



MRC
Clinical
Trials Unit



Repurposing in Practice Opportunities and Challenges

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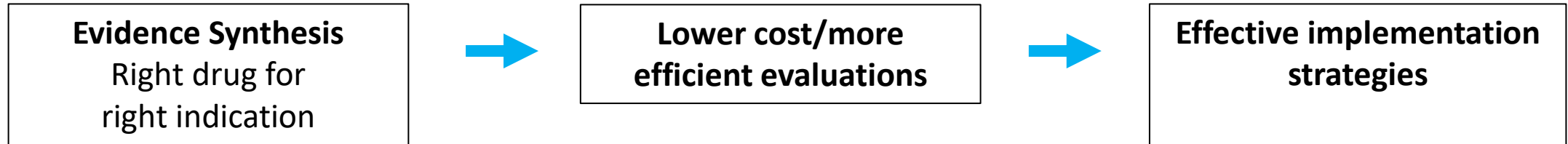
November 2024

Smarter Studies
Global Impact
Better Health

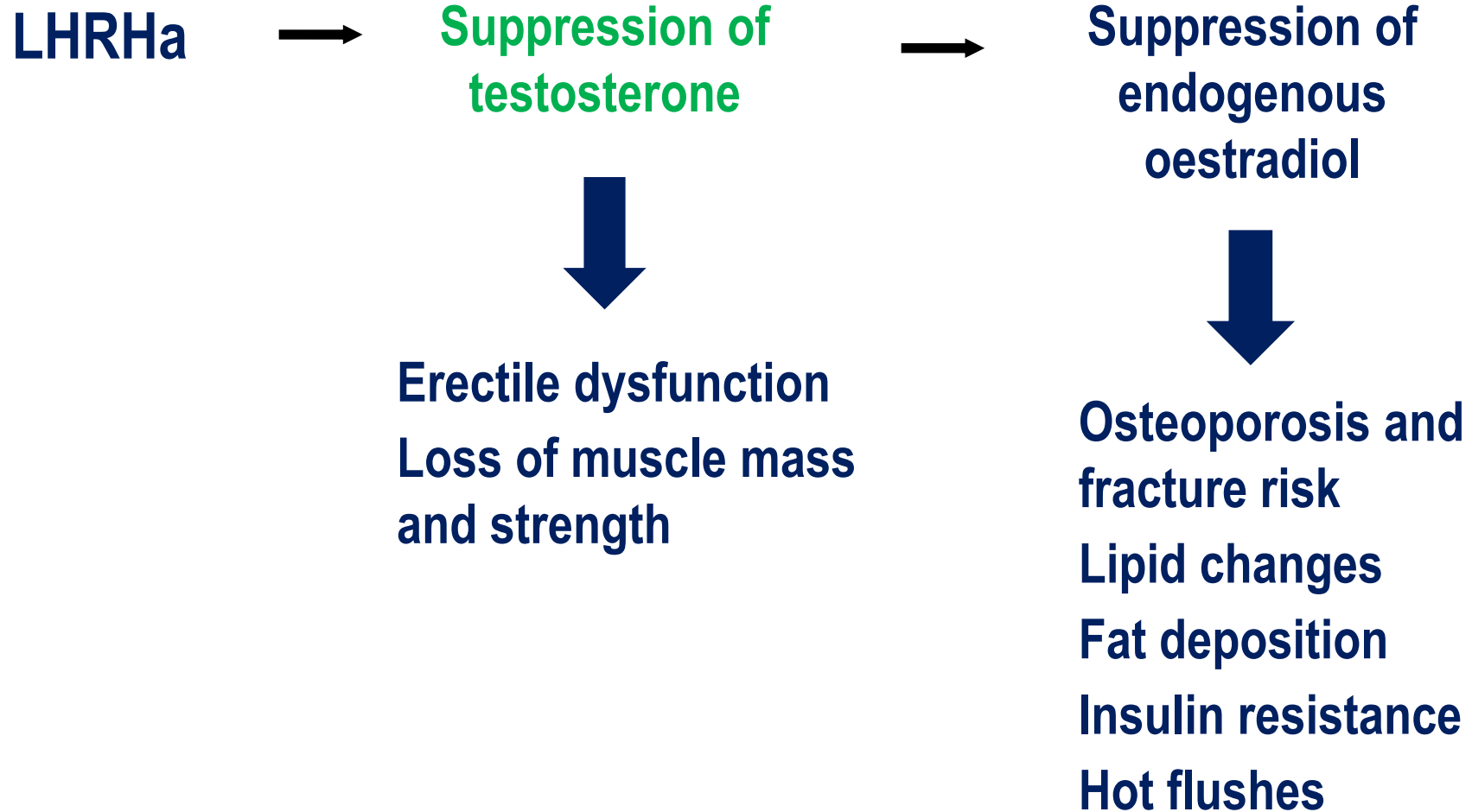
Introduction

- Oncology has strong links to discovery science and new drug development
- However, cancer incidence is increasing most rapidly in low-and-middle income countries (LMICs) where many new drugs are not affordable
- High income countries are also challenged by the costs of healthcare
- Cancer outcomes are improving - focus on reducing toxicity and survivorship issues
- Repurposing offers **opportunities** to address some of these issues

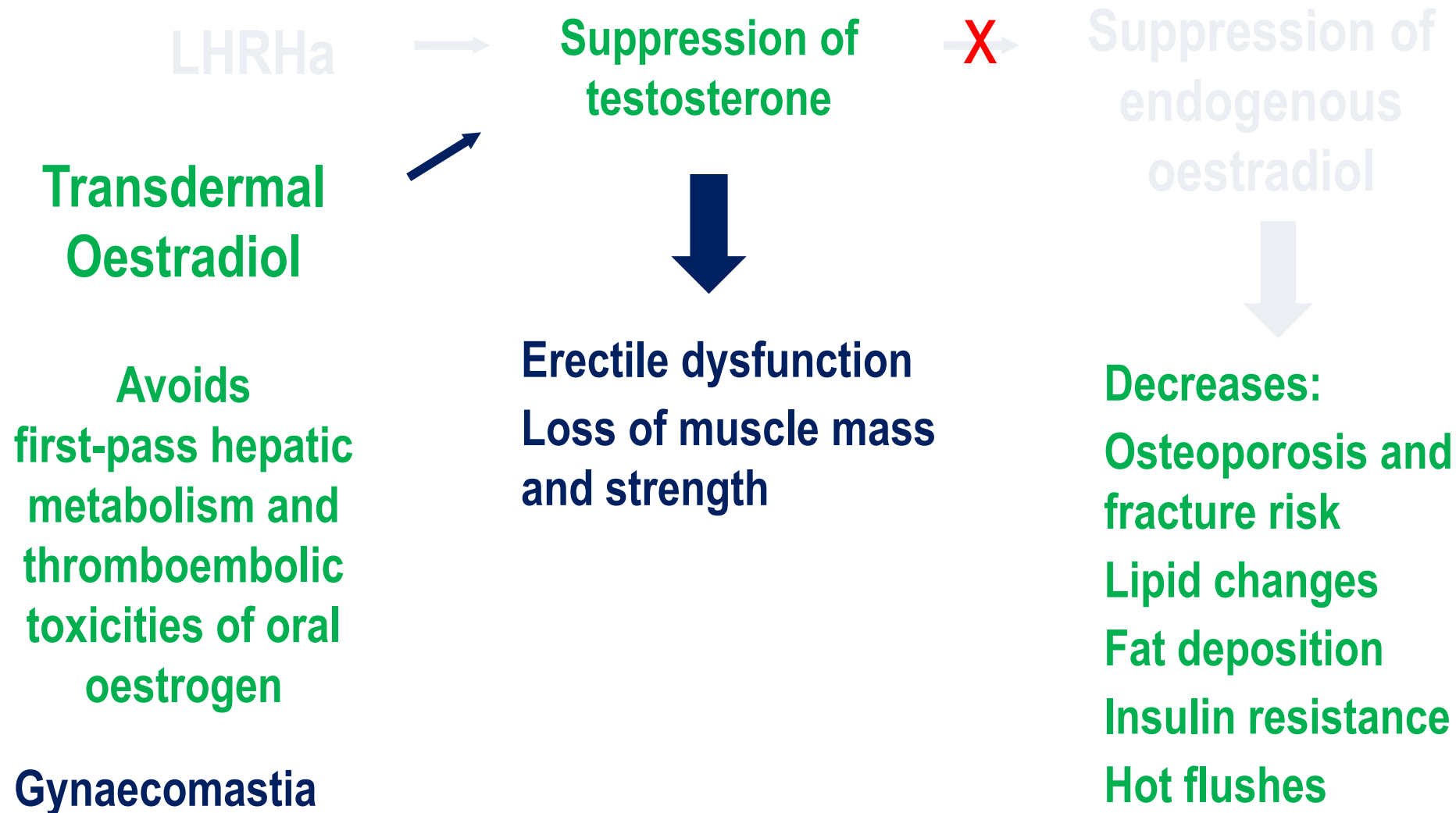
Repurposing Challenges



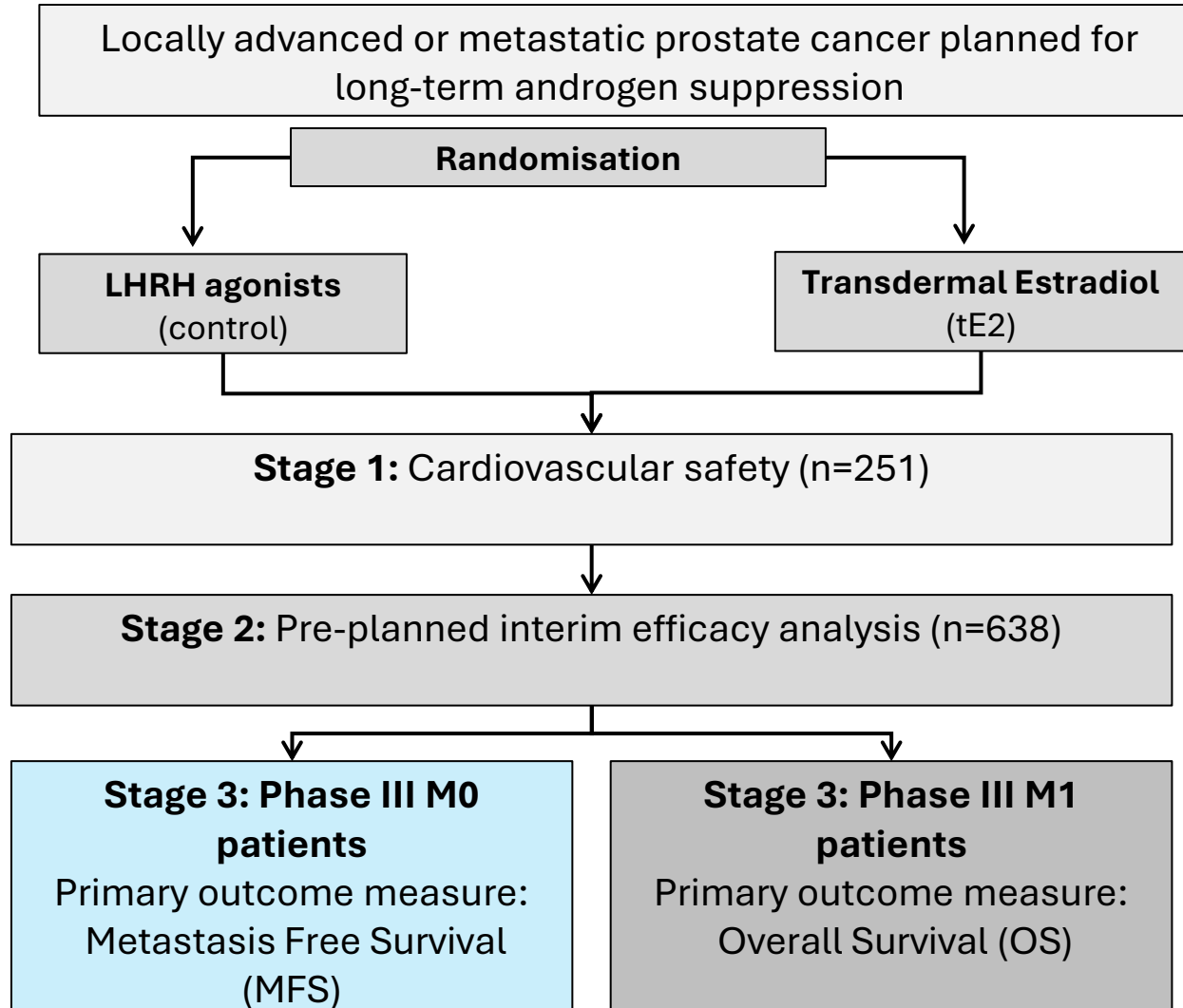
Androgen Suppression – Prostate Cancer



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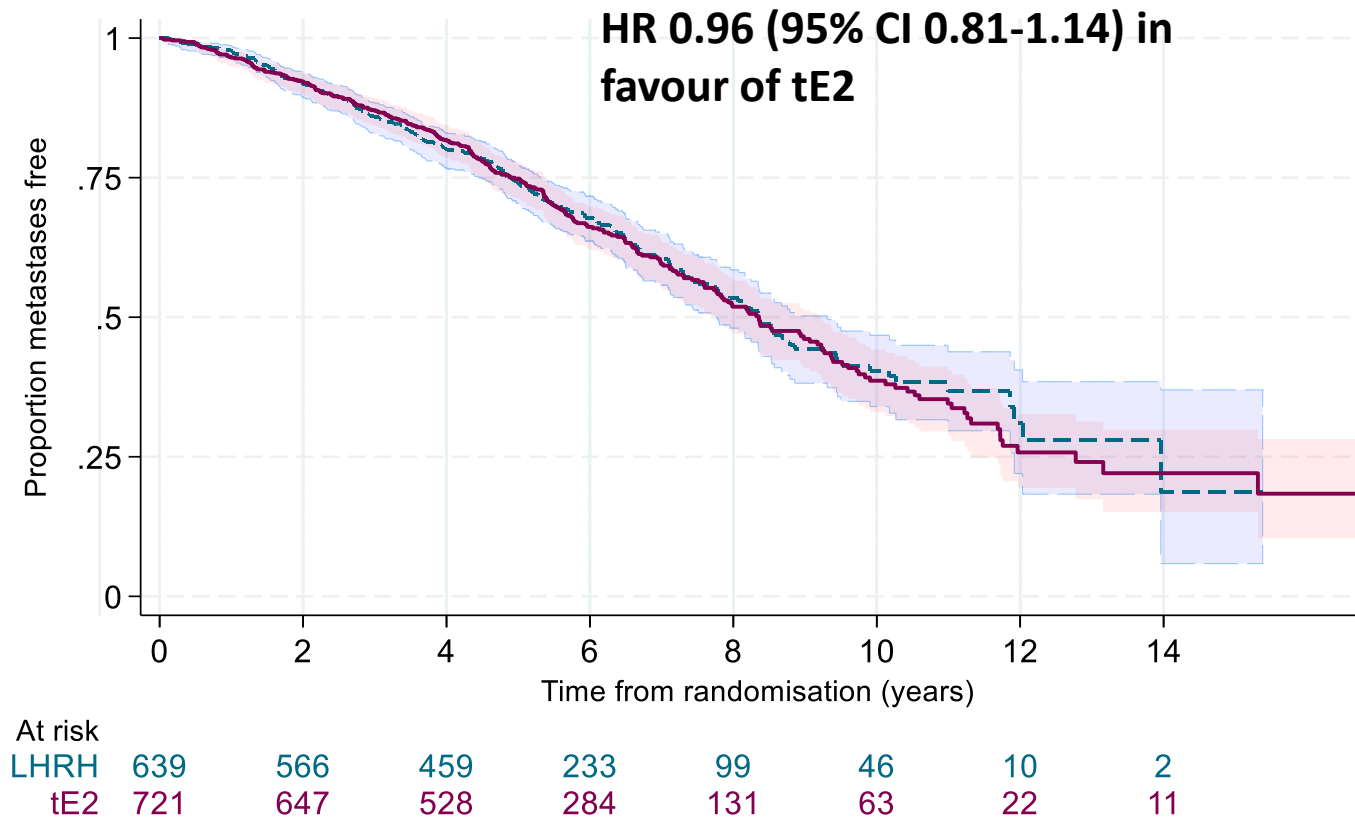


tE2 Development Programme (Phase 2/3 adaptive trial)



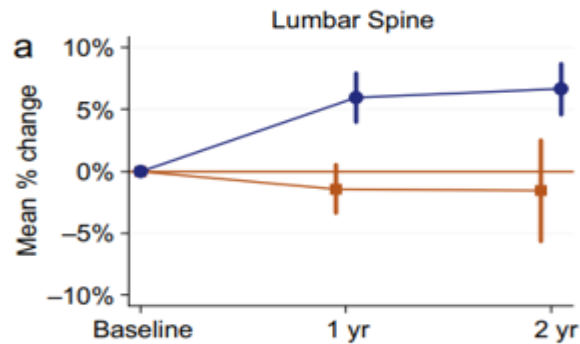
- tE2 patches manufactured and licenced for the relief of menopausal symptoms in women
- Staged approach to evaluation and funding (CRUK)
- Recruitment started in 2007

M0 Primary Outcome - Metastasis Free Survival (MFS)



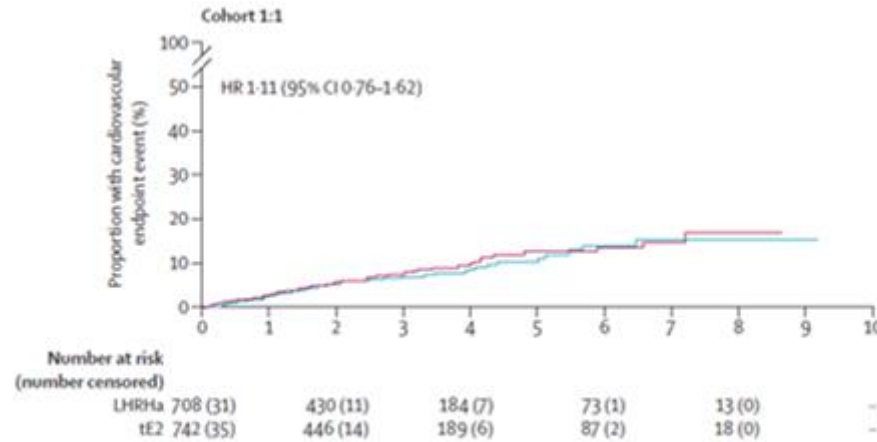
- 1360 participants
- **LHRHa 3-year MFS 87%** giving a target non-inferiority margin of 1.31
- **tE2 3-year MFS 86%**
- Non-inferiority demonstrated excluding a 2% difference in MFS

Transdermal Oestradiol (tE2) v LHRHa Programme Results M0 and M1



Improved Bone Mineral Density¹

● tE2 ■ LHRHa



No excess cardiovascular toxicity²

- Equivalent castration rates
- Improved metabolic profiles
- Improved overall Quality of Life scores. Mean difference in 6-month score +4.2 (1.2, 7.1) in favour of tE2 (p=0.006)³

Remaining Challenges

- Not licensed for this indication
- Direct competitor product for a profitable class of drug
- Lack of wider pharma support for promotion
- NHS repurposing programme – multi-agency initiative – license extension

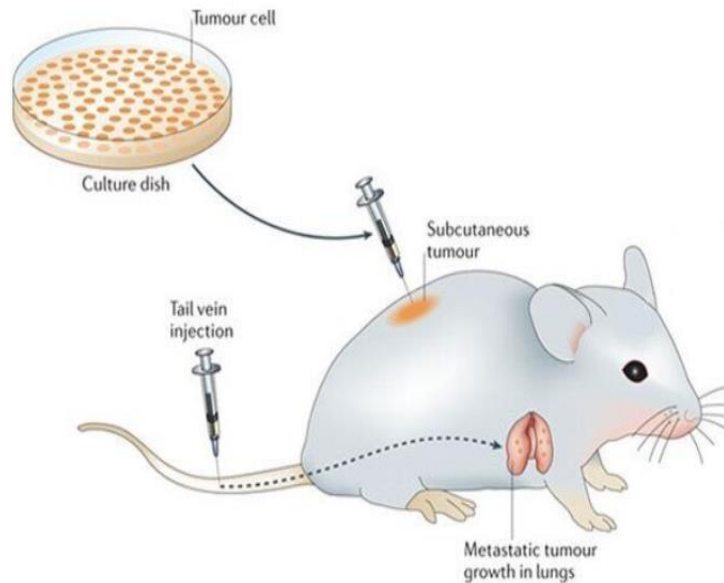
Aspirin as an Anti-Cancer Drug

- Aspirin already repurposed from anti-inflammatory/analgesic to a drug used for cardiovascular protection and treatment
- Additional uses particularly in oncology

Early data – inhibition of metastases

Fibrosarcoma cells injected into tail vein of mice (group 1-4) and a hindleg inoculation (group 5-6)

Aspirin (ASA) 2.5 mg per 4 ml drinking water



Group	Therapy	Tumour	Lung metastases mean $\pm$ se	p
1	Control	MCA2	245 $\pm$ 13	<0.01
2	ASA, 6 days	MCA2	143 $\pm$ 12	
3	Control	T241	24 $\pm$ 3	<0.2
4	ASA, 13 days	T241	17 $\pm$ 3	
5	Control	T241	24 $\pm$ 5	<0.01
6	ASA, 13 days	T241	9 $\pm$ 2	

Anti-metastatic effect of aspirin Gasic *et al. Lancet* 1972

Conventional Framework for Drug Development Trials – Oncology

Promising pre-clinical data - aspirin ✓

- Phase I** **First human use/MTD** - aspirin ✓
- Phase II** **Initial activity – dose and efficacy**
Advanced disease, small, non-randomised, - aspirin X
response rate (tumour shrinkage)
- Phase III** **Comparison with standard therapy**
Start with metastatic disease - aspirin X

Issues not unique to aspirin – statins, metformin, Cox-2 inhibitors (and more)
– need to rethink approach to testing these type of agents

Aspirin - Cancer Primary Prevention Epidemiological Studies

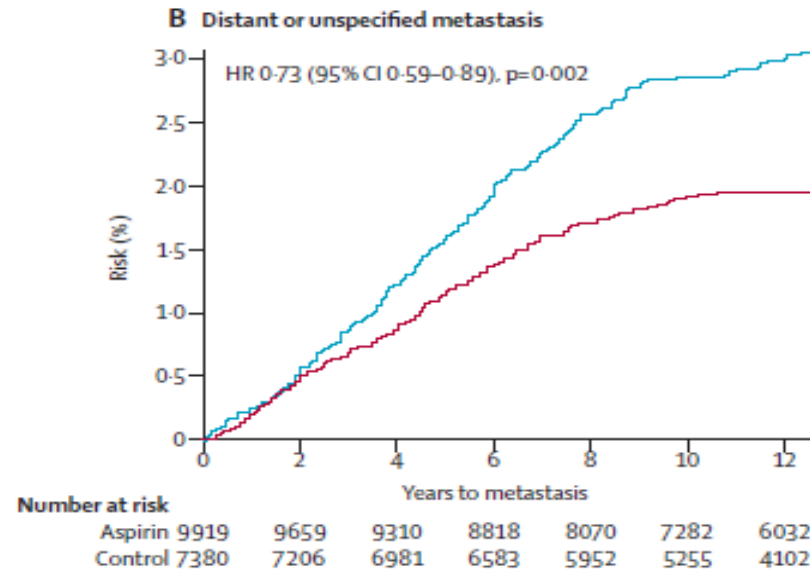
Table 1. Pooled relative risks (RR) and corresponding 95% confidence intervals (CI) for regular aspirin use versus non-use by cancer site and study design

Cancer site, study design	No. of studies	No. of cases	Pooled RR (95% CI)	P value ^a	I ² (%)	P value ^b
Colorectum						
Cohort	15	33 126	0.77 (0.72–0.82)	<0.001	62	<0.001
Nested case-control	11	105 607	0.86 (0.78–0.94)	<0.001	88	
Case-control	19	17 286	0.62 (0.56–0.69)	<0.001	62	
Overall	45	156 019	0.73 (0.69–0.78)	<0.001	86	
Head and neck						
Cohort	1	316	0.78 (0.62–0.98)	—	—	0.106
Nested case-control	2	3940	1.03 (0.90–1.18)	0.196	40	
Case-control	7	6143	0.87 (0.58–1.31)	<0.001	87	
Overall	10	10 399	0.94 (0.76–1.16)	<0.001	83	
Esophagus (squamous-cell)						
Cohort	4	2873	0.65 (0.54–0.80)	0.233	30	<0.001
Nested case-control	2	2070	0.90 (0.78–1.03)	0.641	0	
Case-control	7	1268	0.54 (0.43–0.67)	0.970	0	
Overall	13	6211	0.67 (0.57–0.79)	0.006	57	
Esophagus/gastric cardia (adenocarcinoma)						
Cohort	2	481	0.88 (0.68–1.15)	0.575	0	0.015
Case-control	8	2540	0.56 (0.44–0.73)	<0.001	78	
Overall	10	3021	0.61 (0.49–0.77)	<0.001	76	
Stomach						
Cohort	6	6748	0.58 (0.44–0.76)	<0.001	84	<0.001
Nested case-control	1	980	1.17 (0.98–1.40)	—	—	
Case-control	7	2191	0.63 (0.48–0.83)	<0.001	77	
Overall	14	9919	0.64 (0.51–0.82)	<0.001	91	
Hepato-biliary						

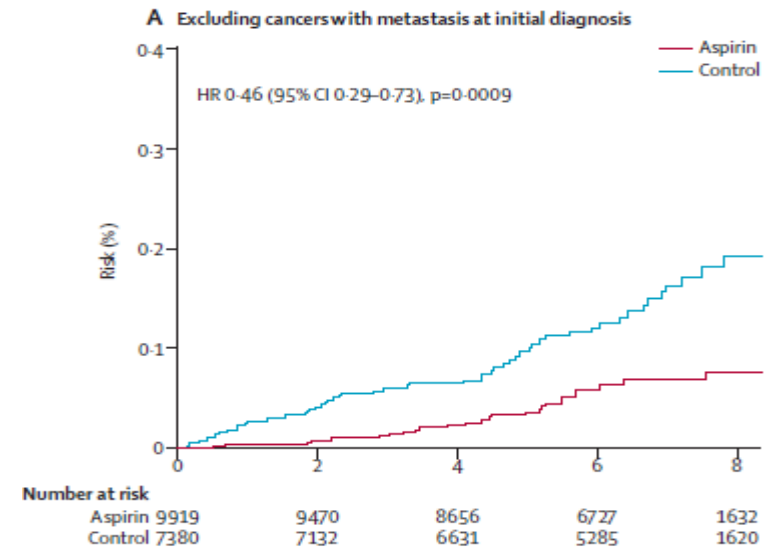
- Colorectal and other GI cancers reduction ~ 30%
- Other tumours benefit ~ 10% or uncertain

Cancer Outcomes from Randomised Vascular Trials

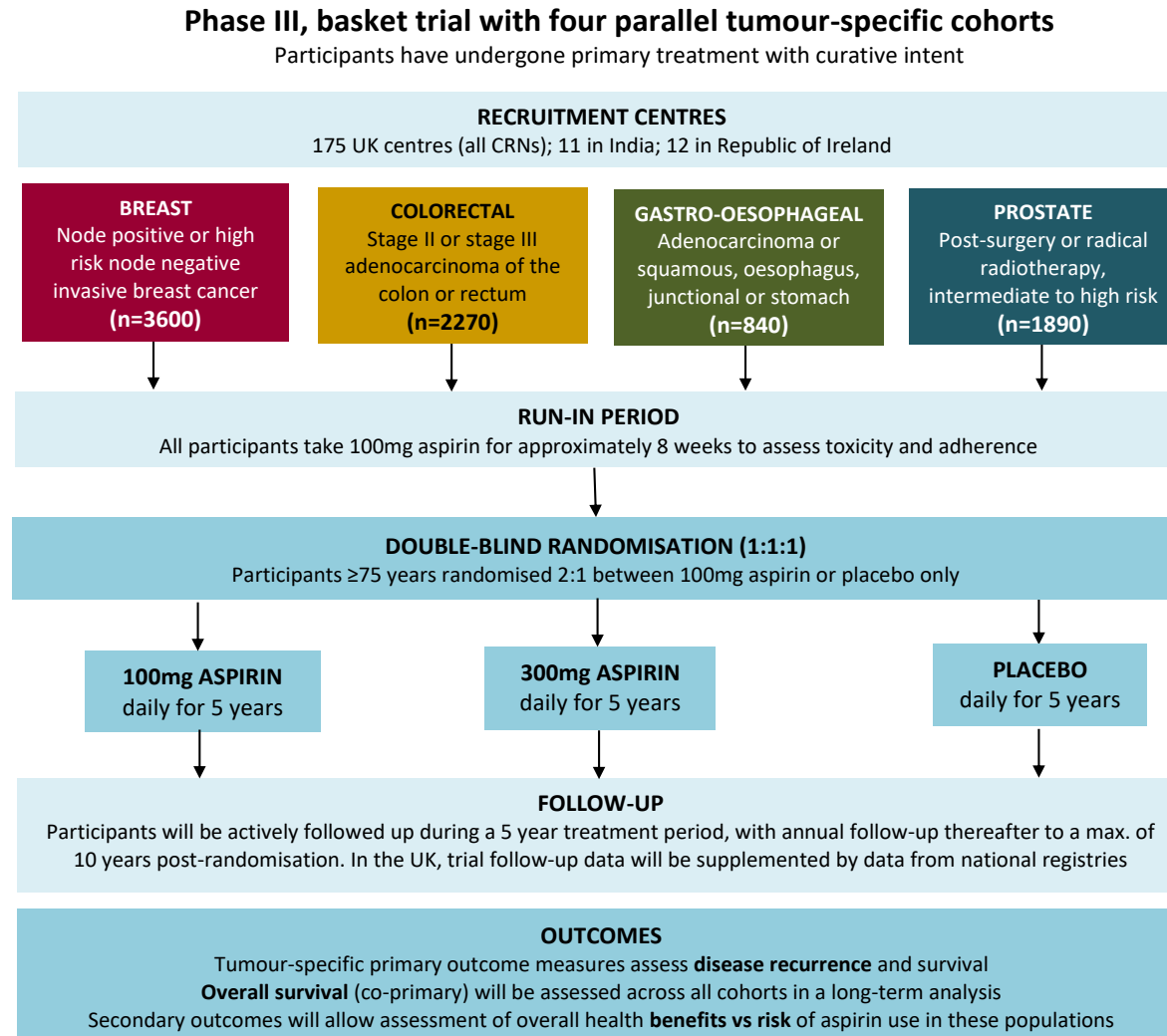
Cancer with metastasis at presentation



Cancer with no metastasis at presentation in which metastasis developed on follow-up



Add-Aspirin Trial – Phase III basket trial

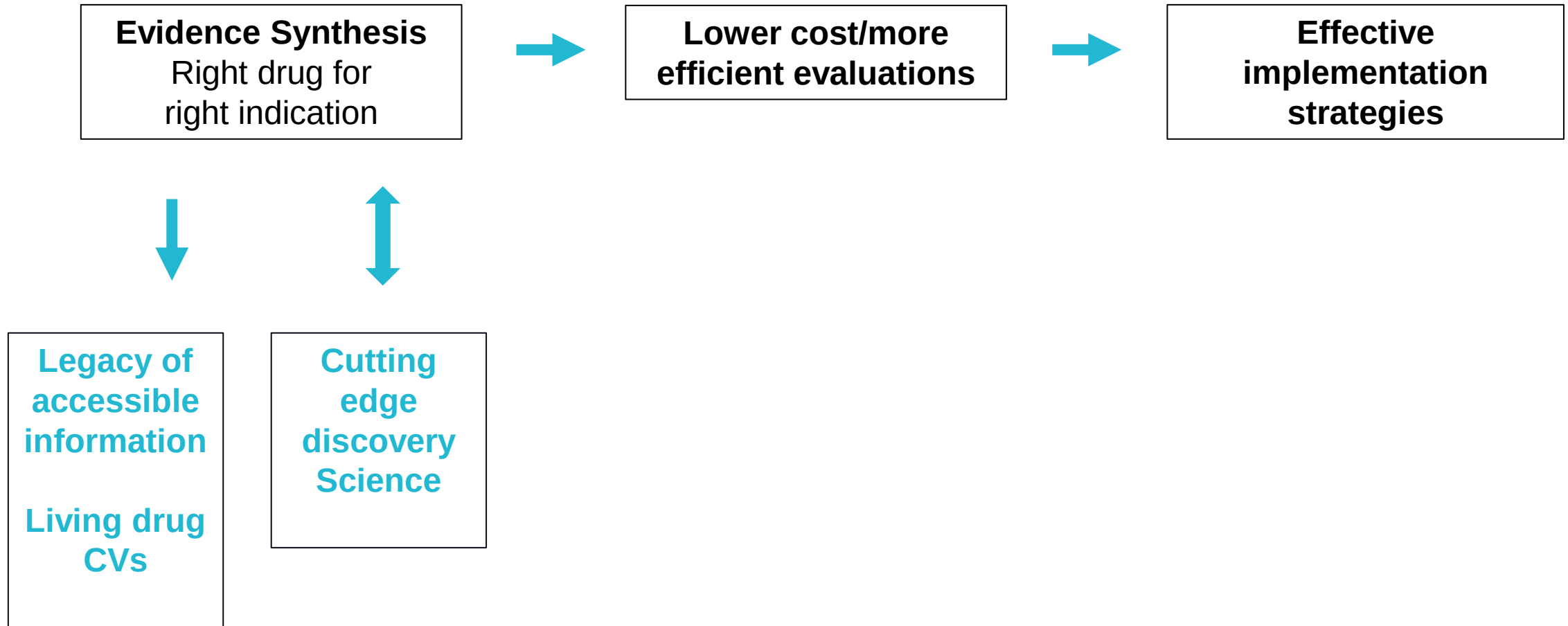


- Adjuvant setting
- 4 individually powered phase III trials with disease-free survival as the primary outcome measure
- Cross cohort co-primary outcome (overall survival 15 years post randomisation)
- > 10,000 participants, 3 countries, co-enrolment with > 70 different studies

Drug Supply

- Many “academic” oncology trials – pharma companies donate drug alongside packaging and distribution
- Add-Aspirin had donated unpackaged aspirin and matching placebo
- Stock initially came from China then Germany, packaged and labelled in Spain, then imported into UK to a holding centre
- Build an IT system linked to the randomisation server, blinded allocation, monitor stock at over 170 UK sites (centres will only hold limited stock) and co-ordinate distribution and delivery to ROI and India
- Increased complexity and regulation due to Brexit, shorter shelf life than agreed and tightening regulation all shipments of the distribution company had to be refrigerated

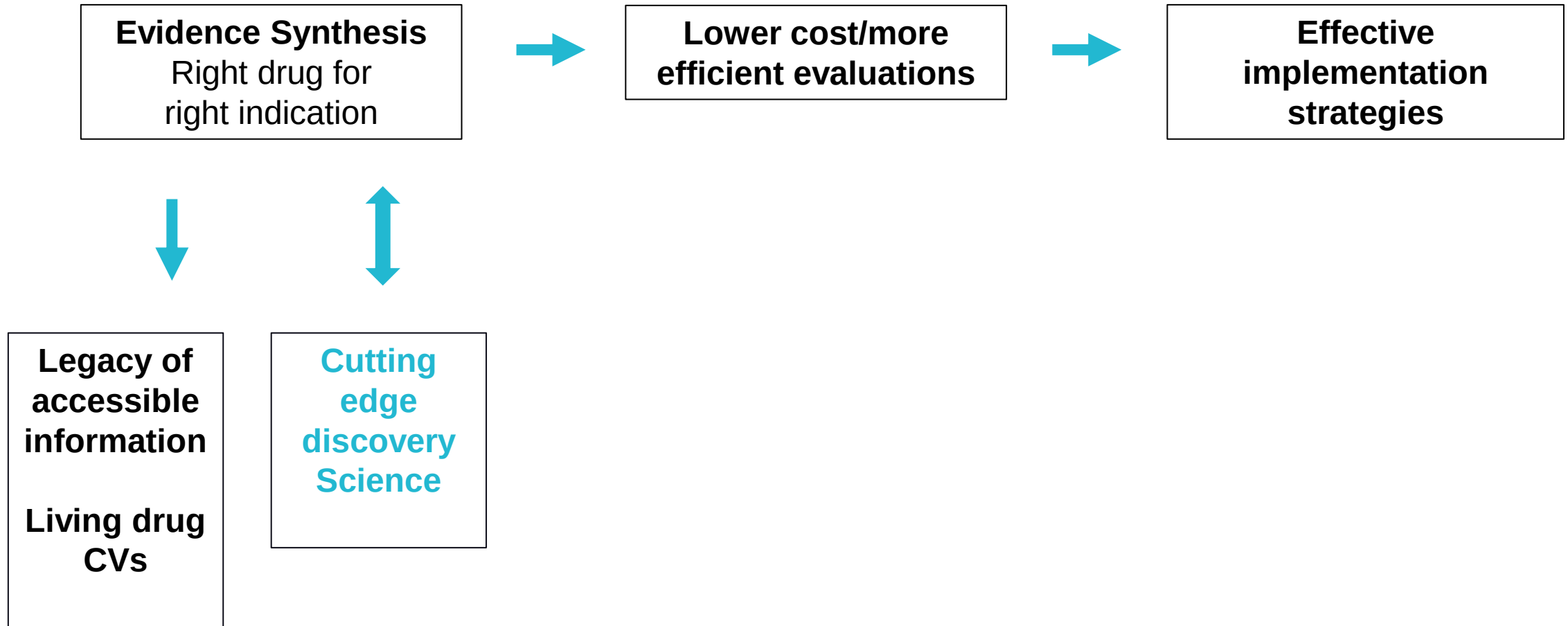
Repurposing Challenges and Potential Solutions



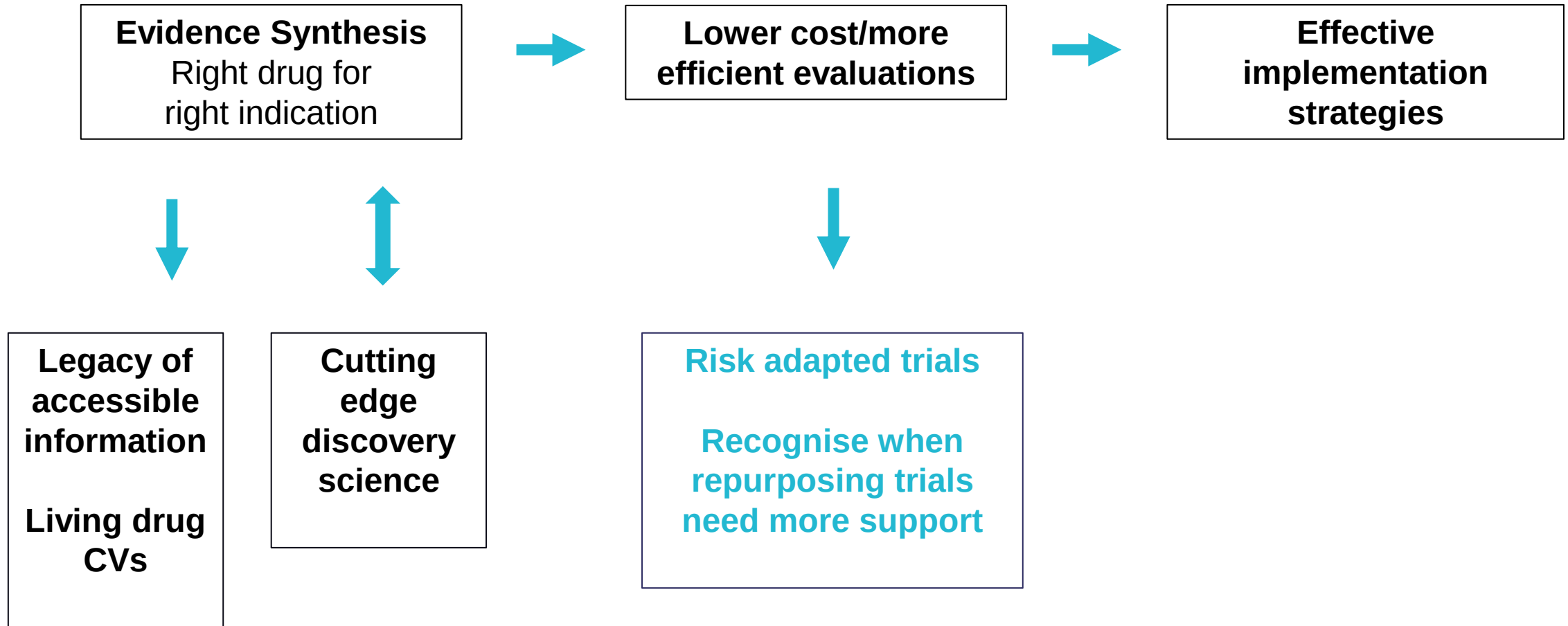
Aspirin and Cancer 2024 - pPtgs1-/- mice

- Specific conditional deletion of COX-1 in megakaryocytes/platelets and are therefore a model of low-dose aspirin effects (pPtgs1-/- mice)
- Crossed with Apcmin/+ mice - develop fewer adenomas, with reduced COX-2 expression and lower proliferative indices than controls
- Demonstrates the importance of platelet Cox-1 in intestinal tumorigenesis
- Explaining the anti-cancer effects of both aspirin and Cox-2 inhibitors

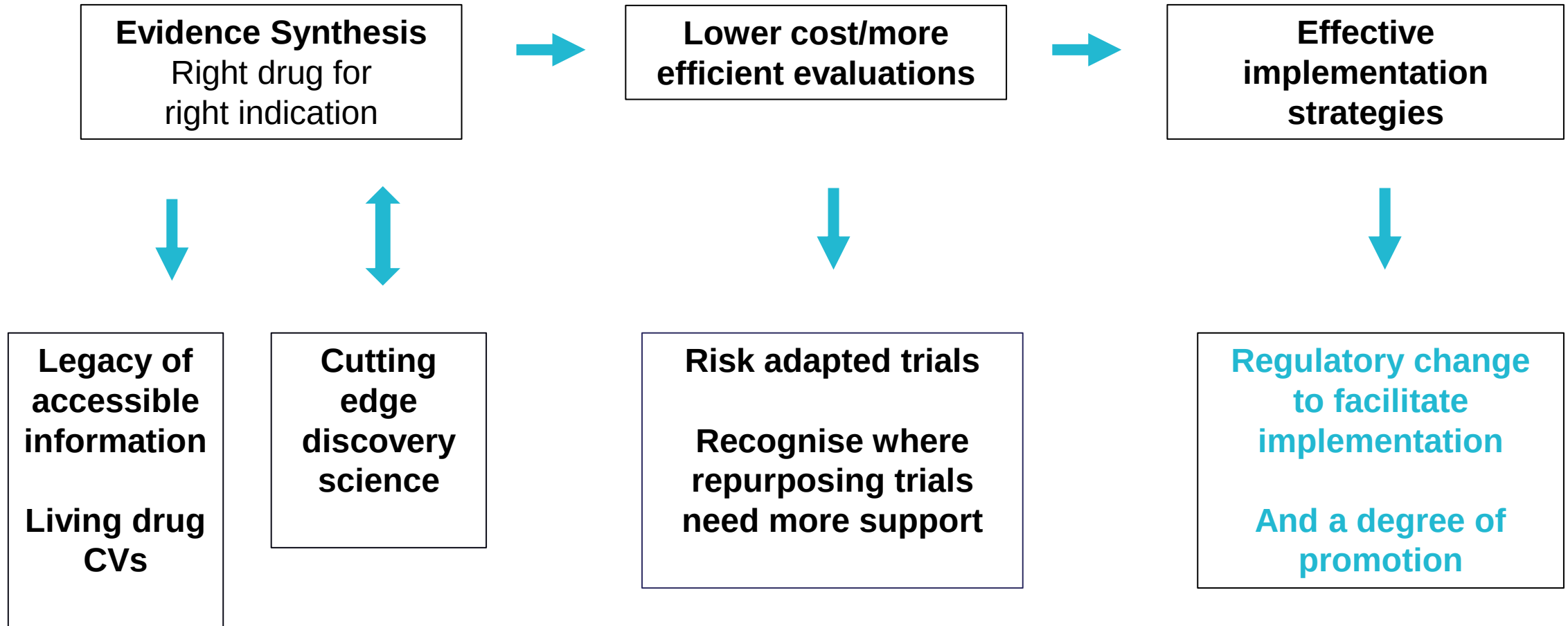
Repurposing Challenges and Potential Solutions



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Repurposing Challenges and Potential Solutions



Acknowledgements

- Patients and families taken part in these trials
- Trial teams, site staff and participant representatives
- Funders (CRUK and NIHR)

