The answer is 17 years, what is the question: Understanding time lags in research evaluation

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December 2012

Presentation is the synthesis of number of different projects and collaborations

RAND EUROPE

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Outline

- **Why time lags matter**
  - **Policy imperative**
  - **Delays reduce the rate of return, but not all delays are bad**
- **What do we know**
- **Some conceptual thoughts**
- **What we need to know**

The historical rise of translational research and the need to 'accelerate' research

- **Crossing the quality chasm: a new health system for the 21st century Institute of Medicine (2001) (US)**
  - *The lag between the discovery of more efficacious forms of treatment and their incorporation into routine patient care is unnecessarily long, in the range of about 15 to 20 years. Even then, adherence of clinical practice to the evidence is highly uneven*

- **Bioscience Innovation and Growth Team (BIGT) report, 2003 (UK)**
  - *Considering the long timelines involved, any acceleration in drug development and approval can make a material difference to patients suffering from life threatening disease, and provide a clear incentive to companies developing treatments*

- **EMRC White Paper: Present Status and Future Strategy for Medical Research in Europe, ESF, 2006**
  - *There is a time lag between research and tangible outcomes, and it is difficult to trace the role of individual research contributions*

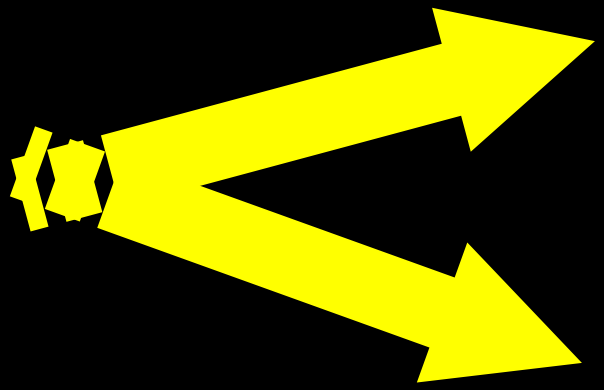
The orthodoxy (and intractability) of 17 years

- **EMRC White Paper: A Stronger Biomedical Research for a Better European Future, 2011**
  - *The study crucially also showed that the time lag between research funding and health return is approximately 17 years*
- **The social impact of research conducted in Russell Group universities (2012) [UK]**
  - *Significant time lags between research and its impact are the norm. It is the nature of research that it is iterative, that it does not stand still, and will continue to push boundaries during its lifespan. A study of research into cardiovascular disease found that it takes on average 17 years for basic research to be translated into treatment benefits*
- **Wellcome Trust response to REF consultation on impact (2009)**
  - *The Trust's view is that the challenges associated with time lags … will be very difficult to address, and are a key reason why we do not support the impact proposal. …. The time frame to commercial uptake of medical products … is typically very long … [on] average …17 years*

Estimating the economic returns from research

To calculate the return on investment, we made four key estimates

How much was spent on research?

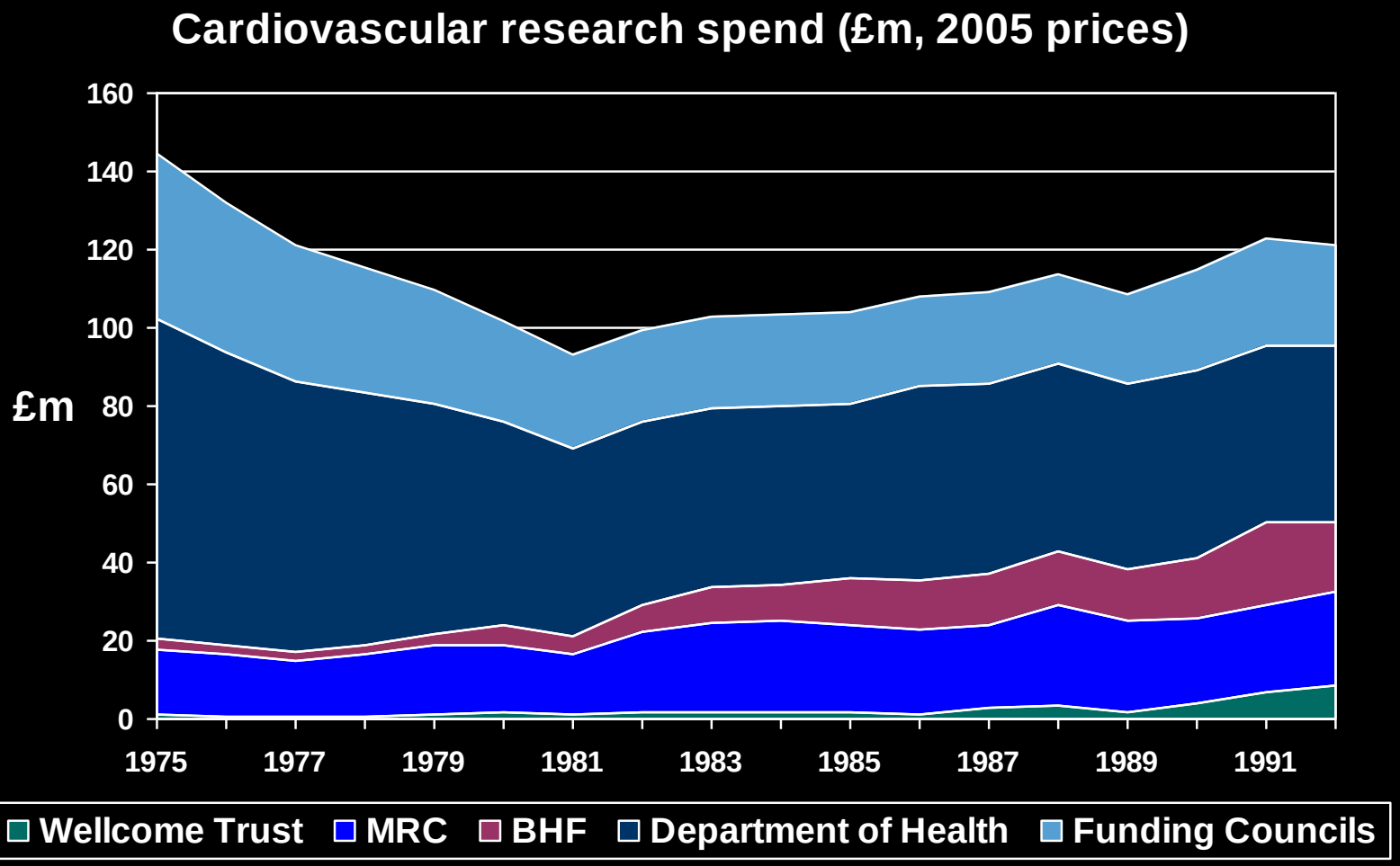


How much health gain?

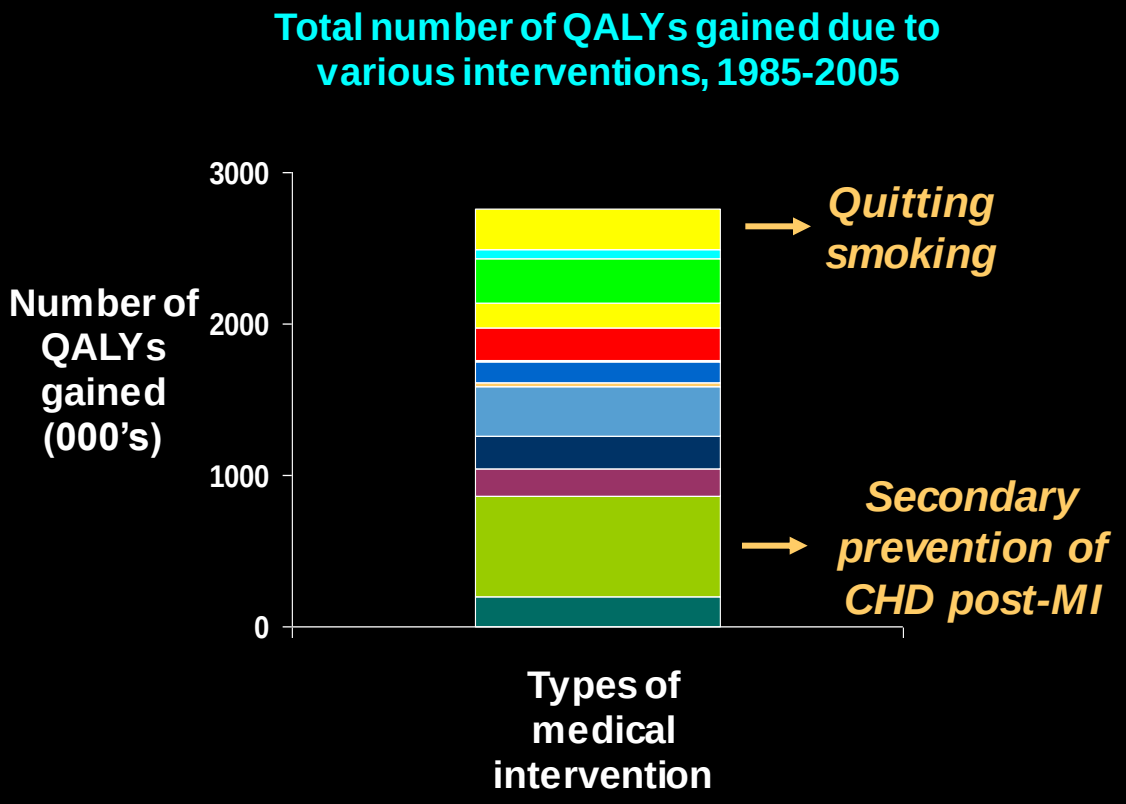
How much spillover?

How long does it take?

From 1975-1992, £2 billion in public and charitable funding went to UK cardiovascular research



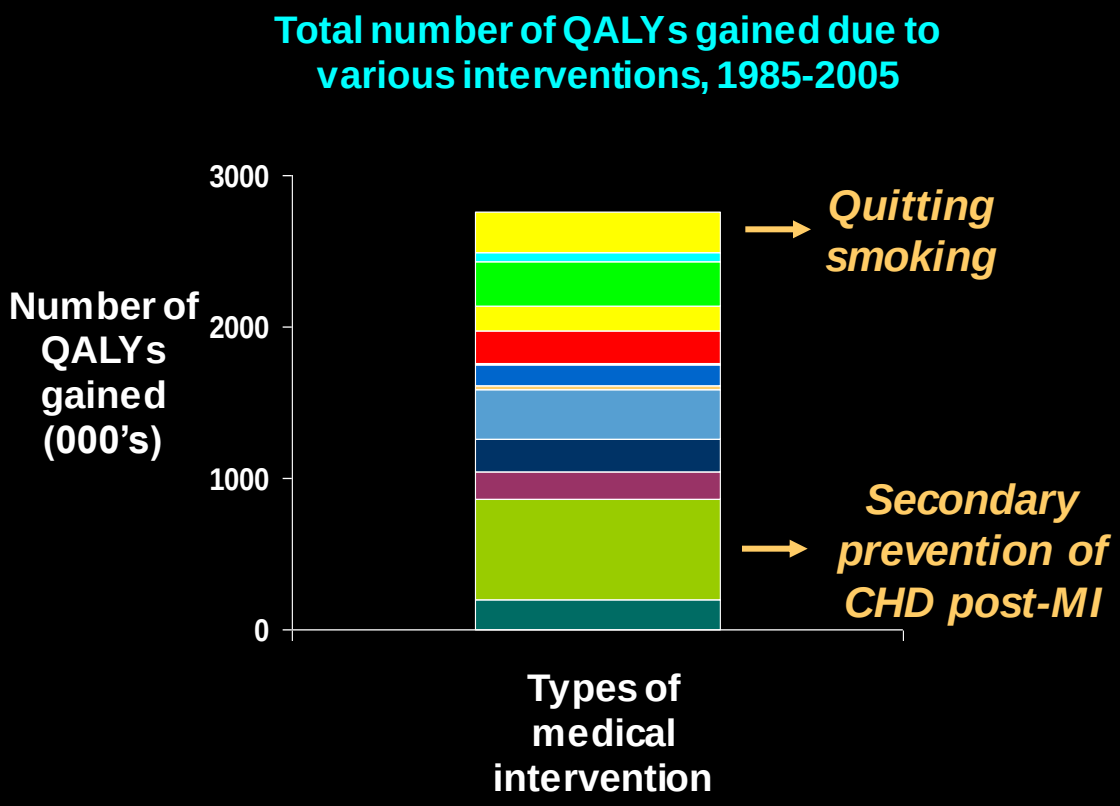
From 1985-2005, net cardiovascular health gains totaled about £53 Billion



We examined *research-based* interventions that have contributed to health gains

Quality Adjusted Life Year (QALY)
=
An additional year of quality life

From 1985-2005, net cardiovascular health gains totaled about £53 Billion



- A total of 2.8m QALYs were gained during this 20-year period
- We assigned each QALY a value of £25,000
- We multiplied the two to get £69 billion worth of health gains
- From that total, we subtracted £16 billion in costs to provide the care

This led us to a net total of £53 billion in health gains

The time lag between spending on research and "health gain" is about 17 Years

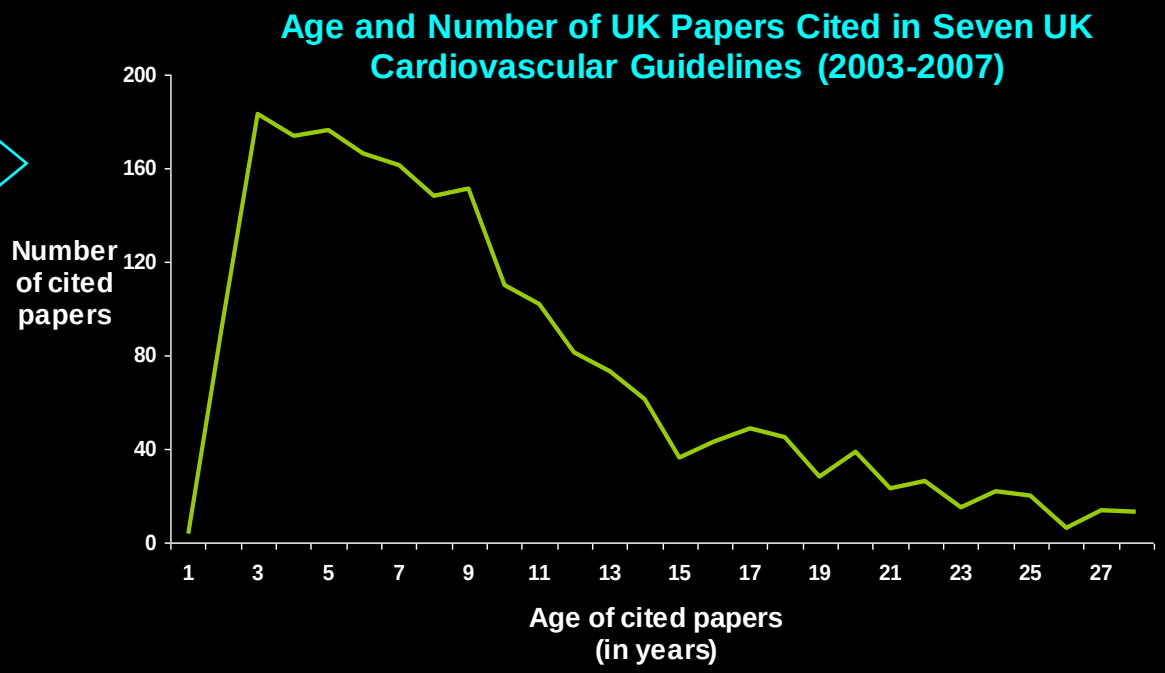
Mean age of cited papers is 12.5 years

+

Period between spending and publication

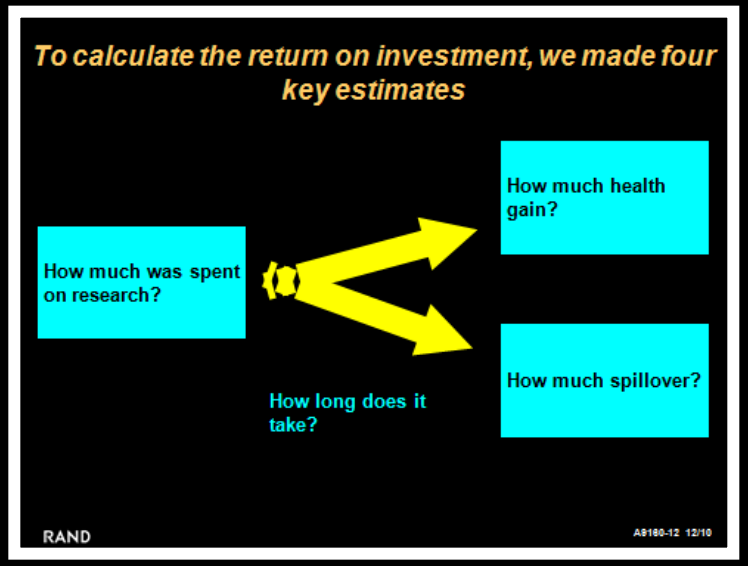
+

Period between recommendation and use



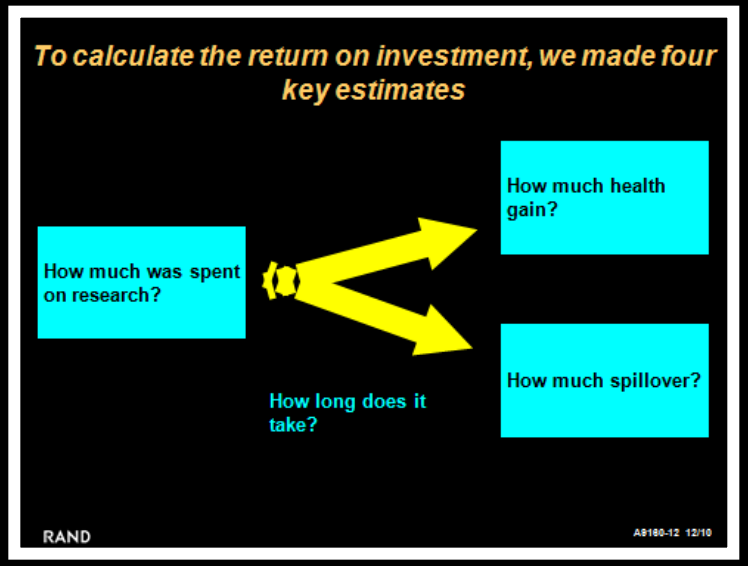
Time Lag = ~17 years

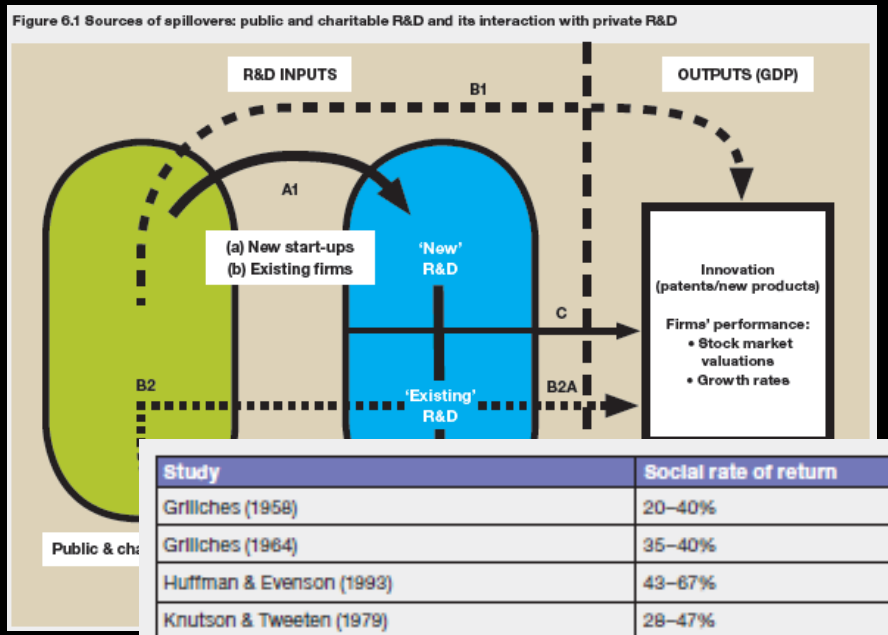
Combing the research spend, monetised health gain and time lag led to an internal rate of return of 9%



9%

And this was added with the impact of spillover effects



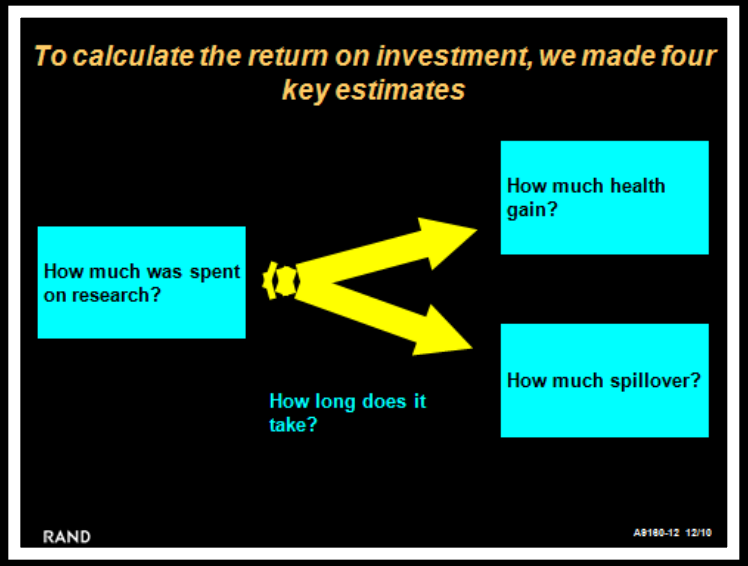


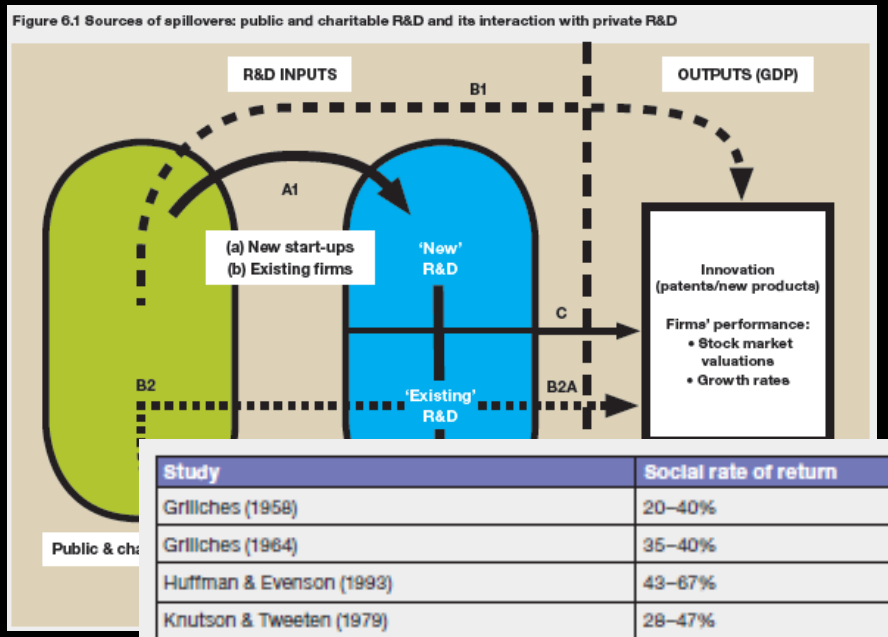
Study	Social rate of return
Griliches (1958)	20–40%
Griliches (1964)	35–40%
Huffman & Evenson (1993)	43–67%
Knutson & Tweeten (1979)	28–47%
Peterson (1967)	21–25%
Schmitz & Seckler (1970)	37–46%

Sources: Griliches (1991), Salter et al. (2000)

9%

Which was 30%, leading to an internal rate of return from public R&D of 39%





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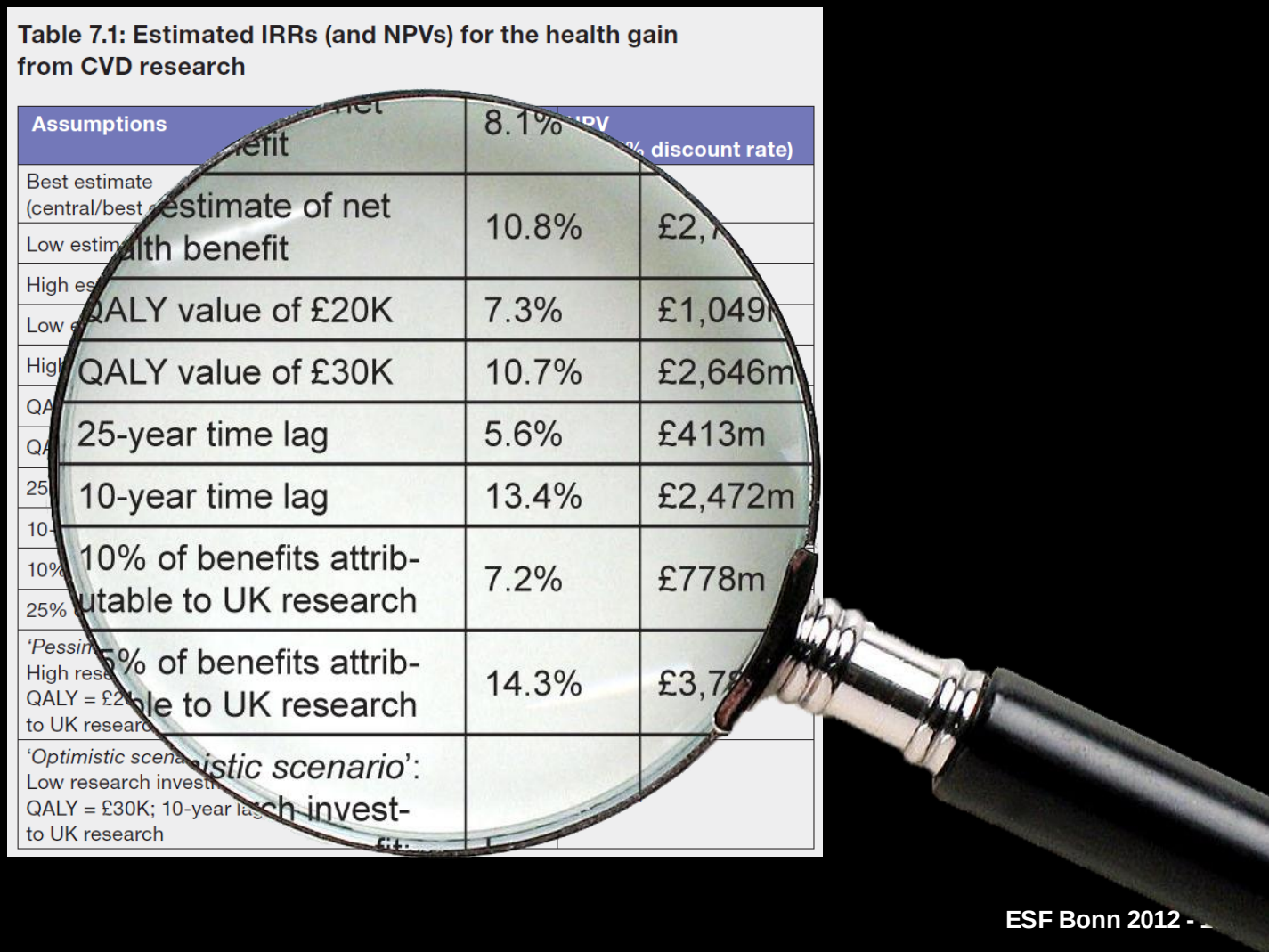
Sources: Griliches (1991), Salter et al. (2000)

9% + 30% = 39%

The time it takes to translate research is key in determining the rate of return from research investments

Table 7.1: Estimated IRRs (and NPVs) for the health gain from CVD research

Assumptions	8.1%	NPV (% discount rate)
Best estimate (central/best estimate of net health benefit	10.8%	£2,7
Low estimate of net health benefit		
High estimate of net health benefit		
Low QALY value of £20K	7.3%	£1,049m
High QALY value of £30K	10.7%	£2,646m
QALY value of £20K		
QALY value of £30K		
25-year time lag	5.6%	£413m
10-year time lag	13.4%	£2,472m
10% of benefits attributable to UK research	7.2%	£778m
25% of benefits attributable to UK research		
'Pessimistic scenario': High research investment; QALY = £20K; 25% of benefits attributable to UK research	14.3%	£3,7
'Optimistic scenario': Low research investment; QALY = £30K; 10-year lag to UK research		



Outline

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  - Policy imperative
  - Delays reduce the rate of return, but not all delays are bad
- **What do we know**
- Some conceptual thoughts
- What we need to know

Literature on time lags is relatively sparse

REVIEW

The answer is 17 years, what is the question: understanding time lags in translational research

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DECLARATIONS

Competing interests
None declared

Funding
This is an independent paper funded by the Policy Research Programme in the Department of Health. The views expressed are not necessarily those of the Department

Ethical approval
Not applicable

Guarantor
JG

Contributorship
ZSM designed, conducted and analysed the literature review, and drafted and revised the paper; JG initiated the project, drafted and revised the paper, and has led a number of studies cited that attempted to measure lags; SW revised the paper

Summary

This study aimed to review the literature describing and quantifying time lags in the health research translation process. Papers were included in the review if they quantified time lags in the development of health interventions. The study identified 23 papers. Few were comparable as different studies use different measures, of different things, at different time points. We concluded that the current state of knowledge of time lags is of limited use to those responsible for R&D and knowledge transfer who face difficulties in knowing what they should or can do to reduce time lags. This effectively 'blindfolds' investment decisions and risks wasting effort. The study concludes that understanding lags first requires agreeing models, definitions and measures, which can be applied in practice. A second task would be to develop a process by which to gather these data.

Introduction

Timely realization of the benefits of expensive medical research is an international concern attracting considerable policy effort around 'translation'.[1,2] Policy interventions to improve translation respond to a vast empirical literature on the difficulties of getting research across research phases and into practice.[3–11]

Both literature and policy tend to assume that speedy translation of research into practice is a good thing. Delays are seen as a waste of scarce resources and a sacrifice of potential patient benefit.[12] Although some lag will be necessary to ensure the safety and efficacy of new interventions or advances, in essence we should aim to optimize lags. One recent study (of which JG and SW were co-authors) estimating the economic benefit of cardiovascular disease (CVD) research in the UK between 1975 and 2005, found an internal rate of return (IRR) of CVD research of 39%.[13] In other words, a £1.00 investment in public/charitable CVD research produced a stream of benefits equivalent to earning £0.39 per year in perpetuity. Of this, 9% was attributable to the benefit from health improvements, which is the focus of this paper. (The remaining 30% arise from 'spillovers' benefiting the wider economy.) This level of benefit was calculated using an estimated lag of 17 years. Varying the lag time from 10 to 25 years produced rates of return of 13% and 6%, respectively, illustrating that shortening the lag between bench and bedside improves the overall benefit of cardiovascular research. What is notable is that all the above calculations depended upon an estimated time lag; estimated because, despite longstanding concerns about them,[14] time lags in health research are little understood.

It is frequently stated that it takes an average of 17 years for research evidence to reach clinical practice.[1,3,15] Balas and Bohen,[16] Grant[17] and Wratschko[18] all estimated a time lag of 17 years measuring different points of the process. Such convergence around an 'average' time lag of 17 years hides complexities that are relevant to

- **Identified 23 papers that quantified time lags**
- **Four studies estimate 17 years**
  - **Grant et al 2000**
  - **Balas and Bohen 2000**
  - **HERG et al 2008**
  - **Wratschko 2009**
- ***"But few were comparable as different studies used different measures of different things at different time points"***

The issue of definition

Start of time lag

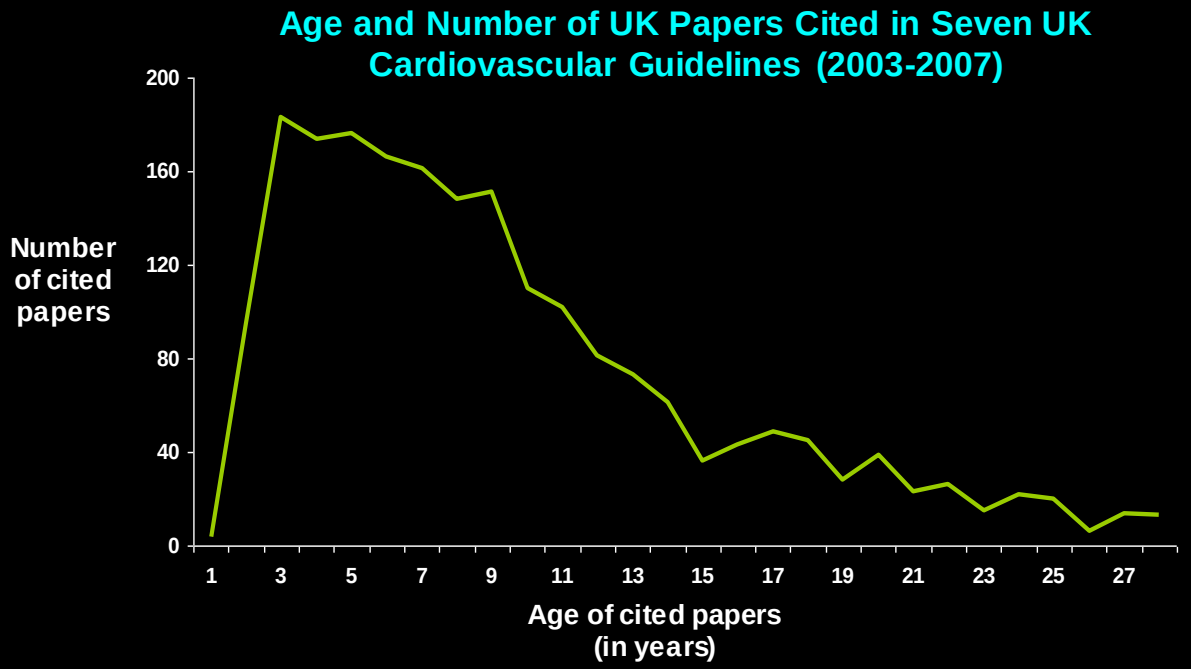
- Publication
  - first description/original research
  - Clinical trial
- Ethics approval
- Clinical test
- Date of trial registration
- Completion of study
- First submission
- Academic research
- Funding began
- Date of enabling scientific research
- Patent

End of time lags

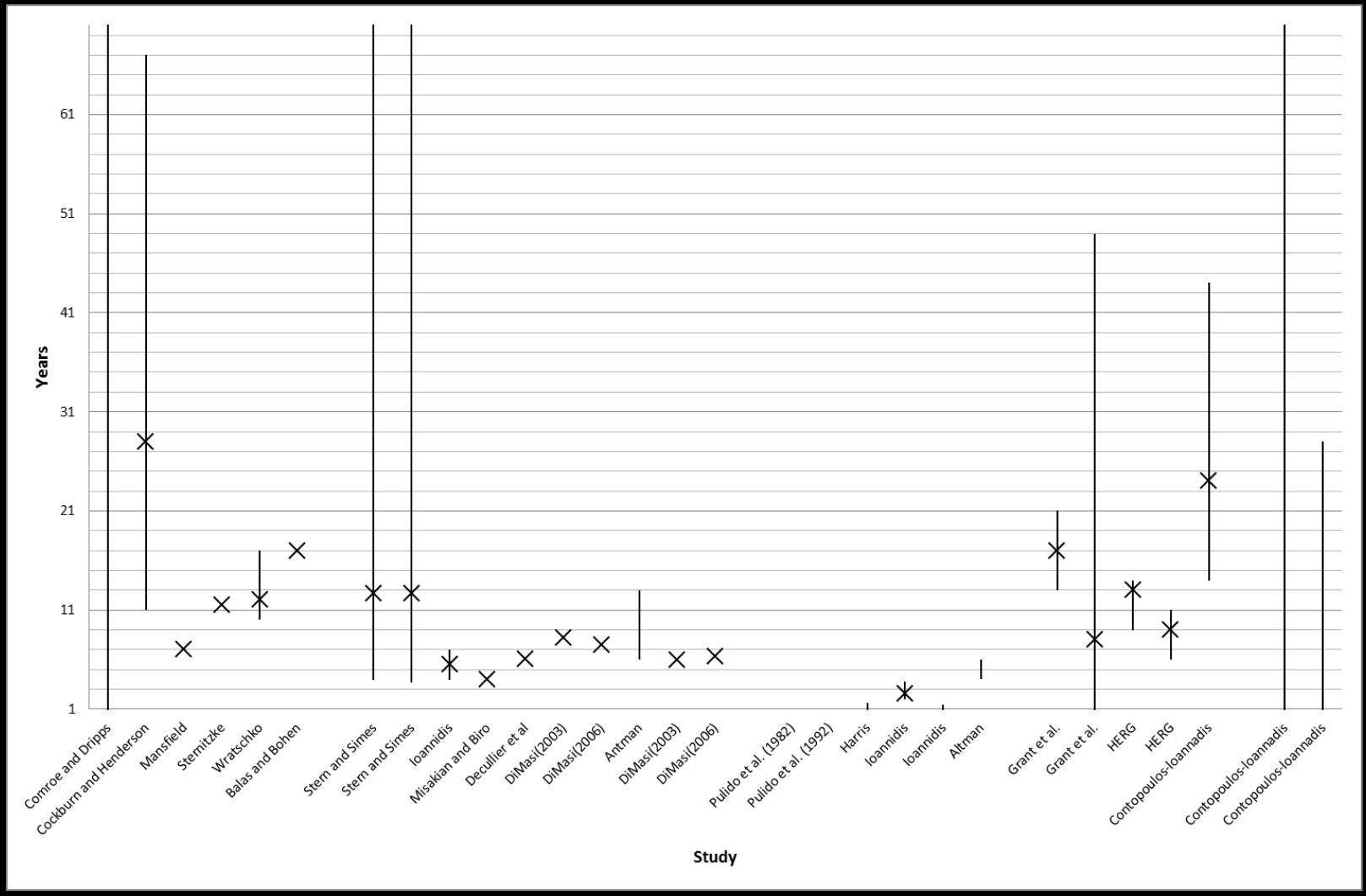
- First human use
- Date for first publication
- Submission to FDA
- Marketing approval
- Guideline
- Date of completion of study
- Publication
  - Describing health effects
- Commercialisation
- Highly cited publication
- Implementation
- Date to market
- New entities
- Clinical advances
- First specific use

The issue of measurement and distributions

- From when to when
- Mean or median (sometimes “average”)
- Ranges are seldom reported
- Aggregation of different phases



Time lags vary in length, but 17 years is a common estimate for 'bench to bedside'



Although lags for private pharmacological development are more homogeneous

Table 2.5. Development times (months)

Publication	Phase I	Phase II	Phase III	Total Phase I–Phase III	Cohort Study
DiMasi et al, 1991	16.2	22.5	29.9	68.6	First tested in humans between 1970 and 1982
DiMasi et al, 2003	21.6	25.7	30.5	77.8	First tested in humans between 1983 and 1994
Abrantes-Metz, Adams and Metz, 2005	19.7	25.1	41.4	86.2	Entered one of the stages of the human clinical trials for the first time between 1989 and 2002
Adams and Brantner, 2006	19	30	30	79	Drugs entering human clinical trials for the first time between 1989-2002
Keyhami, Diener-West and Powe, 2006	N/A			61.2	Drugs approved in the US between 1 January 1992 and 1 January 2002
Adams and Brantner, 2010	16.6	30.7	27.2	74.5	Drugs entering human clinical trials for the first time between 1989-2002
Paul et al, 2010	18	30	30	78	1997-2007[1]
Kaitin and DiMasi, 2011	N/A			78[2]	New product approvals in the US during 2000–2009

[1] We are uncertain about this timeframe as the paper is not explicit.
[2] Kaitin and DiMasi (2011) provide evidence for clinical phases in total without differentiating between phases. The 78 months refers to the subset of FDA-approved compounds between 2000 and 2009.

Mestre-Ferrandiz, *Sussex and Towse (2012)*

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Time lags are the wait between research and impact

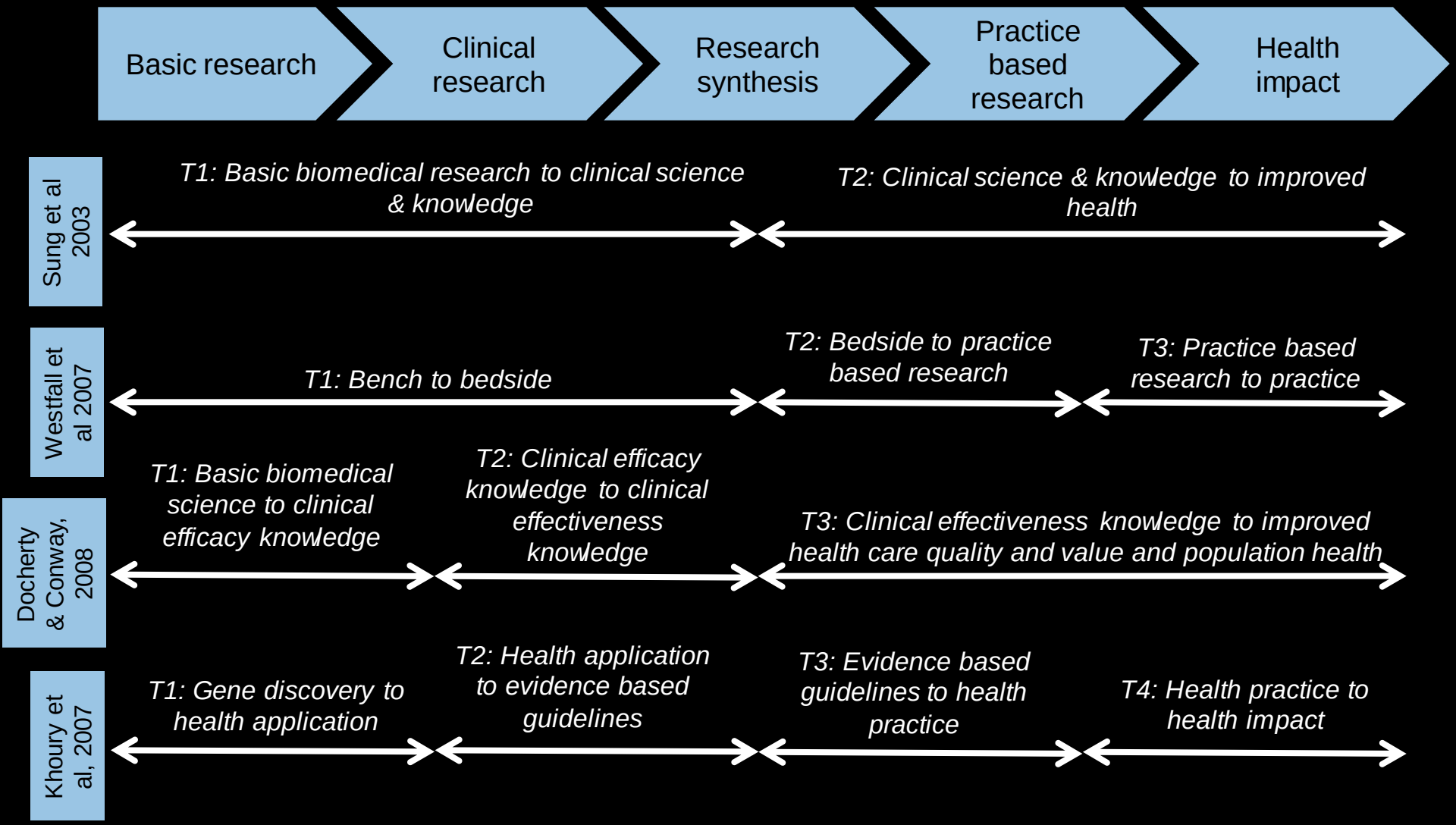
But when does research start and impact occur?

Time lags reduce the value of research

Years of time lag	Value of benefit (assuming a 3.5% real term discount rate)
0	100%
1	97%
2	93%
5	84%
10	70%
15	59%
20	49%
30	34%

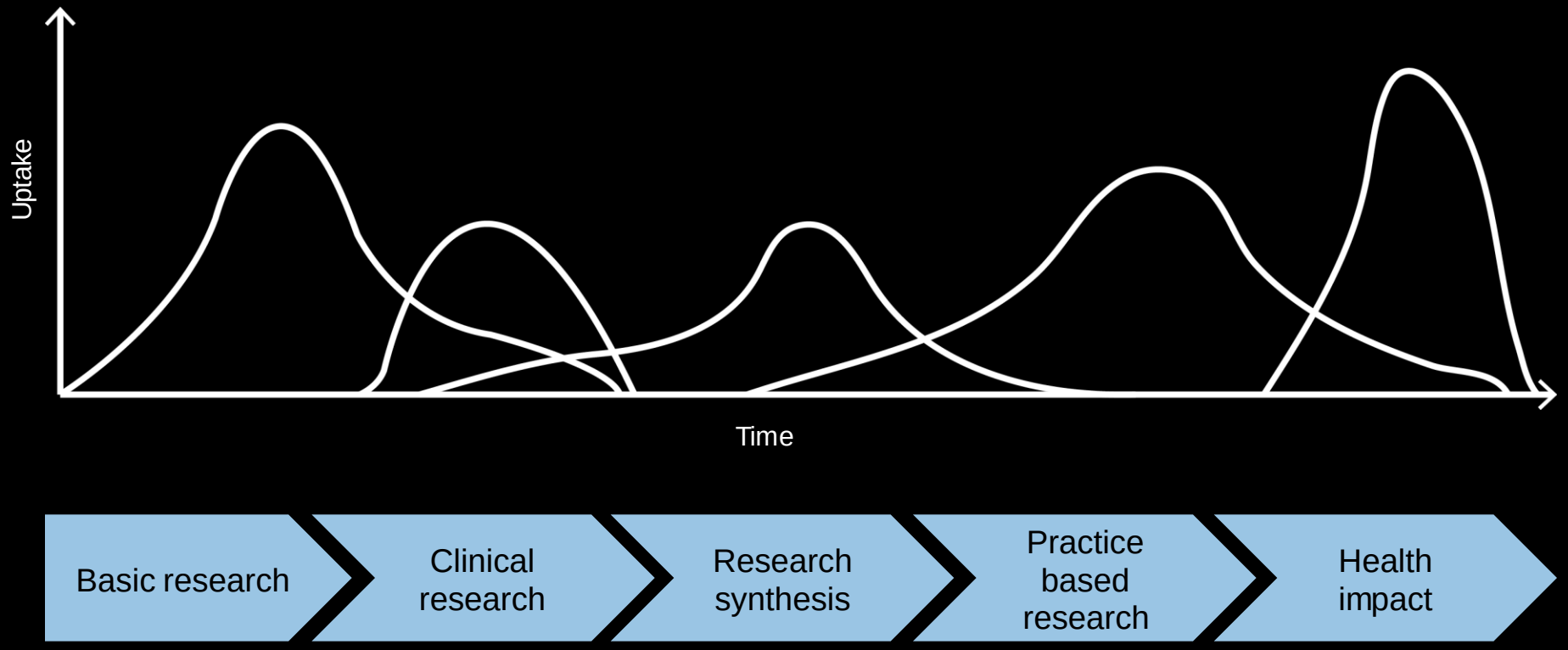
The quicker you translated the greater the return

The overall time lag is made of many smaller lags

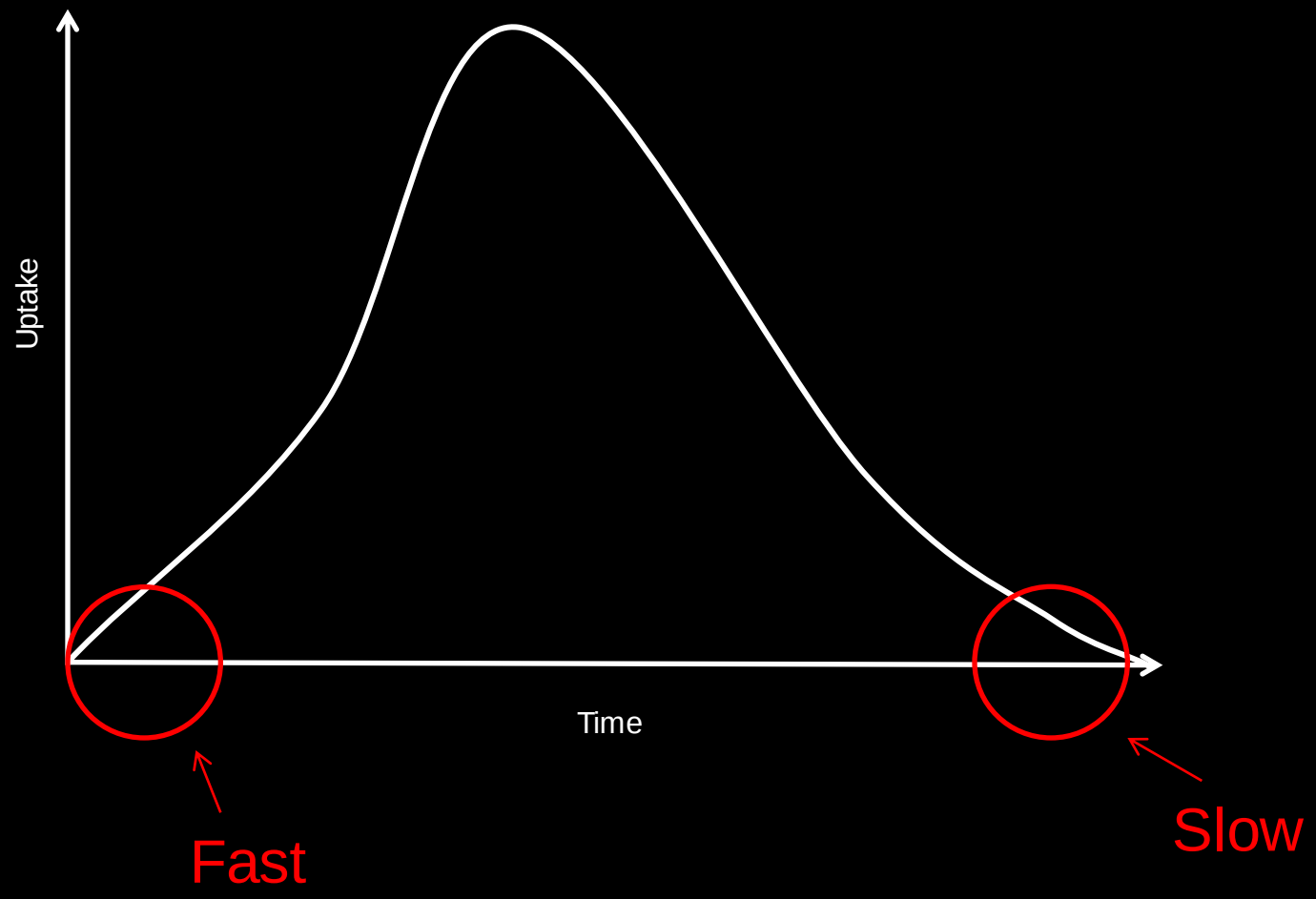


Adapted from Trochim et al 2010

Different stages of the translation process may have different distributions of time lags



Understanding distributions could help identify factors associated with 'fast' or 'slow' translation



Time lags can be affected in a variety of ways

- **Working in parallel**

- **Starting at risk**

- **Improving processes**

There are different types of time lags and some are desirable

Reducible…	…without additional resources	Unnecessary process lags
	…with additional resources	Trade off lags (including Handover lags)
Possibly reducible	…without additional resources	Statutory lags
	…with additional resources	Inspiration lags
Non-reducible		Time requirement lags

Need to develop (and agree) taxonomy if different time lacks

Different time lags may be affected in different ways

		Parallel 	Start at risk 	Improve process 
Unnecessary process lags				Removal
Trade off lags	Group decision lag		Start prior to completion of previous step or start subsequent step before completion of this step	Reduce number of applications that have to be resubmitted Decrease gaps between decisions Redesign process to make individual decisions
	Recruitment lag	Use additional resources to work in parallel e.g. more sites for recruitment		Use more effective methods e.g. database of existing patients
	Handover lag			Develop skills, or integrate teams to reduce number of handovers Develop systems/services to match producers from one step with consumers in next step
Statutory lags				Amend legislation or regulatory guidelines
Inspiration lags		More research teams tackling same problem	Prepare the ground for likely solutions	Improve flow of information to researchers Training of researchers
Time requirement lags			Start other processes prior to completion	Develop 'early indicators' or more sensitive assays

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Advancing a case study approach for a better understanding of time lags

Time lags in medical research:
Advancing a case study approach for a better understanding

One of the key challenges in biomedical and health research is how to ensure that research findings are effectively translated from 'bench to bedside'. We know from previous work that the time it takes to translate research is key in determining the rate of return from research investments[1]. Previous studies suggest that it typically takes 17 years for new discoveries to be put into practice[2]. Existing models of research translation typically refer to the concept of translation 'gaps', but how these gaps are defined, and thus measured, differs significantly between approaches and can lead to results not being comparable. This project uses a case study approach to investigate the time lags in the translation of biomedical and health research. We plan to use the process marker model proposed by Trochim et al (2011)[3] as the basis for our case study approach. Here, specific research translation milestones or events are considered to be process markers, and are clearly defined to enable comparability. We shall attempt to identify dates for each marker, and then time lags can then be assessed relative to these markers.

A key element of this pilot project is to develop and trial this approach as a basis for case studies to investigate time lags. To do this, we plan to conduct six case studies in the fields of cardiovascular and mental health research, which were the focus of the team's previous study on the economic returns from medical research1. We will conduct both backward and forward tracing case studies, ie ones that start with the application of a new therapy or procedure and work backwards to identify the research behind the innovation, and ones that start with specific pieces of research and trace forwards to the subsequent innovations. We intend to cover a range of types of intervention (e.g. a new drug, service delivery, screening programme etc.) as the translation pathways, and hence both the markers and the primary sources of time lags, are likely to differ between types of intervention.

If the method proves successful, we hope in follow-on studies to conduct further case studies using the approach allowing us to produce a more in-depth analysis of the sources of time lags, whether they are desirable or undesirable (a delay in translation to ensure the safety of a new drug, for example, may well be desirable), and how they differ between types of intervention. This will allow us to develop policy relevant recommendations, building on the preliminary analysis of policy-relevant findings we hope to produce on the basis of the findings of the pilot project.

Funder: MRC Methodology Research Programme, MRC's 'Understanding the link between research and economic impact' call for proposals.

Dates: November 2012-October 2013

Team and contacts: *Health Economics Research Group (HERG), Brunel University*: Steve Hanney (stephen.hanney@brunel.ac.uk), Martin Buxton, Chris Henshall;
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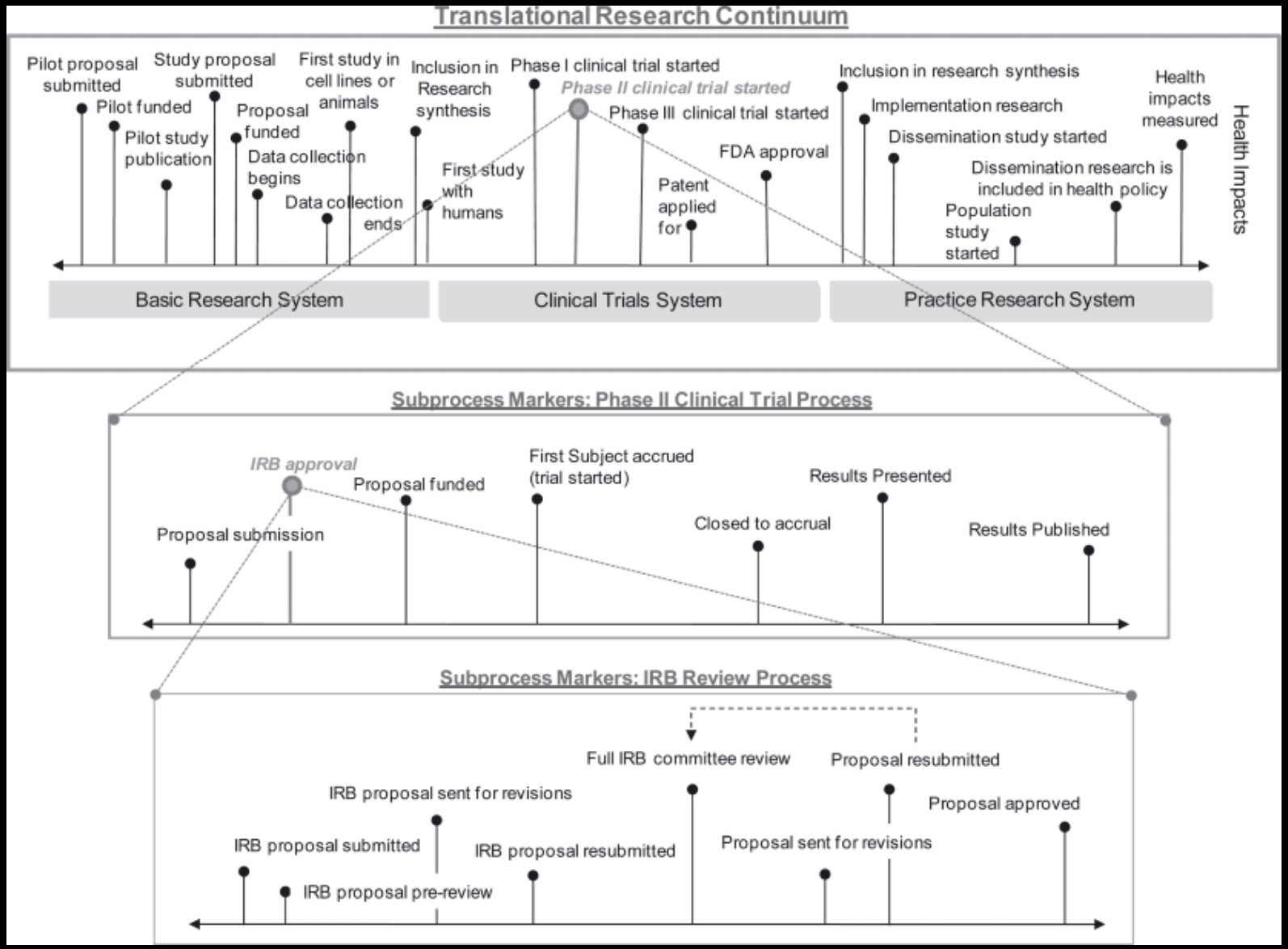
Office of Health Economics (OHE): Jon Sussex (jsussex@ohe.org), Jorge Mestre-Ferrandiz, Michele Pistollato.

RAND EUROPE HERG OHE

[1] HERG, RAND Europe, OHE. *Medical Research: What's it Worth*. London: MRC/Wellcome Trust/Academy of Medical Sciences; 2008
[2] Morris Z S, Wooding S, Grant J. The answer is 17 years, what is the question: understanding time lags in translational research. *J R Soc Med* 2011;104:510–520.
[3] Trochim W, Kane C, Graham M, Pincus HA. Evaluating Translational Research: A Process Marker Model. *Clinical and Translational Science* 2011;4:153-162.

- UK MRC funded, 12 months
- Methodological research
- Case study approach
- Identify and date stamp specific events based on process marker model
- Supplement with literature review focused on industry and policy

Process marker model



From Trochim et al 2010

Generating a long list of key events

Event (Level 1)	Event (Level 2)	Event (Level 3)	Date	Responsible actor	Source
Preliminary studies					
	Study proposal submitted				
	Proposal funded				
	Data collection begins				
	Data collection ends				
	Submission of paper				
	First publication and subsequent publications				
	Highly cited publication				
Study in cell lines or animals (pre clinical)					
	Study proposal submitted				
	Proposal funded				
	Submission of paper				
	First publication and subsequent publications				
	Highly cited publication				
	Inclusion in research synthesis eg review paper				
	[NOTE SURE WHAT GOES HERE - TWO ISSUES A) NON PHARMA TYPE INTERVENTIONS; B) PRE PHASE 1 STUFF]				
First study in humans [Phase 0]					
	Study proposal submitted				
	Ethics approval				
		Ethics proposal submitted			
		Ethics proposal pre-review			
		Ethics proposal sent for revisions			
		Ethics proposal resubmitted			
		Full Ethics committee review			
		Proposal sent fo revisions			
		Proposal resubmitted			
		Proposal approval			
	Proposal funded				
	Results presented				
	Submission of paper				
	First publication and subsequent publications				
	Highly cited publication				
	Inclusion in research synthesis eg review paper				
Phase 1 clinical trial started (eg pharmacovigilance and dose-ranging)					
	Study proposal submitted				
	Ethics approval				
		Ethics proposal submitted			
		Ethics proposal pre-review			
		Ethics proposal sent for revisions			
		Ethics proposal resubmitted			
		Full Ethics committee review			
		Proposal sent fo revisions			
		Proposal resubmitted			
		Proposal approval			
	Proposal funded				
	Results presented				
	Submission of paper				
	First publication and subsequent publications				
	Highly cited publication				
	Inclusion in research synthesis eg review paper				
Phase 2 clinical trial started (eg testing of drug on healthy volunteers)					
	Study proposal submitted				
	Ethics approval				
		Ethics proposal submitted			
		Ethics proposal pre-review			
		Ethics proposal sent for revisions			
		Ethics proposal resubmitted			
		Full Ethics committee review			
		Proposal sent fo revisions			
		Proposal resubmitted			
		Proposal approval			
	Proposal funded				
	Proposal funded				
	Fist subject accrued (trial started)				
	Closed to accrual				
	Results presented				
	Submission of paper				
	First publication and subsequent publications				
	Highly cited publication				
	Inclusion in research synthesis eg review paper				
Phase 3 clinical trial started (eg testing of drug for intended use as therapy)					
	Study proposal submitted				
	Ethics approval				
		Ethics proposal submitted			
		Ethics proposal pre-review			
		Ethics proposal sent for revisions			
		Ethics proposal resubmitted			
		Full Ethics committee review			
		Proposal sent fo revisions			
		Proposal resubmitted			
		Proposal approval			
	Proposal funded				
	Date of trial registration				
	Fist subject accrued (trial started)				
	Closed to accrual				
	Results presented				
	Submission of paper				
	First publication and subsequent publications				
	Highly cited publication				
	Inclusion in research synthesis eg review paper				
	[NOTE SURE WHAT GOES HERE - SOMETHING TO DO WITH POPULATION BASED STUDIES/EFFECTIVENESS]				
Commercialisation					
	Patent applied for				
	FDA approval				
		Submission to FDA			
		Initial submission			
		Resubmission or an unapproved or withdrawn application			
		Appeal of a regulator decision			
		Approval			
	Date to market				
Research Synthesis					
	Inclusion in research synthesis - review paper/editorial/consensus statement				
	Inclusion in research synthesis - Cochrane Collaboartion/systematic review				
	Inclusion in research synthesis - Guideline				
Implementation research					
	Study proposal submitted				
	Proposal funded				
	Submission of paper				
	First publication and subsequent publications				
	Highly cited publication				
	Inclusion in research synthesis eg review paper				
Research is included in health policy					
	Inclusion in White Paper of equivalent				
	Cited in health policy debate				
Health impacts measured					
	Measure of use				
	Or 50% of eligible population using				

Generating a long list of key events

Event (Level 1)	Event (Level 2)
Preliminary studies	
	Study proposal submitted
	Proposal funded
	Data collection begins
	Data collection ends
	Submission of paper
	First publication and subsquent publications
	Highly cited publication
Study in cell lines or animals (pre clinical)	
	Study proposal submitted
	Proposal funded
	Submission of paper
	First publication and subsquent publications
	Highly cited publication
	Inclusion in research synthesis eg review paper

For each event capture date, responsible actor and source

Use existing case studies to population event table and then collate additional information

	Cardiovascular Disease	Mental Health
Drug		
Service delivery		
Device		
Psychosocial		
Public health		

Advancing a case study approach for a better understanding of time lags

Time lags in medical research:
Advancing a case study approach for a better understanding

One of the key challenges in biomedical and health research is how to ensure that research findings are effectively translated from 'bench to bedside'. We know from previous work that the time it takes to translate research is key in determining the rate of return from research investments[1]. Previous studies suggest that it typically takes 17 years for new discoveries to be put into practice[2]. Existing models of research translation typically refer to the concept of translation 'gaps', but how these gaps are defined, and thus measured, differs significantly between approaches and can lead to results not being comparable. This project uses a case study approach to investigate the time lags in the translation of biomedical and health research. We plan to use the process marker model proposed by Trochim et al (2011)[3] as the basis for our case study approach. Here, specific research translation milestones or events are considered to be process markers, and are clearly defined to enable comparability. We shall attempt to identify dates for each marker, and then time lags can then be assessed relative to these markers.

A key element of this pilot project is to develop and trial this approach as a basis for case studies to investigate time lags. To do this, we plan to conduct six case studies in the fields of cardiovascular and mental health research, which were the focus of the team's previous study on the economic returns from medical research1. We will conduct both backward and forward tracing case studies, ie ones that start with the application of a new therapy or procedure and work backwards to identify the research behind the innovation, and ones that start with specific pieces of research and trace forwards to the subsequent innovations. We intend to cover a range of types of intervention (e.g. a new drug, service delivery, screening programme etc.) as the translation pathways, and hence both the markers and the primary sources of time lags, are likely to differ between types of intervention.

If the method proves successful, we hope in follow-on studies to conduct further case studies using the approach allowing us to produce a more in-depth analysis of the sources of time lags, whether they are desirable or undesirable (a delay in translation to ensure the safety of a new drug, for example, may well be desirable), and how they differ between types of intervention. This will allow us to develop policy relevant recommendations, building on the preliminary analysis of policy-relevant findings we hope to produce on the basis of the findings of the pilot project.

Funder: MRC Methodology Research Programme, MRC's 'Understanding the link between research and economic impact' call for proposals.

Dates: November 2012-October 2013

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[1] HERG, RAND Europe, OHE. *Medical Research: What's it Worth*. London: MRC/Wellcome Trust/Academy of Medical Sciences; 2008
[2] Morris Z S, Wooding S, Grant J. The answer is 17 years, what is the question: understanding time lags in translational research. *J R Soc Med* 2011;104:510–520.
[3] Trochim W, Kane C, Graham M, Pincus HA. Evaluating Translational Research: A Process Marker Model. *Clinical and Translational Science* 2011;4:153-162.

- **Develop:**
  - **Definitions for different types of time lags**
  - **Estimates of distributions**
- **If successful will increase number of case studies**
- **Work in progress so please don't cite**
- **Will report in November 2013**

Questions?


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