**Steve Hudson Lecture**
October 2022

Effort, evidence and outcomes: complex interventions for complex problems in appropriate medicines use in older people

Carmel M. Hughes
School of Pharmacy
Queen's University Belfast

Outline

- Simple and complex problems
- Context and changing perspectives
  – Polypharmacy
- Approaches to addressing complex problems
  – Polypharmacy: a research case study
  – Effort, evidence and outcomes
- Reflections

COVID changed science
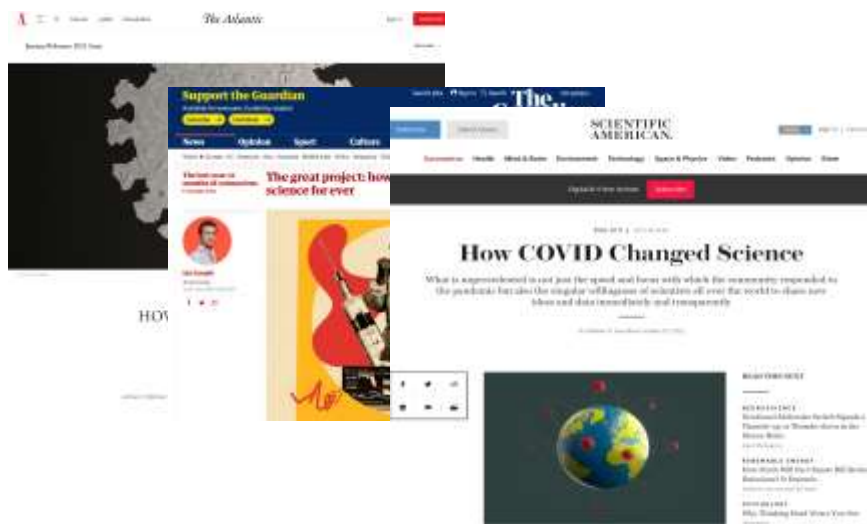
COVID-a simple problem

- Role of trials in producing evidence
  - The pandemic required reliable and clear answers **quickly**
- RECOVERY trial
  - Simple trial design
  - Randomised to one of two treatments
    - Treatment of interest vs standard of care
  - Easily measured definitive outcome
    - Death
  - Reduced bureaucracy leading to rapid recruitment

Shock and awe

- Trial protocol drafted March 10th 2020
- First patient recruited March 19th 2020
- Treatments tested
  – Dexamethasone
  – Hydroxychloroquine
  – Azithromycin
  – Lopinavir-ritonavir
- Current stats
  – ~48,000 participants
  – 200 active sites

How to set up a trial in nine days

Moving from simple to complex

- **Older patients, polypharmacy and multimorbidity**
- What we need to think about
- What do we target and how
- What do we need to evaluate and how

Challenges and changing perspectives on polypharmacy

- **Challenges of medication use in older people**
  - Altered pharmacokinetics/ pharmacodynamics
  - Multimorbidity
  - Polypharmacy
- **Changing perspectives on polypharmacy**
  - Numbers?
  - Definitions?

A balancing act

Polypharmacy

A New Paradigm for Quality Drug Therapy in the Elderly?

Appropriate Polypharmacy and Medicine Safety: When Many is not Too Many

- *"The larger number of pharmaceuticals will always be an important component of the medical care of older Americans."*

"The concept of 'appropriate polypharmacy' recognises that patients can benefit from multiple medications…"

Gurwitz. Arch Intern Med 2004; 164: 1957-59

Cadogan et al., Drug Safety, 2016; 39: 109-116

Getting the balance right between 'many' and 'too many' drugs

How do we move beyond the numbers to attain appropriate polypharmacy?

What's the right strategy to deal with complexity?

Developing a new intervention

- **Developing interventions**
  - Older people (community-dwelling)
  - Heart failure
  - Asthma
  - Older people (nursing homes)
- **Basis of the intervention?**
  - Pragmatism; literature; what we thought might work
  - **ISLAGIATT**

Findings from these studies

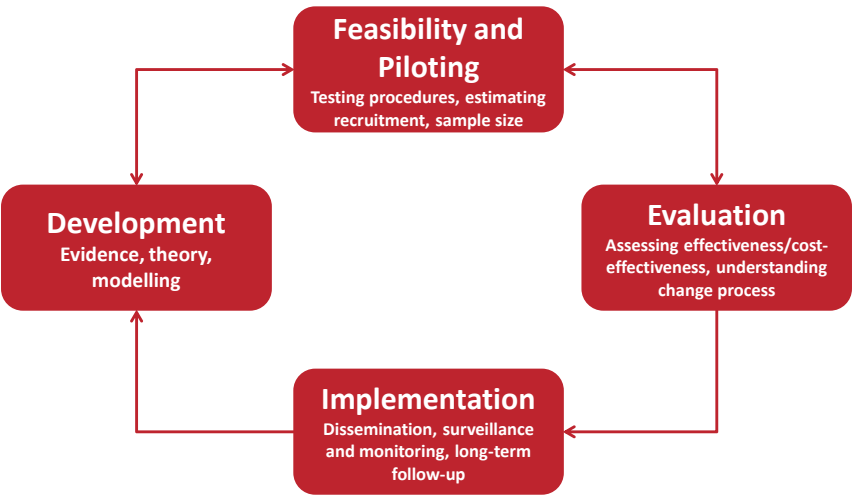- Older people (community-dwelling)
  - Intervention made no difference
- Heart failure
  - Intervention made no difference
- Asthma
  - Intervention made no difference
- Older people (nursing homes)
  - Intervention was effective

How do we move beyond the numbers to attain appropriate polypharmacy?

Developing a complex intervention to deal with complexity

Focusing on behaviour change

Medical Research Council Framework for developing complex interventions

Feasibility and Piloting
Testing procedures, estimating recruitment, sample size

Development
Evidence, theory, modelling

Evaluation
Assessing effectiveness/cost-effectiveness, understanding change process

Implementation
Dissemination, surveillance and monitoring, long-term follow-up

Underpinning evidence

Cochrane Library
Cochrane Database of Systematic Reviews

Interventions to improve the appropriate use of polypharmacy for older people (Review)

Rankin A, Cadogan CA, Patterson SM, Kerse N, Cardwell CR, Bradley MC, Ryan C, Hughes C

- Intervention development lacked detailed description
- Evidence for effectiveness of identified interventions was weak

Theory and modelling

- Can seem very abstract
- What are we trying to do with our intervention?
- To improve prescribing of appropriate polypharmacy
  - Need to focus on prescribing
- **Change prescribing behaviour in relation to polypharmacy**

Approach to developing interventions

Series of systematic steps focusing on behaviour change
1. Specify target behaviour(s)-what needs to change
   - **Prescribing of appropriate polypharmacy**
2. Identify barriers to/facilitators of behaviour change
   - **Theoretical domains framework (TDF)**
3. Consider how to overcome the barriers/facilitators to change the target behaviour(s)
   - **Identify behaviour change techniques (BCTs; 'active ingredients' of the intervention)**
4. Implement an intervention that seeks to change the target behaviour(s)
5. Evaluate if this intervention works

Overview of approach for the prescribing of appropriate polypharmacy
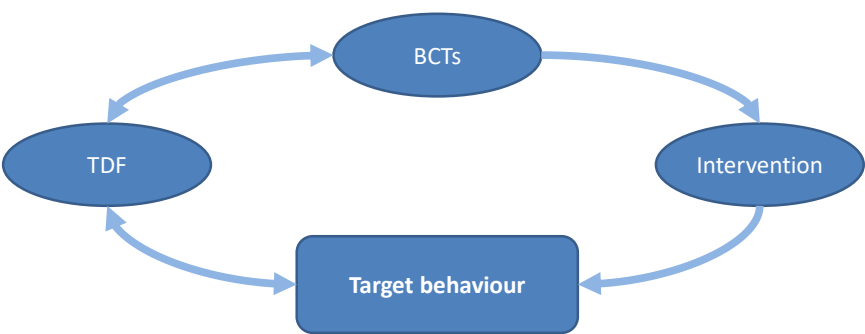
Michie *et al.* 2013. *Ann Behav Med*; **46**: 81-95; Cadogan *et al.*, 2015; *Implem Sci* ; **10**: 161

Theoretical Domains Framework (TDF)

12 theoretical domains relevant to changing healthcare professionals' behaviour.

Theoretical domains	
Knowledge	Skills
Beliefs about capabilities	Emotion
Beliefs about consequences	Behavioural regulation
Motivation and goals	Social influences
Memory, attention and decision processes	Environmental context and resources
Social/professional role and identity	Nature of the behaviours

Michie *et al.* 2005. *Qual Saf Health Care*, **14**:26-33

Key domains for prescribing

- **Domains**
  - Skills
  - Beliefs about capabilities
  - Beliefs about consequences
  - Environmental context and resources
  - Memory, attention and decision processes
  - Social/professional role
  - Social influences
  - Behavioural regulation

Cadogan *et al*., 2015; *Implem Sci* ; **10**: 161

From theory to an intervention component

TDF domain	BCT	Definition	Example
Environmental context and resources	Prompts and cues	Introduce or define environmental or social stimulus with the purpose of prompting or cueing the behaviour. The prompt or cue would normally occur at the time or place of performance	Place a Post-it® note on the door to remind patients to take medicines before leaving the house in the morning

Cane *et al*., 2015; *Br. J Health Psychology*; 20: 130-50

Moving from BCTs to an intervention package

- Evidence
- Context
- Experience

'Developing interventions which are complex in nature requires a balance between science and creativity'

Hoddinott, 2015

22

BCTs embedded in the intervention

Behaviour change technique	Example of how the behaviour change technique is being operationalised as part of the intervention
Action planning	GPs will plan to perform medication reviews on the specified date when patients meeting inclusion criteria present at the practice for a scheduled appointment
Prompts/cues	GPs will be prompted by the receptionist/practice manager to perform medication reviews with older patients meeting inclusion criteria when patients present for a scheduled appointment
Modelling or demonstrating of behaviour	GPs will be provided with a video demonstration of how to perform a medication review with an older patient who is receiving polypharmacy
Salience of consequences	As part of the video demonstration of how to perform a medication review, feedback will be included from the GP and 'patient' to emphasise the potentially positive consequences of performing the review

Cadogan *et al.*, 2015; *Implem Sci* ; **10**: 161; Cadogan *et al.*, 2016; *BMC HSR*; **16**: 661

23

Intervention components

1. A video demonstrating how general practitioners (GPs) can prescribe appropriate polypharmacy during a typical consultation with an older patient
2. A patient recall process (appointment with GP for a medication review)
3. GPs making explicit plans how to ensure target patients were prescribed appropriate polypharmacy
4. GPs receiving prompts from reception staff to carry out this plan when patients arrived at the practice

24

Medical Research Council Framework

Feasibility and Piloting
Testing procedures, estimating recruitment, sample size

Development
Evidence, theory, modelling

Evaluation
Assessing effectiveness/cost-effectiveness, understanding change process

Implementation
Dissemination, surveillance and monitoring, long-term follow-up

25
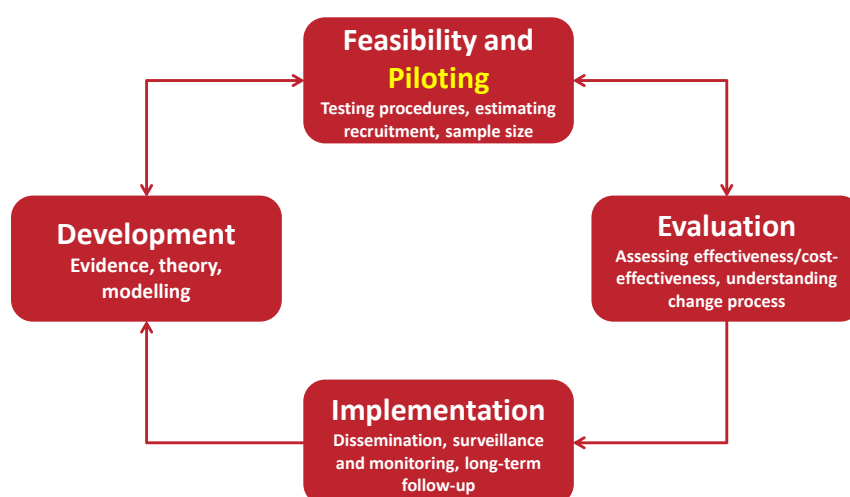
PolyPrime intervention

- To undertake a pilot cluster RCT (cRCT) of a theory-based intervention targeting prescribing of appropriate polypharmacy in primary care (PolyPrime) to assess the feasibility of a definitive cRCT of the PolyPrime intervention

A unique cross-border initiative

- Funded under the CHITIN initiative: **C**ross-border **H**ealthcare **I**ntervention **T**rials in **I**reland **N**etwork
- A cross-border partnership between
  - Public Health Agency (PHA) in Northern Ireland
  - Health Research Board (HRB) in Republic of Ireland
- One of 11 health and social care research trials (HITs) awarded funding

[c h i t i n]
kite-tin

**Cross-border
Healthcare Intervention Trials
in Ireland Network**

26

The Defined Area

- PolyPrime operated within a clearly 'Defined Area' including Northern Ireland and the border region of Ireland

Northern Ireland:

Antrim	Armagh
Down	Fermanagh
Londonderry/Derry	Tyrone

Republic of Ireland:

Cavan	Donegal
Leitrim	Louth
Monaghan	Sligo

Overview of PolyPrime

- 12 GP practices recruited from the Defined Area
  - 10 patients per practice
  - Practices randomised to intervention or control
- Video made available to intervention practices on a secure platform
- Eligible patients invited to attend the practice on two occasions for review
- Data collection at baseline, 6 and 12 months
  - Medication appropriateness, health-related quality of life and cost analysis
  - Process evaluation
  - Progression criteria
- Focus on FEASIBILITY

An external pilot cluster randomised controlled trial of a theory-based intervention to improve appropriate polypharmacy in older people in primary care (PolyPrime)

Study modifications due to COVID

- Study suspended on March 13th 2020
- Revised timeline
  - Study restarted in July 2020
- Revised intervention delivery
  - Telephone or online medication reviews when a face-to-face consultation was not possible
- Revised data collection timelines
  - 9 months rather than 12 months

Phase 2: Main pilot study - what we found

We were able to collect data from practices in order to apply STOPP/START criteria to assess appropriateness

Potentially inappropriate prescribing (STOPP & START combined)				
	Intervention	Control	% point difference (95% CI)	ICC
Baseline n (%)	n=31 27 (87.10%)	n=25 20 (80.00%)		
6 months n (%)	n=24 21 (87.50%)	n=25 20 (80.00%)	7.50 (-13.02, 28.02)	0.0889
9 months n (%)	n=24 21 (87.50%)	n=23 20 (86.96%)	0.54 (-18.55, 19.64)	0.0000

Phase 2: Main pilot study
- what we found (*cont'd*)

We were able to collect data from patients in order to assess health-related quality of life using the EQ-5D-5L and the Medication-Related Burden (MRB)-QoL

	EQ-5D-5L			MRB-QoL			
	Missing items n (%)	Floor effects n (%)	Ceiling effects n (%)	Missing items n (%)	Floor effects n (%)	Ceiling effects n (%)	Correlation coefficient
Baseline n=67	3 (4.5)	0 (0)	14 (20.9)	9 (13.4)	0 (0)	5 (7.5)	-0.39
6 months n=47	0 (0)	0 (0)	9 (19.2)	10 (21.3)	0 (0)	4 (8.5)	-0.59
9 months n=47	1 (2.1)	0 (0)	0 (0)	6 (12.8)	0 (0)	6 (12.8)	-0.58

Phase 2: Main pilot study
- what we found (*cont'd*)

We were able to collect data to estimate the GP resource use and costs (£ GBP) associated with the intervention

Resource use	Estimated time per participant mins	Cost £
Stage 1: Planning & preparation for delivery - viewing online video, preparing for each review	15.47	65.44
Stage 2: Delivery - undertaking the reviews, other related tasks	52.65	222.71
Total cost per participant		**£288.15**

Phase 2: Main pilot study
- what we found (*cont'd*)

We were able to collect data using two methods to calculate total health service use costs (£) over 9 months

	Self-reported by patients			GP-record		
	Intervention (n=22) Mean (95% CI)	Control (n=20) Mean (95% CI)	Difference (95% CI)	Intervention (n=22) Mean (95% CI)	Control (n=20) Mean (95% CI)	Difference (95% CI)
Total cost	532.23 (237.90, 826.55)	1556.95 (-348.47, 3462.37)	-1024.72 (-2802.38, 752.93)	694.41 (460.40, 928.42)	1335.95 (28.32, 2643.58)	-641.54 (-1867.44, 584.35)
Total cost by collection method	£1020.19 (129.19, 1911.19)			£999.90 (387.23, 1612.58)		

Phase 3: Process evaluation
- what we planned

- Study-specific data collection forms completed by the practice staff
- Audio-recordings of medication review appointments
- Interviews with GPs, practice staff and patients

Study modifications to process evaluation

- Feedback interviews with GPs and practice staff
  - Completed via telephone or video call when a face-to-face interview was not possible
- Face-to-face feedback interviews with patients
  - Replaced with postal feedback questionnaires

Phase 3: Process evaluation
- what we found

The intervention components were delivered as intended (fidelity)

Intervention component	Data collected	Total	Delivered as intended
Online video	Median number of times the GPs accessed the video (range)	4 (3-6)	☑
Weekly meetings	Median number of weekly meetings held (range)	2 (1-2)	☑
Prompts	Median number of prompts delivered (range)	2 (1-8)	☑
Patient recall	The number of appointments scheduled and attended (n)	24	☑
	Audio recordings of appointments indicated that medication reviews were undertaken by GPs as intended		☑

Phase 3: Process evaluation
- what we found (*cont'd)*

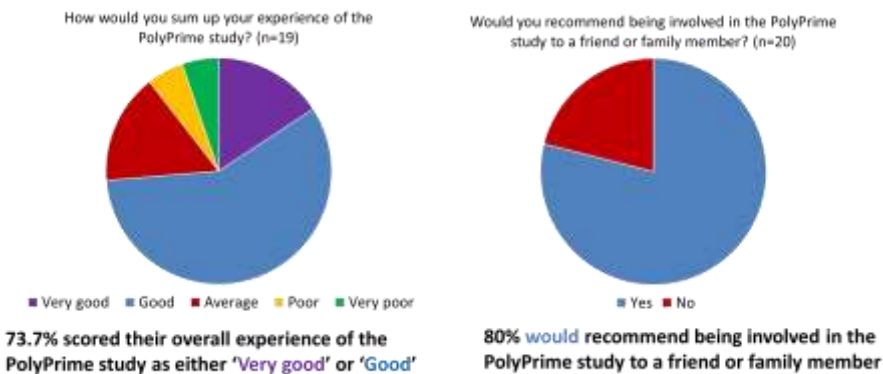**The intervention was acceptable to GPs and practice staff**

"I think so yeah, yeah, yes... Em why would I say it? From the experience of doing it it seemed to go well and people seemed happy em they were happy when I spoke to them again which is a key thing and they didn't try to dodge my calls and em were happy to engage and seemed interested and enthusiastic about it so em yeah so I was happy with it yeah." [GPP11]

"Yeh, it [support provided by the research team] was excellent." [PM24]

"Probably the the the most time consuming part was just was just identifying the patients in the first place… Just literally getting the paperwork [sending patient recruitment packs] to them you know that was probably probably the the worst of it and that was not… that was not particularly time consuming." [GPP22]

Phase 3: Process evaluation
- what we found (*cont'd)*

The intervention was acceptable to patients

How would you sum up your experience of the PolyPrime study? (n=19)

■ Very good ■ Good ■ Average ■ Poor ■ Very poor

73.7% scored their overall experience of the PolyPrime study as either 'Very good' or 'Good'

Would you recommend being involved in the PolyPrime study to a friend or family member? (n=20)

■ Yes ■ No

80% would recommend being involved in the PolyPrime study to a friend or family member

Progression criteria

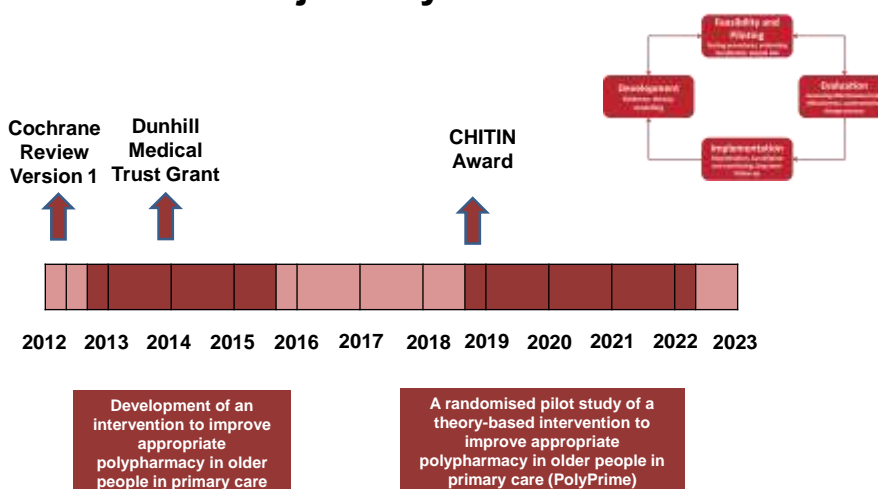| Concept	Progression criteria		
	Stop	Amend	Go
GP practice recruitment	If ≤5 GP practices are recruited within 8 months	If 6–9 GP practices are recruited and/or it takes longer	If ≥10 GP practices are recruited to take part in ≤ 6 months
GP practice retention	If ≤5 GP practices are retained	If 6-9 GP practices can be retained	If ≥10 GP practices can be retained
Patient recruitment	If ≤59 patients are recruited within 5 months	If 60–95 patients are recruited within 5 months	If ≥96 patients are recruited within 5 months
Patient retention	If ≤49% of patients are retained	If 50–79% of patients are retained	If ≥80% of patients are retained
Completeness of outcome data	≤49% of each patient self-report and GP-reported outcome measure complete	If 50-79% of each patient self-report and GP-reported outcome measure complete	If ≥80% of each patient self-report and GP-reported outcome measure complete

Assessment against the progression criteria

Concept	Results	
GP practice recruitment	12 GP practices were recruited within 7 months	Go
GP practice retention	9 GP practices were retained until the end of the study period	Amend
Patient recruitment	68 patients were recruited within 4 months	Amend
Patient retention	69% (47/68) patients were retained in the study (i.e. had GP record data available for primary outcome analysis)	Amend
Completeness of outcome data	94% of primary and secondary outcome data were complete	Go

Key findings from the pilot study

- Feasible to recruit GP practices and deliver PolyPrime intervention in primary care across two jurisdictions
- Feasible to collect GP record and patient self-reported data
  - High return rates and completeness of data
- Uncertainties remain surrounding patient recruitment and retention
  - Partly attributable to COVID impact
  - Further work needed to establish effectiveness of strategies to increase patient recruitment and retention rates

Our journey to here……

Cochrane Review Version 1

Dunhill Medical Trust Grant

CHITIN Award

2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022 2023

Development of an intervention to improve appropriate polypharmacy in older people in primary care

A randomised pilot study of a theory-based intervention to improve appropriate polypharmacy in older people in primary care (PolyPrime)

Step-by-step….

Effort leading to evidence?

- **A systematic approach to intervention development**

- **Detailed, thorough, exhaustive**

- **Time-consuming**
  - Balance between rigour (following the science) and practical approach
  - Feasibility and pilot testing will add to the timeline of obtaining results

- **Important question**
  - Will following the science on intervention development lead to a more effective intervention which, in turn, will generate the evidence?

Effort and evidence in the COVID trials

- Simplicity of design
  - Process and outcomes
- Rapid review
- Building on experience and track record
  - Referred to trial protocols developed in late 1980s
- Infrastructure
  - Research and health system
  - Long-established and well-resourced

How to set up a trial in nine days

COVID has changed the world

Evidence-based medicine and COVID-19: what to believe and when to change

- Changing context
  - Geopolitical and economic uncertainty
  - Priorities in healthcare
    - Backlog in care provision
  - Priorities in research
    - What are the key questions?

BUT….

- Reinforcement of the need for evidence generated from high quality studies

More important than ever

*"Could the current economic crisis be the making of evidence-based medicine?....
Perhaps it's only now, in this harshest of financial climates, that we'll really have to put the evidence to work"*

Godlee, BMJ 2009

Acknowledgements

- Colleagues, post-doctoral fellows and students
- Funders
  - HSC Research and Development Division, Dunhill Medical Trust, CHITIN Initiative
- Study participants
- ESCP