WORKSHOP (W9)

BRIDGING THE GAP BETWEEN EFFICACY AND EFFECTIVENESS

USING BOTH REAL-WORLD AND TRIAL-BASED EVIDENCE TO IMPROVE CLINICAL DECISION MAKING

Monday, 10 September 2018
3:45 PM - 4:45 PM

ISPOR Asia Pacific 2018, Tokyo, Japan

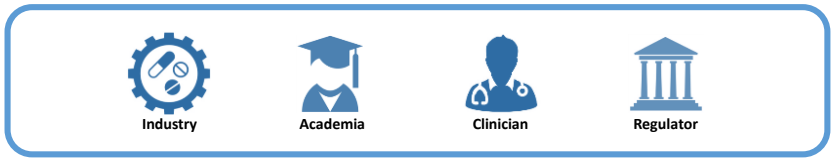
Speakers

Dr. Bor-Sheng Ko (Kevin), National Taiwan University Hospital, TW

Dr. Fei-Yuan Hsiao (Sharon), National Taiwan University, TW

Dr. Ming-Hui Tai (Mindy), Amgen Inc, USA

Dr. Han-I Wang (Annie), University of York, UK



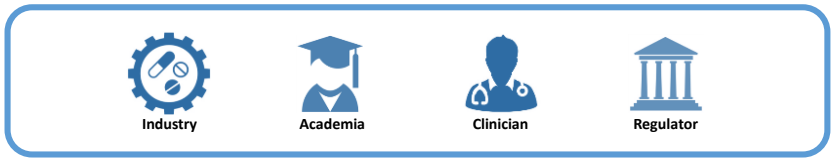
Speakers

MSc. Hsin-Yi Tsai (Chris), Amgen Inc, TW

Dr. Fei-Yuan Hsiao (Sharon), National Taiwan University, TW

Dr. Chia-Hui Tan (Elise), Ministry of Health and Welfare, TW

Dr. Han-I Wang (Annie), University of York, UK



Outline

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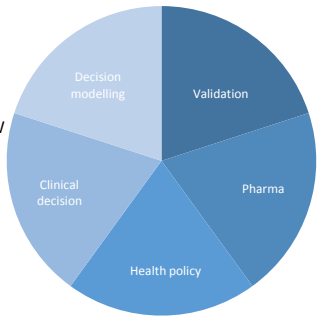
Q & A



Real-world evidences for Changing Disease Landscape by Novel Therapy

Multiple myeloma as an example

Bor-Sheng Ko, M.D. Ph.D.
Assistant Professor and Attending Physician, NTUH, Taiwan
President, Taiwan Society of Pharmacoeconomics and Outcome Research (TaSPOR)

Hsin-Yi Tsai (Chris), MSc
Head of Value, Access and Policy, Amgen Inc, Taiwan

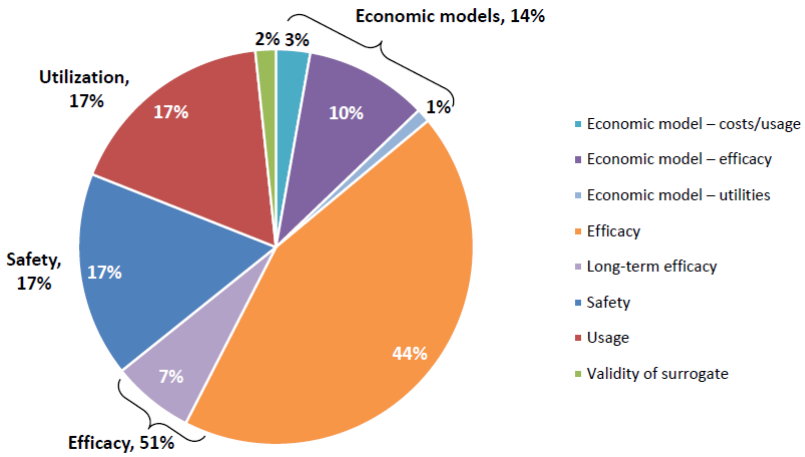
Live polls

How is the use of RWE in HTA submission?

1%, **5%**, 10%, 50%

Jaksa A (2018, June). Use of Real World Evidence in HTA Decision-Making from 7 Agencies. Paper presented at the HTAi, Vancouver, Canada

Types of evidence using RWD in HTA submission

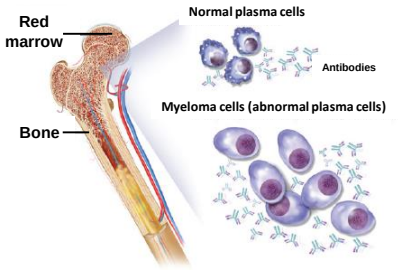


Jaksa A (2018, June). Use of Real World Evidence in HTA Decision-Making from 7 Agencies. Paper presented at the HTAi, Vancouver, Canada

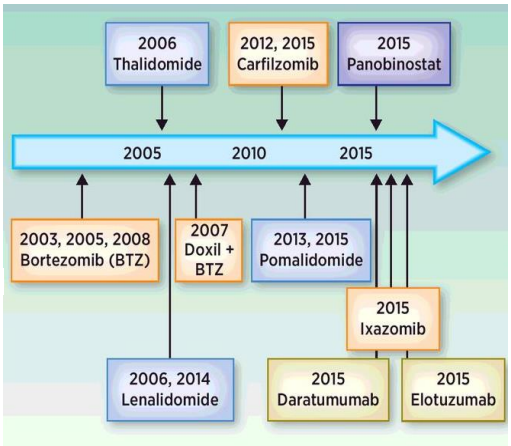
Multiple myeloma:

An old disease with recent therapeutic advances

- First described in 1844, with a lady with multiple fracture
- Abnormal plasma cell proliferation
- A disease in elderly
- Incurable and fatal, within less than 3 years



- More than 8 drugs approved by FDA in the past 10 years



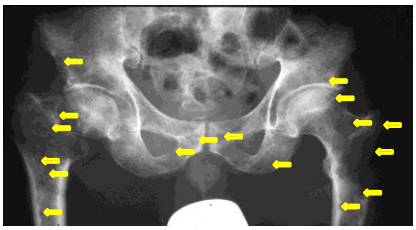
Clin Cancer Res; 22(22); 5419–27

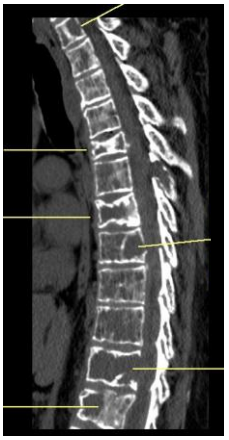
Bone events in myeloma:

A common and suffering complication

- Multiple osteolytic lesions, with fractures
- Even not completely recovered after treatment
- Novel drugs developed:
  - Low-potency bisphosphate: clondronate, palmidronate
  - High-potency bisphosphate: zolendronate
  - RANKL inhibitor: denosumab

Med Chir Trans 1844;27:435-61



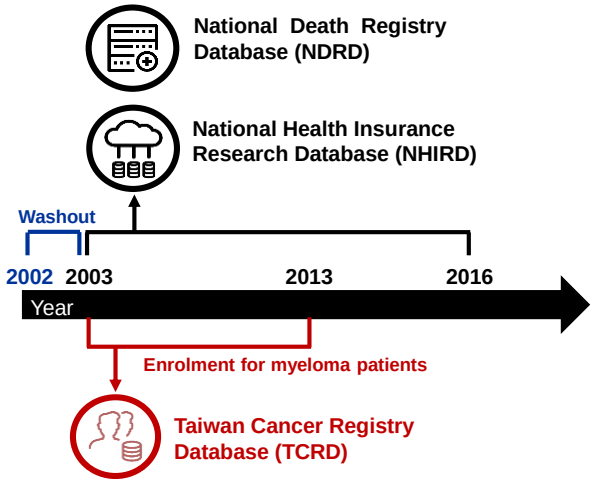


http://www.aboutcancer.com/myeloma_images.htm

Study rationales/aims:

- **To examine the incidences for myeloma in Taiwan**
  - For disease burden
- **To describe the survival of myeloma in Taiwan**
  - Not clear in East Asia, especially in the era of novel therapy
  - Hardly to analyze the Impacts of single novel drug, because they are usually used in combination and in different lines
  - Improvement in care also contribute for survival
- **To describe the incidences of bone events, and also the impacts of drugs in Taiwan Myeloma patients**

Study design:

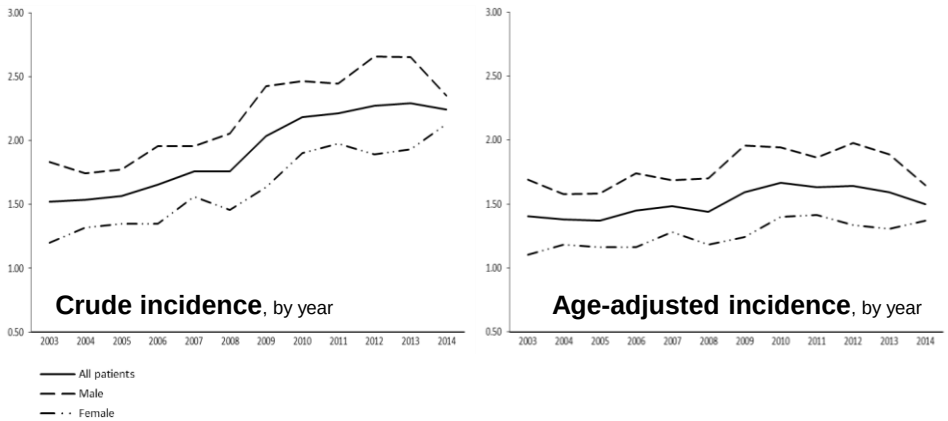


- Link 3 database, with cross validation
- Enroll only adult patients (> 18 y/o)
- Bone events within 3 months prior to diagnosis are counted.

- **N=4660**
- 2914 bone events

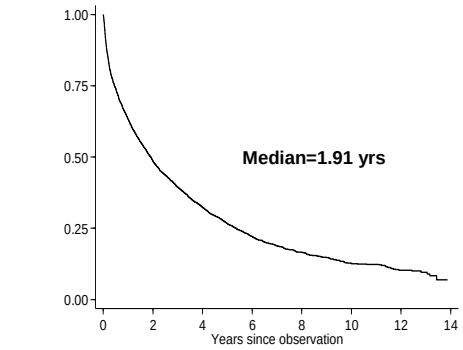
The incidence of myeloma is increasing in Taiwan.

- Anyway, the trends is ameliorated by age adjustment.
- Probably due to aging population in Taiwan



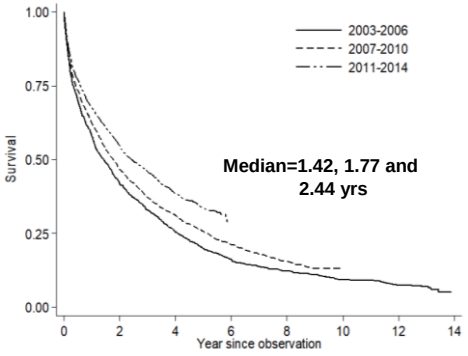
The survival for myeloma patients is in improving in Taiwan.

- **The cutting points are correlated to novel drug reimbursement:**
  2007: Bortezomib
  2011: Lenalidomide



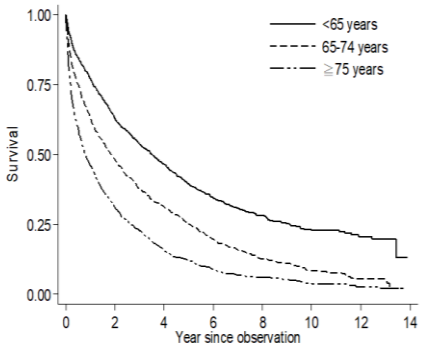
Number at risk

All Patients	4660	2261	1165	534	253	118	45	0



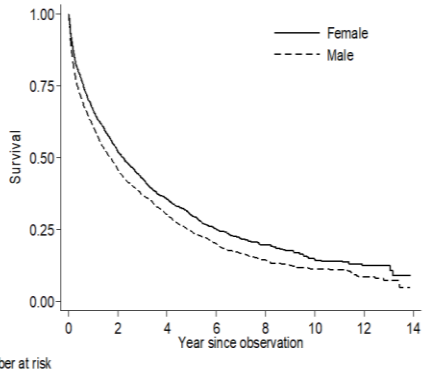
Age and gender impact on survival also.

- **The gender effects are not clearly described in literature. Await for further exploration.**



Number at risk

<65 years	1822	1138	656	314	163	81	30	0
65-74 years	1395	674	331	154	64	25	10	0
≧75 years	1443	449	178	66	26	12	5	0



Number at risk

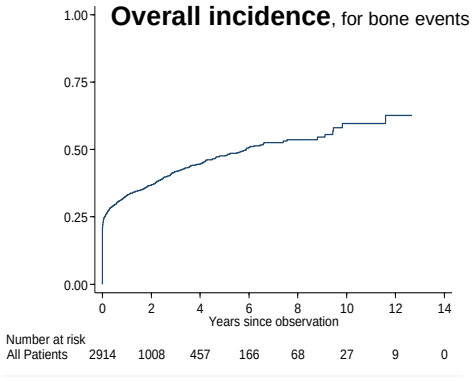
Female	1999	1043	540	250	130	59	25	0
Male	2661	1218	625	284	123	59	20	0

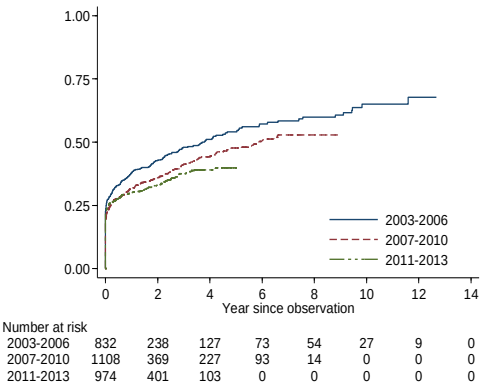
Multi-variate analysis confirms the findings.

	Total patient years	Number of Deaths	Adjusted HR	P>z	95%CI	
Gender						
Male	6684	2100	**1.19**	<0.001	1.11	1.27
Female	5699	1464	1.00			
Age						
<65	6358	1163	1.00			
65-74	3592	1110	**1.58**	<0.001	1.46	1.72
75-	2433	1291	**2.48**	<0.001	2.29	2.68
Diagnosed year						
2003-2006	3693	1154	1.00			
2007-2010	4507	1309	**0.87**	0.001	0.81	0.95
2011-2014	4183	1101	**0.70**	<0.001	0.64	0.76
CCI						
CCI=0	5765	1279	1.00			
CCI=1-2	4950	1515	**1.32**	<0.001	1.22	1.42
CCI>=3	1668	770	**1.84**	<0.001	1.69	2.02
Geographical areas						
Taipei & Northern	6192	1673	1.00			
Central & Southern	5801	1771	**1.10**	0.007	1.02	1.17
Eastern	390	120	1.12	0.227	0.93	1.35

Incidence of bone events:

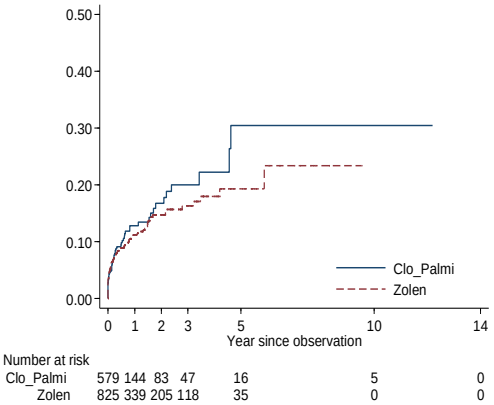
- **40-50% patients will experience the events, and half of them at diagnosis**
- **Improving in medical treatment reduce the incidences of bone events**





Correlating bone events with bisphosphates:

- **Low-potent bisphosphates are marginally correlated with higher rate of bone events.**



Sex Differences in Clinical Benefits of Rituximab-Containing Chemotherapy for Diffuse Large B Cell Lymphoma (DLBCL)

J Womens Health (Larchmt). 2018 Jun 20

Fei-Yuan Hsiao (Sharon), PhD

Associate Professor, National Taiwan University, Taipei, Taiwan

Standing director, Taiwan Society of Pharmacoeconomics and Outcome Research (TaSPOR)

國立臺灣大學 National Taiwan University

TASPOR

Background

Efficacy vs. Effectiveness

	Clinical trial	RWD in healthcare
Sample size	100~10,000	million to billion (rare events)
Follow-up time	1~5 years	life-long treatment (delayed effect)
Outcome measurement	Surrogate (mid-term)	Final outcome
Patient population	Restricted	Diverse
Comparator selection	Placebo	Current standard (Head-to-head comparison)

Introduction

Older men seem to have **poorer responses** to **rituximab (R)** -containing chemotherapy for DLBCL in clinical practice?

Sex difference in both rituximab metabolism and clinical outcomes of DLBCL was found in previous studies

Limitations of previous research and knowledge gap

Heterogeneity possibly introduced by post-hoc analysis **Generalizability ?**

Sex differences in baseline characteristics

Blood. 2012;119(14):3276-84.
Lymphoma. 2014;2014:12.
Leuk Lymphoma. 2013;54(1):53-57.
Leuk Lymphoma. 2008;49(3):462-469.

Introduction

Objective

To investigate the **sex differences** in terms of DLBCL and its treatments using data from

- **Taiwan Cancer Registry Database (TCRD)**
- **National Health Insurance Research Database (NHIRD)**
- **National Death Registry (NDR)**

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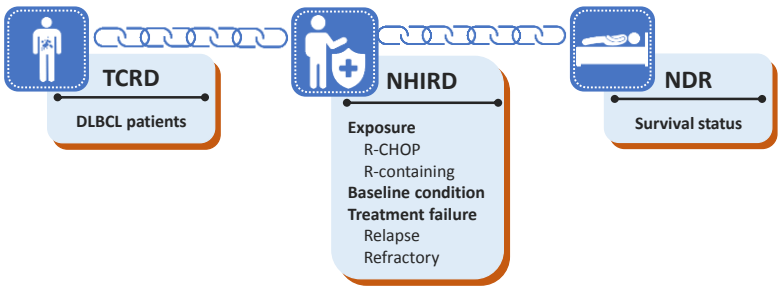
Methods

Study design

Retrospective cohort study



4

Main Results

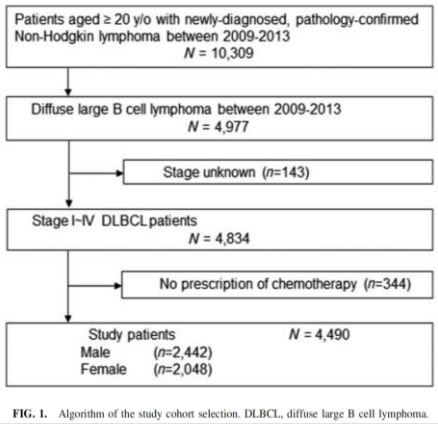
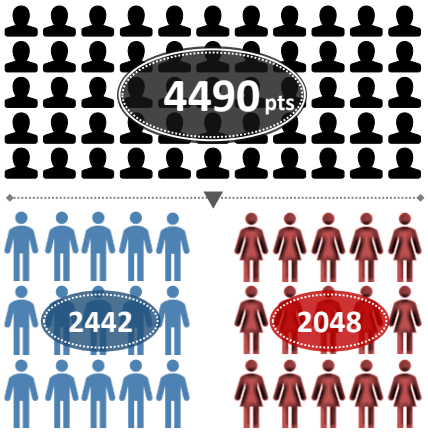


FIG. 1. Algorithm of the study cohort selection. DLBCL, diffuse large B cell lymphoma.



5

Main Results

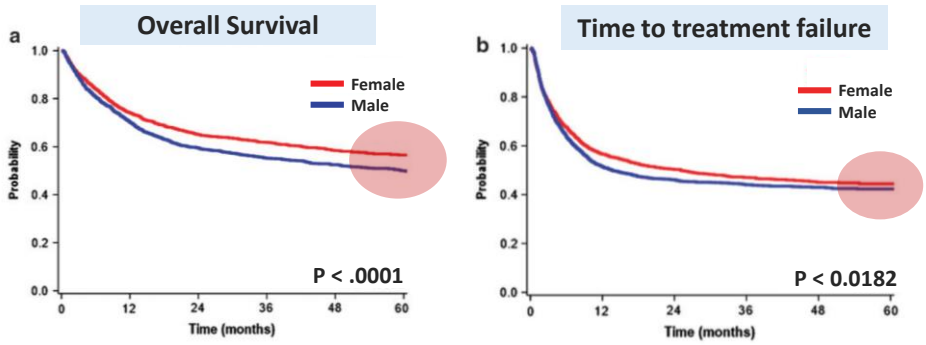


FIG. 2. Kaplan–Meier plots of OS and TTF. (**a**) OS and (**b**) TTF of the patients with DLBCL receiving treatments. OS, overall survival; TTF, time to treatment failure. Color images available online at www.liebertpub.com/jwh

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Main Results

TABLE 2. UNIVARIATE AND MULTIVARIATE ANALYSIS OF OVERALL SURVIVAL, AND TIME TO TREATMENT FAILURE IN PATIENTS WITH DIFFUSE LARGE B CELL LYMPHOMA

SURVIVAL, AND TIME TO TREATMENT
CELL LYMPHOMA

	Time to treatment failure			
	Univariate		*Multivariate*	
Variables	*HR (95% CI)*	p	*HR (95% CI)*	p
Sex				
Female	1	0.0188	1	0.1178
Male	1.10 (1.02–1.19)		1.07 (0.98–1.16)	

	Overall survival				*Time to treatment failure*			
	Univariate		*Multivariate*		*Univariate*		*Multivariate*	
Charlson comorbidity index								
0	1	<0.0001	1	<0.0001	1	<0.0001	1	0.0746
1	1.34 (1.19–1.50)		1.04 (0.92–1.16)		1.18 (1.07–1.30)		1.05 (0.95–1.16)	
2+	2.07 (1.86–2.31)		1.31 (1.17–1.47)		1.45 (1.32–1.59)		1.13 (1.02–1.25)	
Practice setting								
Medical center	1	0.0107	1	0.0253	1	0.4117	1	0.8071
Others	1.13 (1.03–1.25)		1.12 (1.01–1.23)		1.04 (0.95–1.13)		1.01 (0.93–1.10)	

CI, confidence interval; HR, hazard ratio.

Main Results

FIG. 3. aHR comparing women and men for OS and TTF in different subgroups. aHR and 95% CIs are presented using the observation group as the reference group. aHR, adjusted hazard ratio; CIs,

	All-cause death			Treatment failure		
	HR	(95%CI)	p-value	HR	(95%CI)	p-value
All patients	1.18	(1.07- 1.29)	0.0005	1.07	(0.98- 1.16)	0.1178
Induction Chemotherapy						
R-CHOP	1.30	(1.13- 1.49)	0.0002	1.16	(1.04- 1.30)	0.0105
Other R-Tx	1.09	(0.93- 1.27)	0.3204	1.04	(0.90- 1.21)	0.5975
Non-R Tx	1.11	(0.90- 1.36)	0.3533	0.90	(0.75- 1.08)	0.2699
II	1.18	(0.96- 1.45)	0.1267	1.07	(0.90- 1.26)	0.4479
III	1.09	(0.90- 1.32)	0.3747	0.97	(0.82- 1.14)	0.6834
IV	1.19	(1.04- 1.36)	0.0139	1.05	(0.92- 1.19)	0.4654
Rituximab dosing						
<=600	1.30	(1.16- 1.47)	<0.0001	1.19	(1.07- 1.33)	0.0014
>600	0.99	(0.79- 1.24)	0.9462	0.95	(0.79- 1.15)	0.5851

0.6 1.0 1.4 1.8
Favor female

Conclusions

1st nationwide and real-world cohort to discuss the sex difference of the rituximab use and its clinical benefits in DLBCL patients

Generalizability

Sex differences in baseline characteristics

Female sex is an independent prognostic factor in the DLBCL patients receiving rituximab-containing induction chemotherapies.

9

Impact of Safety-Related Regulations on Codeine Use in Children: A Quasi-Experimental Study Using Taiwan's National Health Insurance Research Database

Drug Saf. 2017 Jul;40(7):615-627

Fei-Yuan Hsiao (Sharon), PhD

Associate Professor, National Taiwan University, Taipei, Taiwan

Standing director, Taiwan Society of Pharmacoeconomics and Outcome Research (TaSPOR)

國立臺灣大學 National Taiwan University

TASPOR

Background

Efficacy vs. Effectiveness (same in the "Safety")

	Clinical trial	RWD in healthcare
Sample size	100~10,000	million to billion (rare events)
Follow-up time	1~5 years	life-long treatment (delayed effect)
Outcome measurement	Surrogate (mid-term)	Final outcome
Patient population	Restricted	Diverse
Comparator selection	Placebo	Current standard (Head-to-head comparison)

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Background

Efficacy vs. Effectiveness (same in the "Safety")

■We know everything about a drug at approval?

Pre-clinical
- Basic science
- Synthesis
- Animal studies
- IND (Investigational New Drug)

Clinical (RCTs)
- Phase I
- Phase II
- Phase III
- NDA (New drug application)

FDA Approval

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Introduction

Use of codeine-containing products in pediatric patients

- The benefit remains unclear
- **Severe adverse events: respiratory depression and death**
- Safety warnings by professional organizations and regulatory bodies
  -The US FDA, the EMA, Health Canada, the AAP and the ACCP

Are these drug safety communications "effective"?

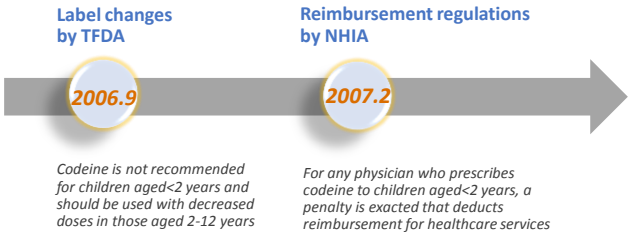
Efficacy vs Effectiveness of "policy intervention"?

Lancet. 2006;368(9536):704.
Pediatrics. 2012;129(5):e1343-1347.
Br J Anaesth. 2013;110(2):175-182.
Pediatrics. 2014;133(5):e1139-1147.

Introduction

Are these drug safety communications "effective"?

Efficacy vs Effectiveness of "policy intervention"?



TFDA=Taiwan Food and Drug Administration, NHIA=National Health Insurance Administration

Introduction

Objective

To investigate the impact of the two safety-related regulations in Taiwan on the use of codeine for upper respiratory infection or cough from

National Health Insurance Research Database (NHIRD)

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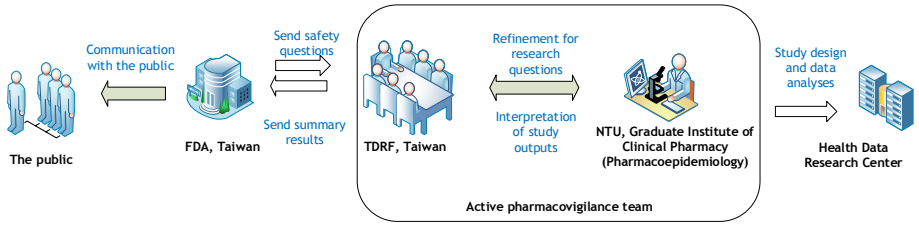
Methods

Collaborative Infrastructure

Retrospective cohort study



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Methods

Study design

Before–after design

Interrupted time series design

- Pre-regulation period: 2003 Q1 – 2006 Q2
- Transition period: 2006 Q3 – 2007Q2
- Post-regulation period: 2007 Q3 – 2010 Q4

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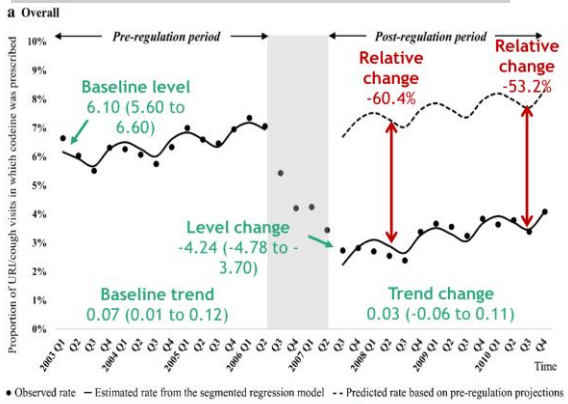
Main Results

Use of codeine after the safety regulations



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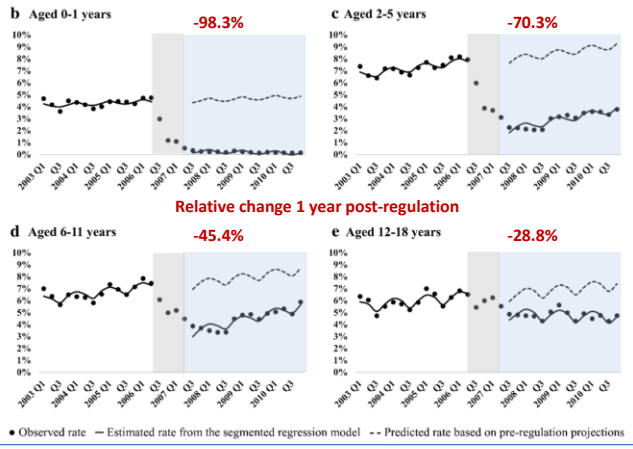
Main Results



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Conclusions

Real-world data to provide valuable information for future policymaking.

The importance of **continued assessments** to ensure sustained effectiveness of policy interventions

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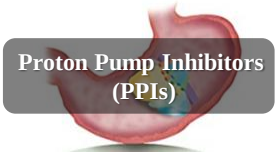
Proton Pump Inhibitors and Risk of Hepatocellular Carcinoma in Patients with Chronic Hepatitis B or C

HEPATOLOGY 2018 Sep 02

Chia-Hui Tan (Elise), PhD
National Research Institute of Chinese Medicine, Ministry of Health and Welfare, Taiwan
Director, Taiwan Society of Pharmacoeconomics and Outcome Research (TaSPOR)
Institute of Health Care Administration, National Yang-Ming University, Taiwan

Background



Adverse side effects

- Bone fracture/Enteric infection/pneumonia/ dementia/CKD…

CVD and CVA

- Myocardial Infraction
- Stroke

Developing cancer

- Gastric cancer
- Hepatocellular carcinoma (HCC)

Liver-related disease (HCV)

- Cirrhosis/Hepatic decompensation/HCC

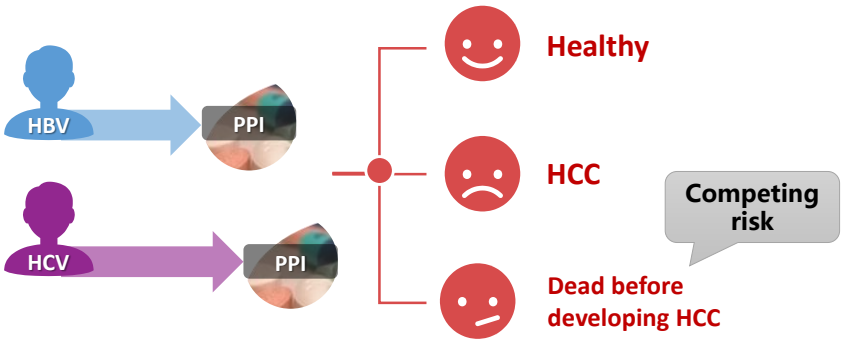
Background

- **Objective**

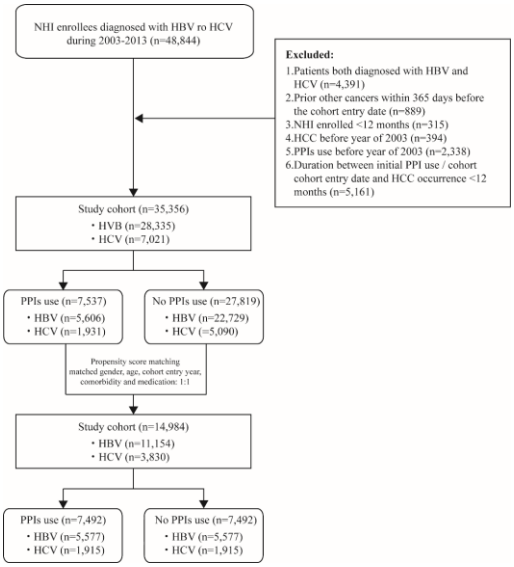
  To help elucidate the association between PPI use and the risk of developing HCC among patients with chronic HBV or HCV infections

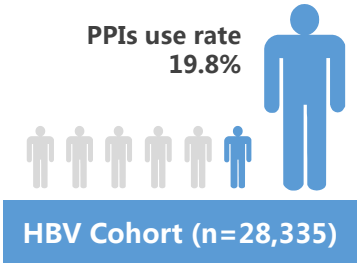
Methods

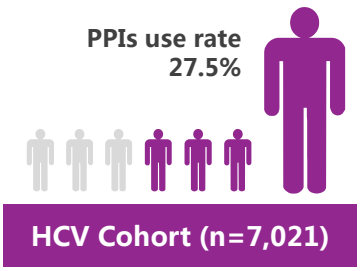
- **Longitudinal study and Propensity score matching (PSM)**
- **HBV or HCV cohort from 2003-2013**
  - The antiviral therapy for HBV and HCV was reimbursed by Taiwan's NHI since 2003



Main Results

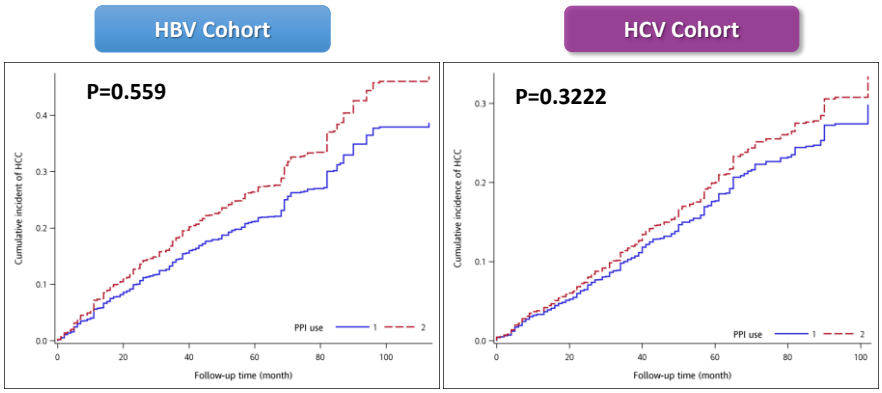






Main Results

Cumulative incidences of HCC after adjusting for competing mortality

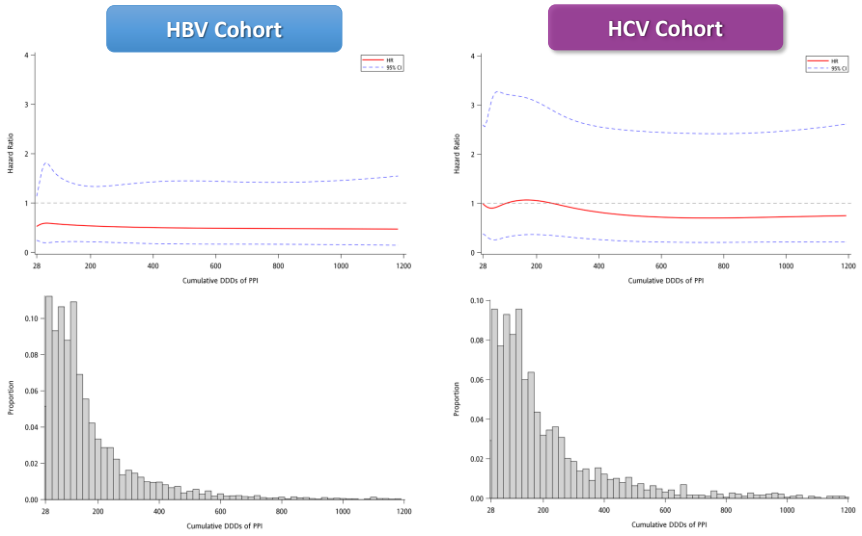


Main Results

	n	Follow-up time, median (IQR), months	IR per 1000 Person-months (95% CI)	IRR (95% CI)	aHR(95%CI) with competing risks	*P*
HBV cohort	11,154	53 (31-78)	0.38 (0.33-0.43)			
No PPIs use	5,577	53 (31-79)	0.33 (0.27-0.40)	1.00	1.00	0.18
PPIs use	5,577	53 (31-78)	0.42 (0.36-0.50)	1.30 (1.00-1.68)	1.25 (0.90-1.73)	
cDDD						
0-27	5,577	53 (31-79)	0.33 (0.27-0.40)	1.00	1.00	0.14
28-119	2,034	49 (27-76)	0.44 (0.33-0.59)	1.35 (0.96-1.90)	1.28 (0.79-2.06)	
120-364	1,868	49 (29-74)	0.46 (0.34-0.62)	1.41 (0.99-1.99)	1.34 (0.87-2.04)	
≥365	1,675	61 (38-85)	0.37 (0.26-0.51)	1.13 (0.78-1.64)	0.77 (0.48-1.26)	
HCV cohort	3,830	51 (30-78)	0.99 (0.86-1.13)			
No PPIs use	1,915	51 (29-77)	0.91 (0.74-1.11)	1.00	1.00	0.25
PPIs use	1,915	52 (30-79)	1.07 (0.88-1.28)	1.17 (0.90-1.54)	1.19 (0.88-1.61)	
cDDD						
0-27	1,915	51 (29-77)	0.91 (0.74-1.11)	1.00	1.00	0.08
28-119	562	49 (27-74)	1.20 (0.84-1.66)	1.32 (0.90-1.93)	1.44 (0.92-2.26)	
120-364	607	46 (26-73)	0.76 (0.49-1.13)	0.83 (0.53-1.30)	0.78 (0.46-1.30)	
≥365	746	60 (36-86)	1.20 (0.90-1.56)	1.32 (0.95-1.83)	1.32 (0.89-1.97)	

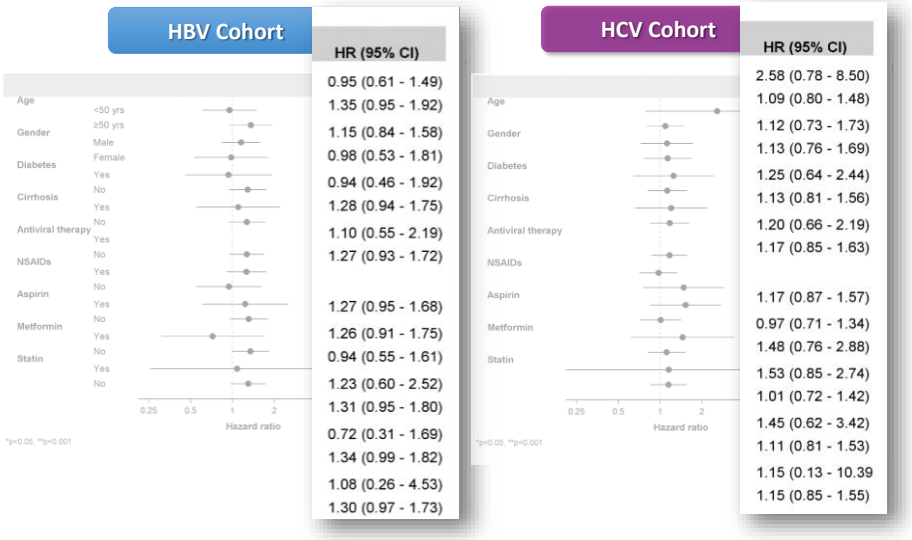
Main Results

Dose response curve for the hazard and 95% CI of HCC



Main Results

Subgroup analysis among patients with different baseline characteristics



Conclusions

Why

- **PPI use is not associated with the risk of developing HCC among patients with chronic HBV or HCV infections**
- **RWD could help to clinical decision making**
- **Standard protocol of RCT vs. real-world practice**

Thanks.

Any questions?
You can find me at

elisetam.g@gmail.com

Decision modelling: using trial and real world data (RWD)

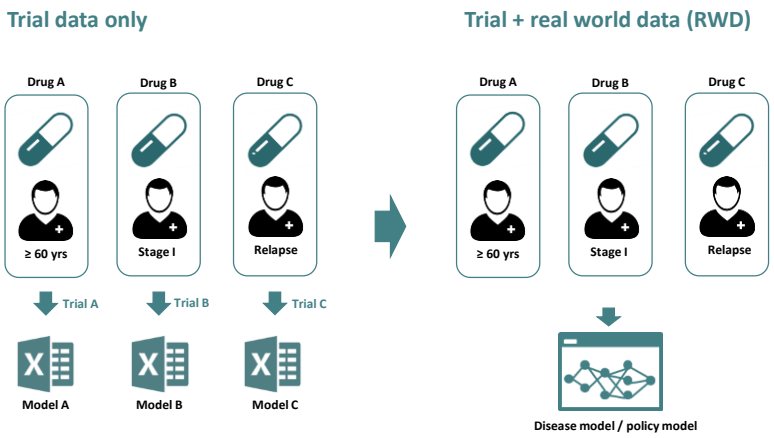
A Discrete Event Simulation Model on a UK Population Based Observational Cohort

Han-I Wang, PhD
Health Economist
University of York, UK

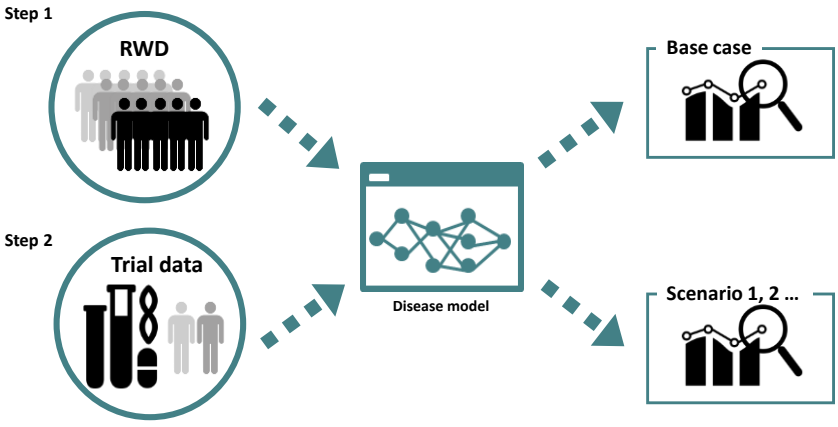
Current issues in decision modelling

Current issues in decision modelling

Objectives



The concept



VALUE IN HEALTH ▮ (2018) ▮▮▮–▮▮▮

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A Generic Model for Follicular Lymphoma: Predicting Cost, Life Expectancy, and Quality-Adjusted-Life-Year Using UK Population–Based Observational Data

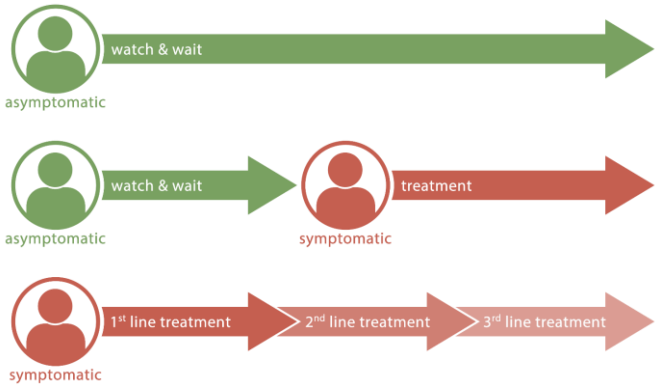
Han-I Wang, PhD[1,], Eve Roman, PhD[1], Simon Crouch, PhD[1], Eline Aas, PhD[2], Cathy Burton, MD[3], Russell Patmore, MD[4], Alexandra Smith, PhD[1]*

[1]*Epidemiology & Cancer Statistics Group (ECSG), Department of Health Sciences, University of York, York, UK;* [2]*Department of Health Management and Health Economics, University of Oslo; Oslo, Norway;* [3]*Haematological Malignancy Diagnostic Service, St. James's University Hospital, Leeds, UK;* [4]*Queen's Centre for Oncology and Haematology, Castle Hill Hospital, Hull, UK*

ABSTRACT

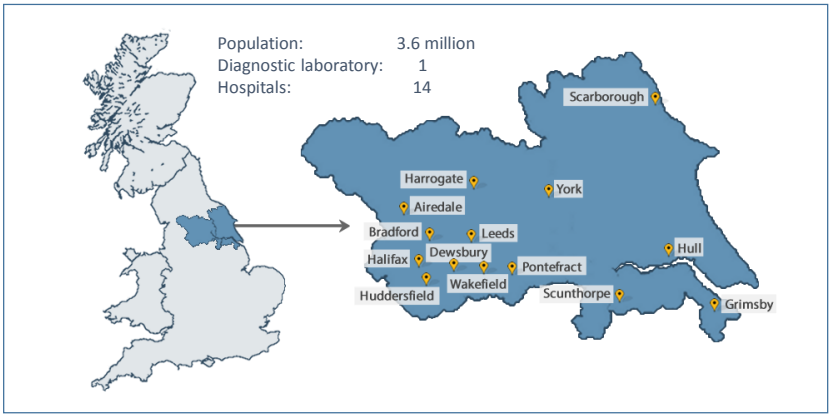
Objectives: To use real-world data to develop a flexible generic decision model to predict cost, life expectancy, and quality-adjusted life-years (QALYs) for follicular lymphoma (FL) in the National Health Service budget for hematological cancers as a whole. Assuming that treatment effects reported in trials are applicable to all patient groups, scenario analyses for two recent

Follicular lymphoma (FL)



1. Data source

Haematological Malignancy Research Network (HMRN, www.hmrn.org)



Epidemiology & Cancer Statistics Group (ECSG), University of York (www.hmrn.org)

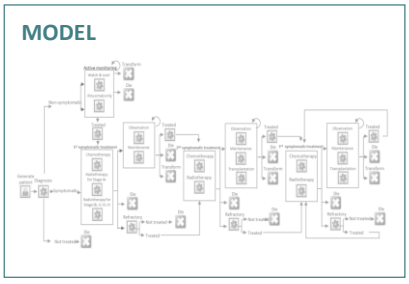
3. Base case results: two types of results

Incidence-based results

Prevalence-based results

Incidence-based results

No. of newly diagnosed FL per year in the UK (n=1860)



Source: Haematological Malignancy Research Network (HMRN, www.hmrn.org)

Incidence-based results

Results (5,000 iterations)

	Life time horizon			
	N	Cost (£) Mean (95% CI)	LYs Mean (95% CI)	QALYs Mean (95% CI)
Overall	1860	18,705 (18,631-18,781)	9.08 (9.06-9.11)	7.35 (7.34-7.37)
Observation only	550 (548-551)	5,296 (5,290-5,301)	8.22 (8.20-8.24)	7.40 (7.38-7.41)
Not Treated	37 (36-38)	6,165 (6,093-6,237)	0.21 (0.20-0.21)	0.12 (0.12-0.12)
Treated	1,273 (1,271-1,274)	24,872 (24,765-24,979)	9.72 (9.69-9.75)	8.46 (8.43-8.48)
1st line only	720 (717-722)	13,456 (13,388-13,525)	8.27 (8.24-8.31)	8.07 (8.06-8.14)
2nd line plus				
Without SCT	499 (497-502)	36,000 (35,828-36,171)	10.85 (10.81-10.90)	8.34 (8.30-8.38)
With SCT	77 (76-78)	60,261 (59,791-60,730)	15.79 (15.70-15.87)	12.15 (12.09-12.21)

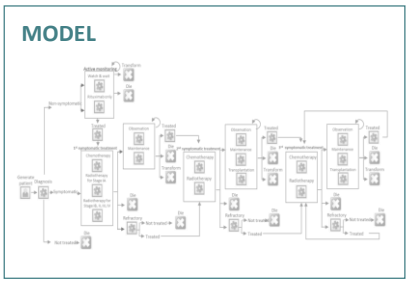
SCT: stem cell transplantation

Prevalence-based results

Base case

Allow burn-in period of 30 years

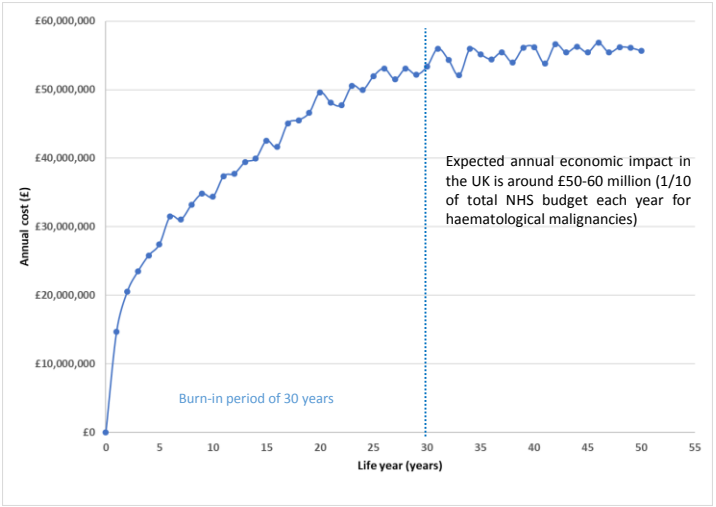
FL Incidence rate in the UK



Source: Haematological Malignancy Research Network (HMRN, www.hmrn.org)

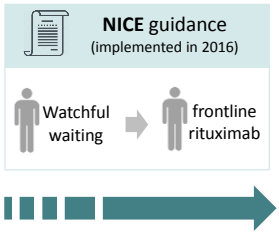
Prevalence-based results

Base case

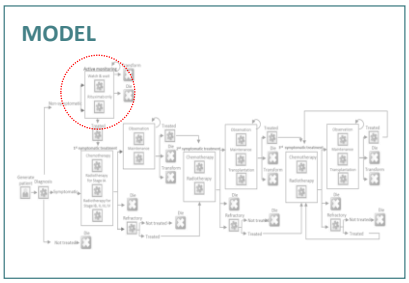


4. Scenario analysis

Frontline rituximab



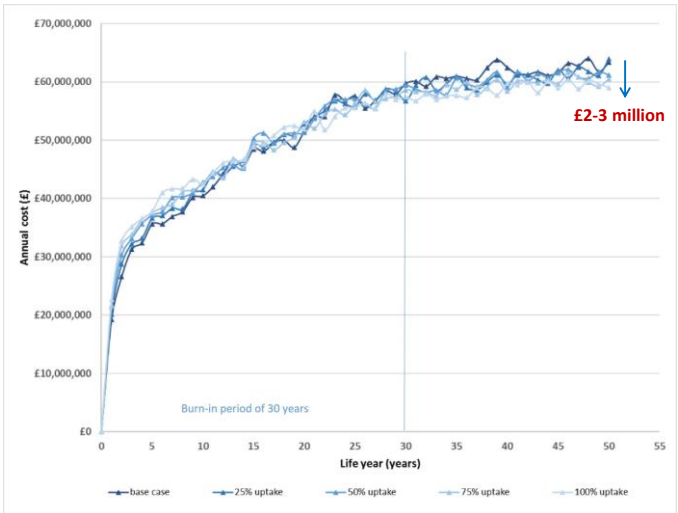
Allow burn-in period of 30 years



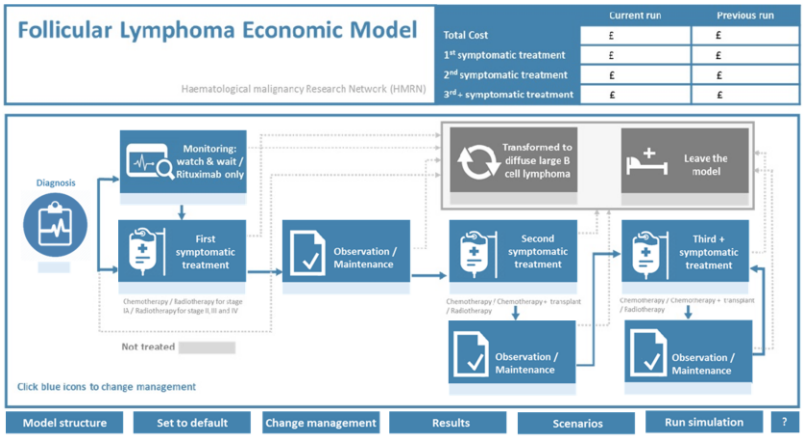
Time to start of new treatment: HR 0.35 (95% CI: 0.22-0.56)

Source: NICE guidance: www.nice.org.uk/guidance/ng52 and Ardeshna KM, Qian W, Smith P et al. (2014) Rituximab versus a watch-and-wait approach in patients with advanced-stage, asymptomatic, non-bulky follicular lymphoma: an open-label randomised phase 3 trial. The Lancet Oncology , 15(4), 424-435

4. Scenario analysis



5. Decision aid: model front end



https://www.hmrn.org/economics/models

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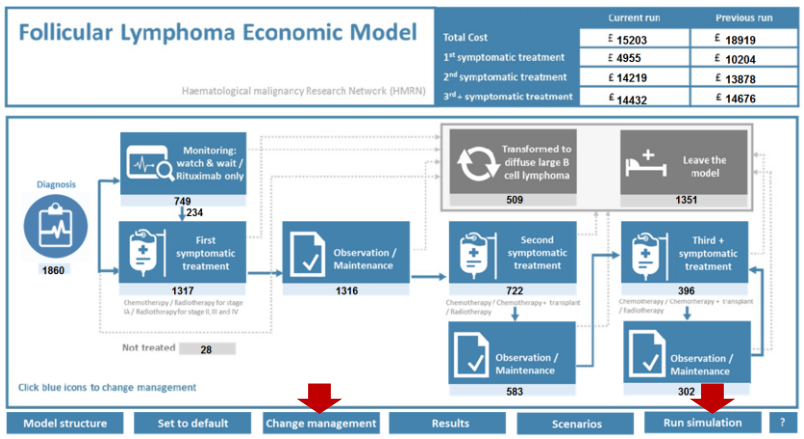

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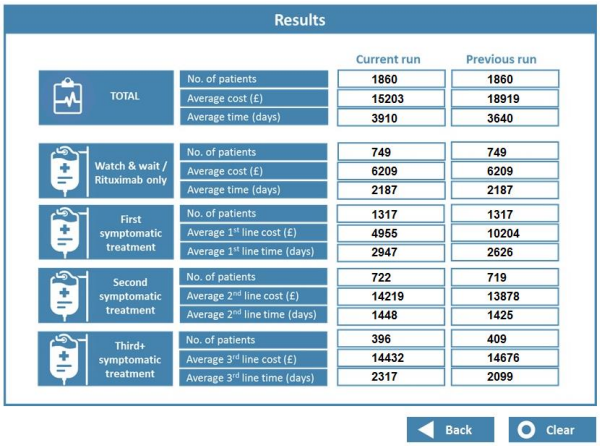

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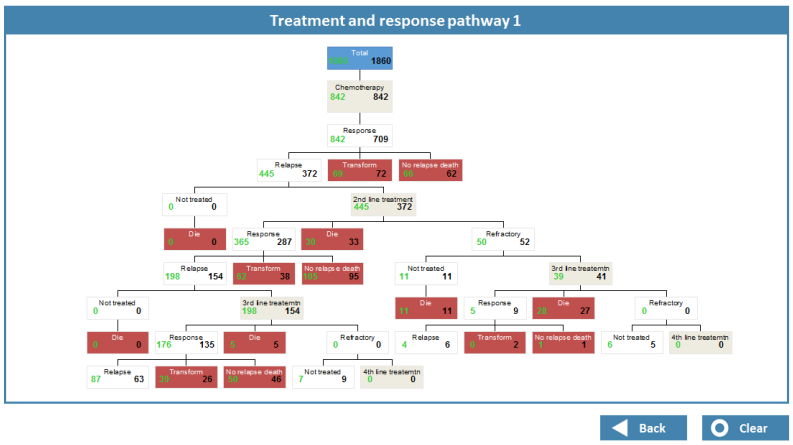

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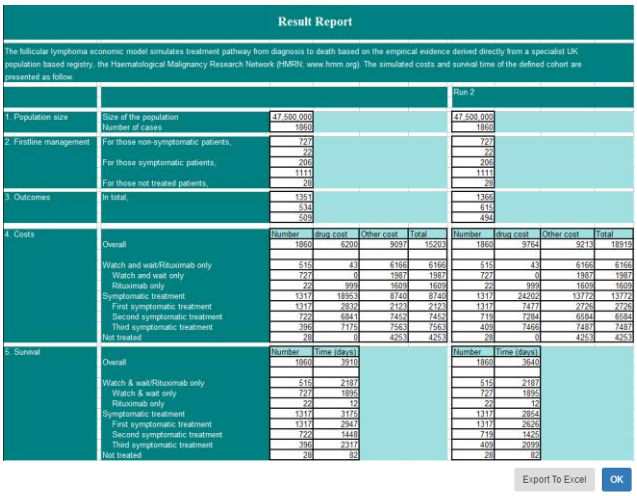

Result Report

The follicular lymphoma economic model simulates treatment pathway from diagnosis to death based on the empirical evidence derived directly from a specialist UK population based registry, the Haematological Malignancy Research Network (HMRN; www.hmrn.org). The simulated costs and survival time of the defined cohort are presented as follow.

		Run 2							
1. Population size	Size of the population	47,500,000				47,500,000			
	Number of cases	1860				1869			
2. Firstline management	For those non-symptomatic patients,	727				727			
		22				22			
	For those symptomatic patients,	206				206			
		1111				1111			
	For those not treated patients,	28				28			
3. Outcomes	In total,	1351				1366			
		534				613			
		505				494			
4. Costs		Number	drug cost	Other cost	Total	Number	drug cost	Other cost	Total
	Overall	1860	6200	9097	15203	1869	9764	9213	18919
	Watch and wait/Rituximab only	515	43	6166	6166	515	43	6166	6166
	Watch and wait only	727	0	1987	1987	727	0	1987	1987
	Rituximab only	22	999	1609	1609	22	999	1609	1609
	Symptomatic treatment	1317	18953	8748	8748	1317	24202	13772	13772
	First symptomatic treatment	1317	2832	2123	2123	1317	7477	2726	2726
	Second symptomatic treatment	722	6841	7452	7452	719	7284	6584	6584
	Third symptomatic treatment	396	7175	7563	7563	409	7466	7487	7487
	Not treated	28	0	4253	4253	28	0	4253	4253
5. Survival		Number	Time (days)			Number	Time (days)		
	Overall	1860	3910			1869	3640		
	Watch & wait/Rituximab only	515	2187			515	2187		
	Watch & wait only	727	1895			727	1895		
	Rituximab only	22	12			22	12		
	Symptomatic treatment	1317	3175			1317	2854		
	First symptomatic treatment	1317	2947			1317	2626		
	Second symptomatic treatment	722	1448			719	1425		
	Third symptomatic treatment	396	2317			409	2099		
	Not treated	28	82			28	82		

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https://www.hmrn.org/economics/models

Conclusion

- This is the **first study** to model individual FL patients through the entire treatment pathway using both **real-world evidence** and **trial data**.
- The model can predict **costs**, **life-years** and **QALYs** of entire FL treatment pathways.
- Future applications of the developed model could include evaluation of new technologies and interventions to **support healthcare decision-making**, especially in the era of personalised medicine.

Thank you for your attention

University of York
The Department of Health Sciences

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