

Cochrane reviews and uncertainty: Evidence based trial design

7th March 2018

Trusted evidence.
Informed decisions.
Better health.



Public health priorities

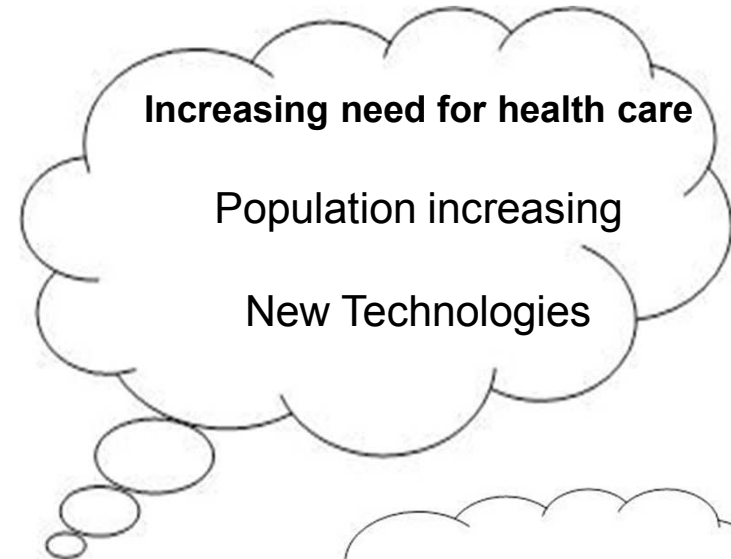
Reducing avoidable sight loss

- ~28000 incident sight loss per year in the UK

Effective rehabilitation of those with sight impairment²⁻⁴

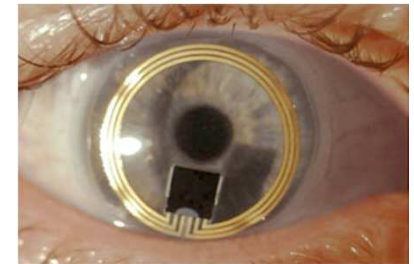
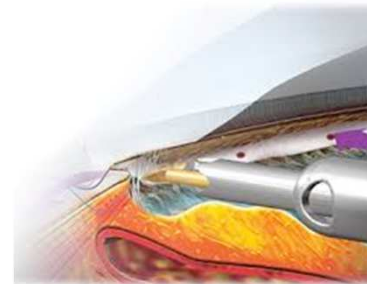
1. <https://digital.nhs.uk/catalogue/PUB30154>
2. <http://www.hscic.gov.uk/catalogue/PUB14798/regi-blin-part-sigh-eng-14-rep.pdf>
3. <http://www.gov.scot/Publications/2010/10/26094945/12>
4. Quartilo C et al, Eye 2016. April;30(4):602-7

Trusted evidence synthesis

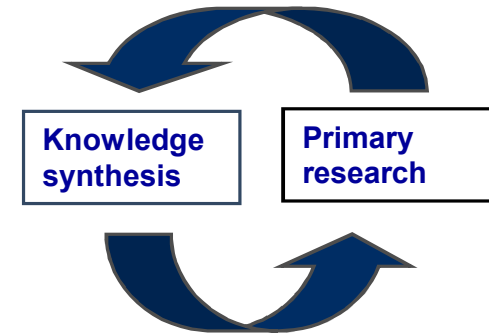


What do we mean by an Technology?

Intervention to promote health, prevent and treat disease and improve rehabilitation and long term care

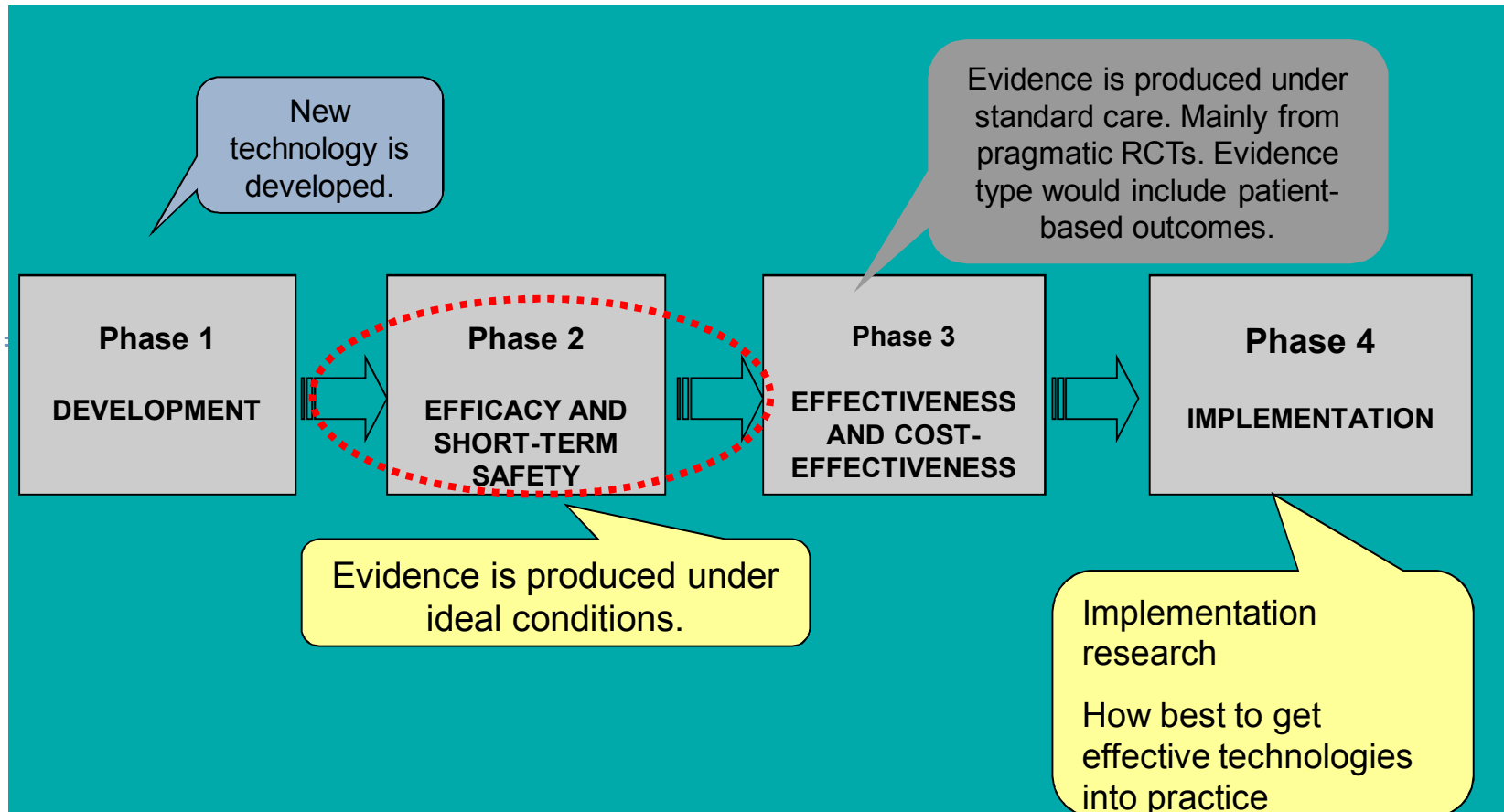


Trusted evidence synthesis: Knowns and unknowns



Systematic reviews

- Evaluation of Interventions (Health Technologies)
- Identifies uncertainty
- Informs the design of the future Randomised Controlled Trial (RCT)
- Essential for a properly designed and fundable study



Factors influencing choice:

1. Does a new technology work?

Is it safe?

Keratoconus



Keratoconus

- Corneal collagen cross-linking (CXL) is an emerging technology and being adopted worldwide in the management of keratoconus
- Is corneal collagen cross-linking (CXL) a good treatment for slowing down the progression of keratoconus?

**Corneal collagen cross-linking for treating keratoconus
(Review)**

Corneal collagen cross-linking for treating keratoconus (Review)

Syakakis E, Karim R, Evans JR, Bunce C, Amissah-Arthur KN, Patwary S, McDonnell PJ, Hamada S

- Three randomised controlled trials. 219 eyes were randomly allocated to treatment with CXL or no treatment. In all three studies the surgery was done in the same way. None of the studies included children.
- ‘.....On average, treated eyes (CXL) had less steep corneas and better uncorrected vision...’
- ‘Poorly reported studies with methodological weaknesses’
- ‘..Evidence for the use of CXL in Keratoconus is limited due to lack of properly conducted RCTs..’
- Main uncertainty: safety and efficacy in children and young people with progressive keratoconus
- Evidence synthesis informs the trial design

National Institute Health Research, Efficacy Mechanism and Evaluation (EME) programme have funded the Keralink study

Keralink: Efficacy and safety of CXL in children and young people

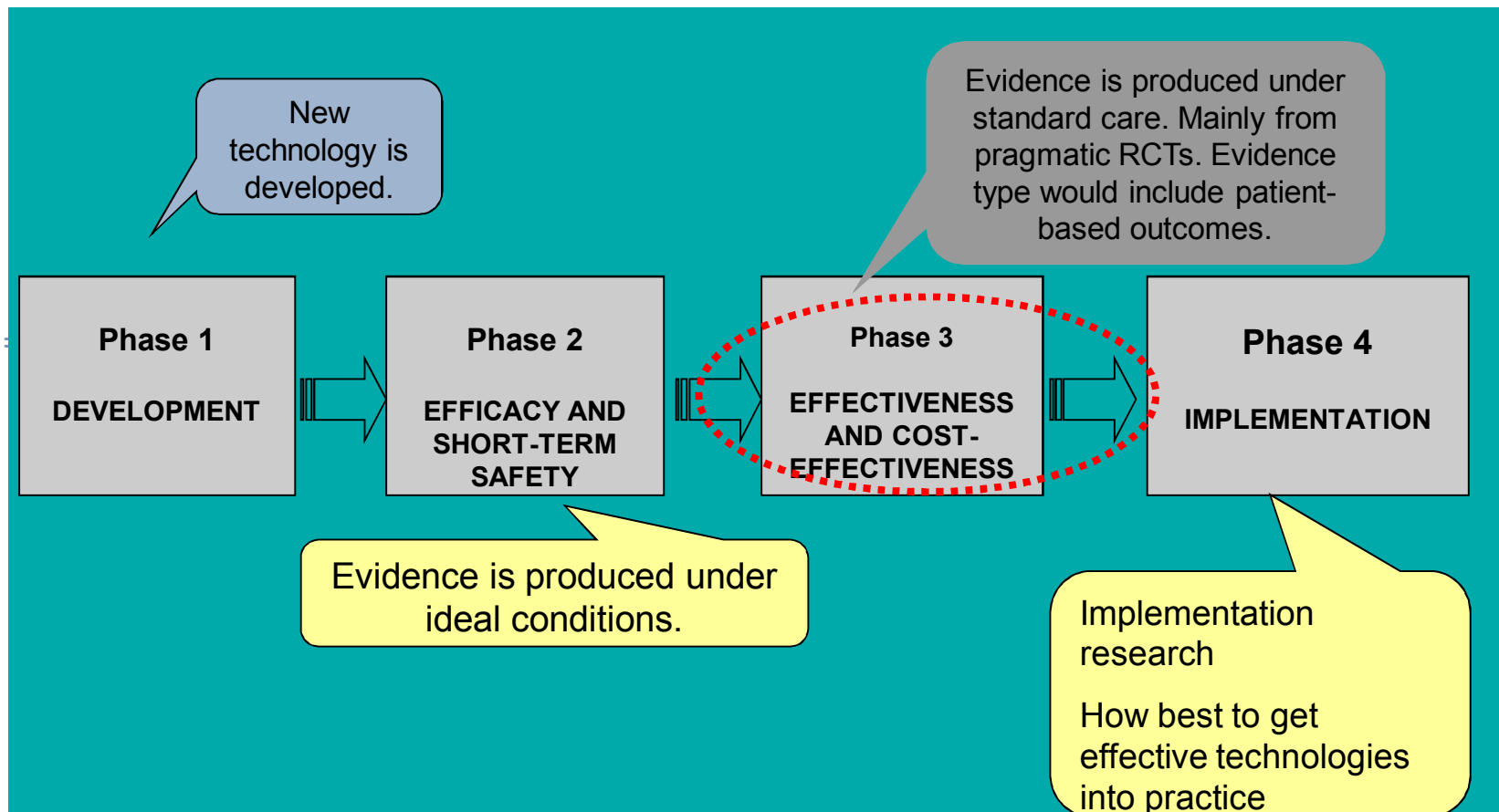
Design: Multicentre single masked RCT involving 60 participants- Intervention arm to have CXL in one or both eyes followed by standard care, control arm to have standard care. Follow-up for 18 months.

Target population: Progressive keratoconus patients aged <17 years.

Inclusion Criteria: Aged 10-16 years with keratoconus progression (at least 1.5 dioptres) confirmed in one or both eyes by Pentacam corneal topography.

Primary outcome : Kmax in the study eye at 18 months post randomisation

Timetable: October 2015- September 2019



Factors influencing choice: 2

Does 'it' work in clinical care? Comparative effectiveness and cost effectiveness.

Health Technology Assessment (HTA)

HTA considers the effectiveness, appropriateness and cost of technologies

Does the Technology work?

For whom?

At what cost?

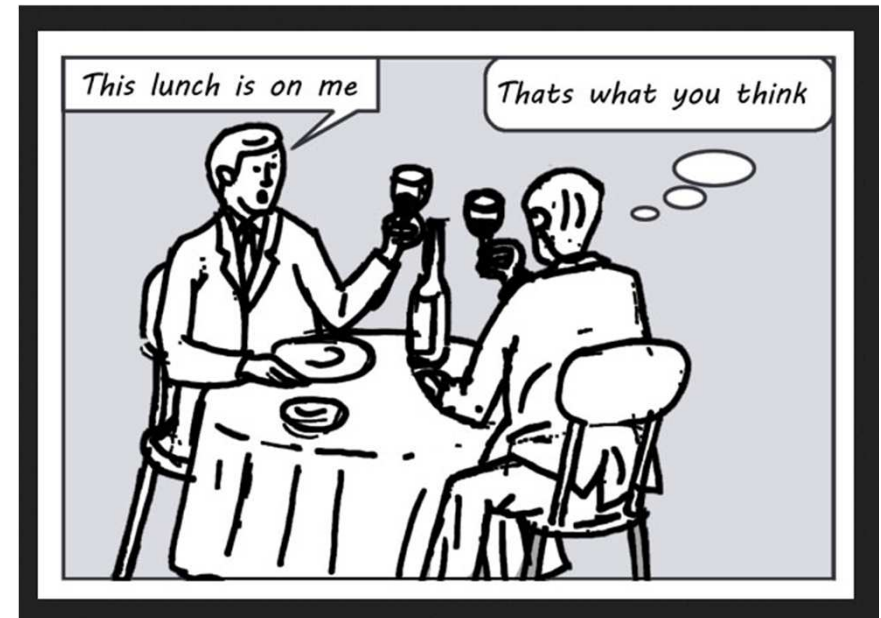
How does it compare with alternatives?

Investment and disinvestment

Health Economic definition of cost

Every time we choose to use resources to meet one need, we give up the opportunity to use those resources to meet another need

OPPORTUNITY COST is the value of the opportunity forgone as a result of engaging resources in an activity, i.e. value of the next best alternative you give up by adopting the 'new technology'



Example 2: Laser Assisted Cataract Surgery


- Cataract is a common cause of visual impairment
- Current standard surgery is ultrasound phacoemulsification cataract surgery
- Innovation suggests that use of the Femtosecond laser to make the incision might improve visual and patient reported outcome
- But the use of such laser systems are expensive and may not be affordable by health services
- Should a health service adopt the new technology?

Laser-assisted cataract surgery versus standard ultrasound phacoemulsification cataract surgery (Review)

Day AC, Gore DM, Bunce C, Evans JR

- 16 RCTS involving 1245 adults.
- 11 studies reported financial links with manufacturers of the laser platforms
- Studies generally poorly reported with methodological flaws
- Small differences favouring laser assisted surgery (-0.03 logMar visual acuity (95% CI -0.05-0.00))
- Evidence graded as low certainty
- No studies reported patient reported or health economic outcomes

Femtolaser assisted Cataract surgery: The FACT study

Randomised, single-masked non-inferiority trial of femtosecond laser-assisted versus manual phacoemulsification cataract surgery for adults with visually significant cataract: the FACT trial protocol 

PI

Alexander C Day^{1, 2}, Jennifer M Burr³, Catey Bunce^{1, 2}, Caroline J Doré⁴, Yvonne Sylvestre⁴, Richard P L Wormald^{1, 2}, Jeff Round⁴, Victoria McCudden⁴, Gary Rubin^{1, 2}, Mark R Wilkins² on behalf of the FACT Group

Author affiliations

Funded by NIHR HTA programme

<https://www.journalslibrary.nihr.ac.uk/programmes/hta/130446/> - /



DESIGN: Multi-centre randomised controlled trial of laser versus manual phacoemulsification cataract surgery. Sample size: 900 participants

SETTING: Secondary care. NHS cataract day surgery units in England
TARGET POPULATION: Adults with age related cataract.

HEALTH TECHNOLOGY: Intervention: Laser assisted cataract surgery Control: Phacoemulsification cataract surgery (standard care)

INCLUSION CRITERIA: Symptomatic age related cataract, one or both eyes.

PRIMARY OUTCOME: Unaided visual acuity at 3 months. **SECONDARY OUTCOMES:** Include health economic and patient reported outcomes

MEASUREMENT OF OUTCOMES AND COSTS: 3 & 12 months after surgery

TIMETABLE: Reporting end of 2018

Other examples

Effectiveness of Clear Lens Extraction in Angle Closure Glaucoma (PACG)

Funded by MRC and subsequently NIHR-EME

Treatment of Advanced Glaucoma

Funded by NIHR-HTA programme

Underpinned by Cochrane reviews



Lens extraction for chronic angle-closure glaucoma (Review)

Friedman D, Vedula SS

Medical versus surgical interventions for open angle glaucoma (Review)

Burr J, Azuara-Blanco A, Avenell A, Tuulonen A

Clear Lens Extraction in PACG



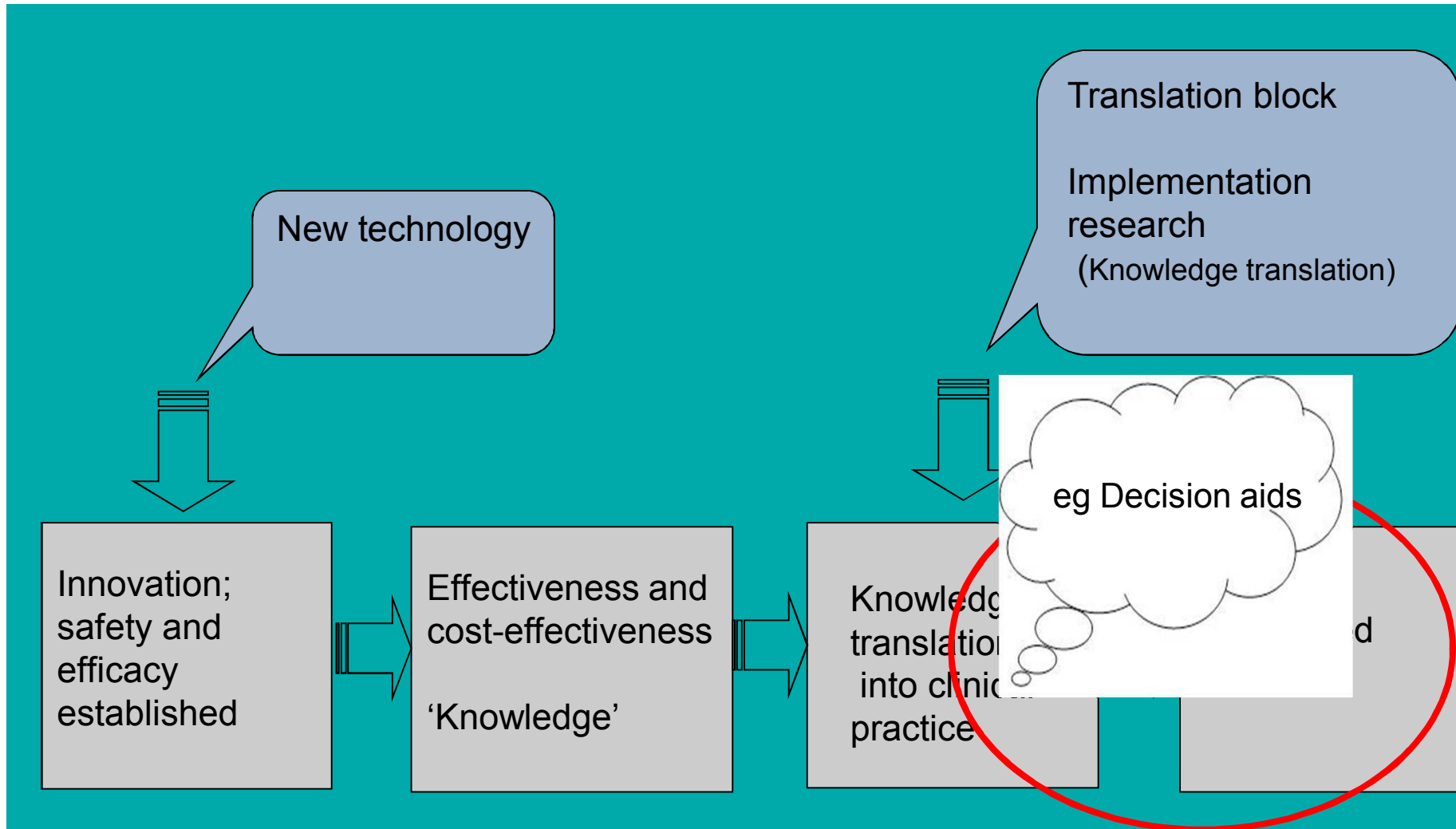
Findings Of 419 participants enrolled, 155 had primary angle closure and 263 primary angle-closure glaucoma. 208 were assigned to clear-lens extraction and 211 to standard care, of whom 351 (84%) had complete data on health status and 366 (87%) on intraocular pressure. The mean health status score (0·87 [SD 0·12]), assessed with the European Quality of Life-5 Dimensions questionnaire, was 0·052 higher (95% CI 0·015–0·088, $p=0\cdot005$) and mean intraocular pressure (16·6 [SD 3·5] mm Hg) 1·18 mm Hg lower (95% CI $-1\cdot99$ to $-0\cdot38$, $p=0\cdot004$) after clear-lens extraction than after standard care. The incremental cost-effectiveness ratio was £14284 for initial lens extraction versus standard care. Irreversible loss of vision occurred in one participant who underwent clear-lens extraction and three who received standard care. No patients had serious adverse events.

Interpretation Clear-lens extraction showed greater efficacy and was more cost-effective than laser peripheral iridotomy, and should be considered as an option for first-line treatment.

Findings inform

- Treatment Policy
- Individuals: Shared decisions based on quality data on the risk and benefits of the “new treatment” compared with usual care

Challenges: Adoption



Interventions to increase attendance for diabetic retinopathy screening (Review)

Lawrenson JG, Graham-Rowe E, Lorencatto F, Burr J, Bunce C, Francis JJ, Aluko P, Rice S, Vale L, Peto T, Presseau J, Ivers N, Grimshaw JM

Research Question: what evidence is there to support the effectiveness of interventions aiming to increase the uptake of diabetic retinopathy screening?

Study design: initially limited to Randomised Controlled Trials (RCTs) and Cluster Randomised Trials

Population: People with Type 1 or Type 2 diabetes, healthcare professionals responsible for diabetes care

Intervention: QI strategy targeted at the individual, healthcare professional or the healthcare system

Control/comparator: those eligible for screening who do not receive the trial intervention or receive standard care

Outcome: uptake of DR screening

Interventions to increase attendance for diabetic retinopathy screening (Review)

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- **66 trials included involving around 350,000 participants**
- Quality Improvement interventions (Behaviour Change Techniques) to support uptake of DRS services are likely to 'work'
- Patient, Health Care Professional or system
- Eg enhanced patient information sheets; introducing processes to improve convenience for patients e.g. online management/ booking systems or monitoring tools (e.g. diabetes passports) could be worthwhile.
- Identified the components of a behavioural intervention to be tested in a future RCT

Conclusion

- Increasing demand for health care.
- Choices are required
- Decisions should be based on trusted evidence
- Only when we identify ‘knowns and unknowns’ can we make the best decisions for our patients in terms of where to invest and disinvest in ‘technologies’ that are not optimal and identify priorities for future research.

Questions?

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