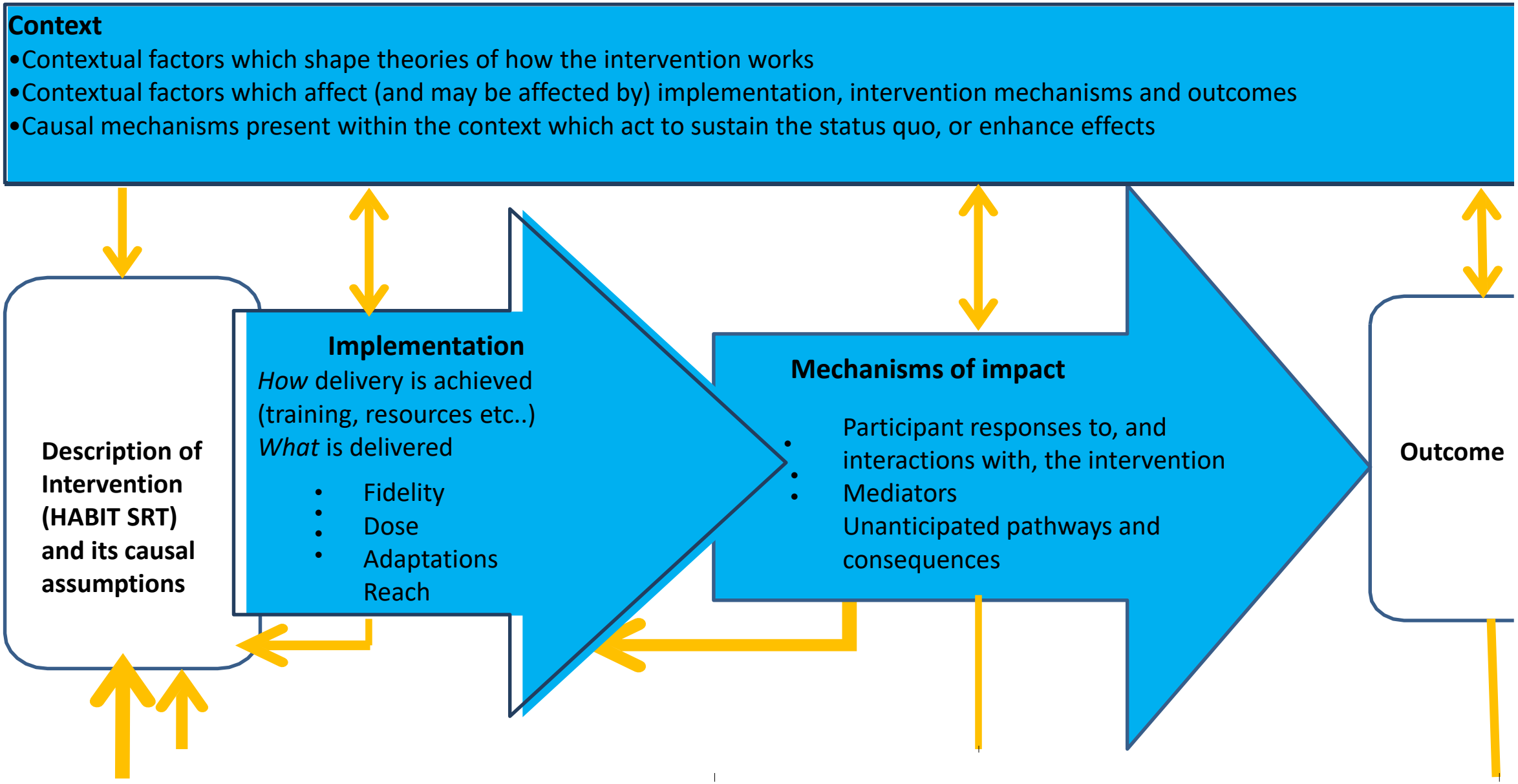
Functioning is broken down into 3 layers

- Implementation
- Mechanisms of Impact
- Contextual Factors

Semi structured interviews

- 15 trial participants
- Nurses
- GPs/Surgery staff

Remember a complex intervention may have one or multiple components, these interact to produce change


Context
•Contextual factors which shape theories of how the intervention works
•Contextual factors which affect (and may be affected by) implementation, intervention mechanisms and outcomes
•Causal mechanisms present within the context which act to sustain the status quo, or enhance effects
Description of Intervention (HABIT SRT) and its causal assumptions
Implementation
How delivery is achieved (training, resources etc..)
What is delivered
Fidelity
Dose
Adaptations
Reach
Mechanisms of impact
Participant responses to, and interactions with, the intervention
Mediators
Unanticipated pathways and consequences
Outcome

Implementation

- Patients expectations from SRT
- Nurse training (**Fidelity:** was SRT delivered as intended/deviations from protocol & challenges)
- Patient appointment times (**Dose:** e.g. receive correct length of appointment time)
- Patient lifestyle factors (**Adaptions:** impact on efficacy of intervention delivery.
- Tweaking & Negotiations: delivery of SRT is patient dependent
- **Extent of Adaption** to delivery: did these affect the **fidelity**
- Did SRT **Reach** the patient as intended (protocol/training)

Mechanisms of impact

- MRC guidance – we looked at the **causal mechanisms** how does the delivered intervention produce change.
- how did participants interact with nurses
- Patient/nurse response to SRT with outcomes produced by these interactions
- Understanding how participants & nurses interact is crucial to understanding how the intervention worked
- Crossover was vital nurse/patient interaction
- Reasons for withdrawal from intervention/trial

Contextual factors

- Context : How does context – affect implementation and outcomes?
- context includes anything external to the intervention either impedes or strengthens it affects.
- context may change in response to the intervention
- changes may cause adaptions to delivery

Contextual factors

- Considered wider implementation
- Sustainability
- Trial components/functioning of the trial
- GP staff attitudes
- Delivery in a real life setting (not in allocated research time)
- Cost effectiveness
- Freeing up GP time
- Other staff may deliver SRT
- Pros and Cons
- External – E.g. COVID -19 unforeseen circumstances (Force Majeure)

Useful Reading

- www.mrc.ac.uk/complexinterventionsguidance
- 2000 *MRC Framework for the Development and Evaluation of RCTs for Complex Interventions to Improve Health*
- Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ 2008:337:a1655. doi: 10.1136/bmj.a1655
- Framework for design and evaluation of complex interventions to improve health. BMJ 2000; 321: 694-6
- Designing and evaluating complex interventions to improve health care: BMJ 2007; 334;455-459. doi:10.1136/bmj.39108.379965.BE