The importance of integrating medication adherence in pharmacoeconomic analyses: the example of osteoporosis

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MTA Seminar. August, 25th 2011

Postdoctoral project (3-years)

- Preferences for osteoporosis treatment
- Development of a decision aid

Seminar

- ISPOR medication compliance and persistence special interest group
- *"The clinical and economic burden of poor adherence with osteoporosis medications in Ireland"*

  Hiligsmann M[1-2], McGowan B[3], Bennett K[3], Barry M[3] & Reginster JY[2]

  1 Maastricht University, 2 University of Liège 3 Trinity College of Dublin

  (ISPOR, poster & ESPACOMP, oral)
- *"The importance of integrating medication adherence in pharmacoeconomic analyses: the example of osteoporosis"*

  Expert Review of Pharmacoeconomics & Outcomes Research

Cost-effectiveness analysis

- Data from phase III clinical trials

⇒ cost-effectiveness of intervention/drug in clinical trial

- Data from phase IV (post-marketing)

⇒ cost-effectiveness of intervention/drug in the community

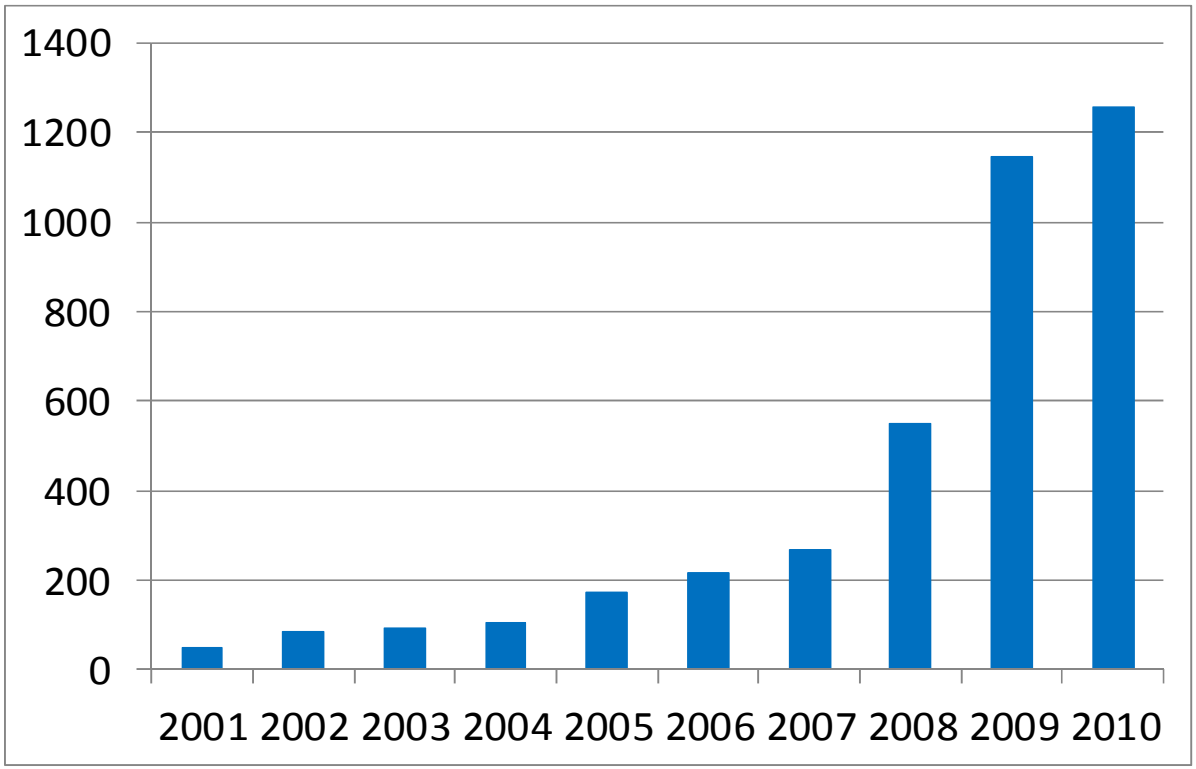
- Clinical effectiveness versus efficacy: poor compliance and failure to persist

Medication compliance and persistence

- Poor and suboptimal in chronic diseases
- ↓ treatment effectiveness
- Impact on healthcare costs (↓ therapy costs, ↑ disease costs)

⇒ May have an impact on cost-effectiveness

Medication compliance - a hot topic



Number of PubMed articles using “medication adherence” as search term

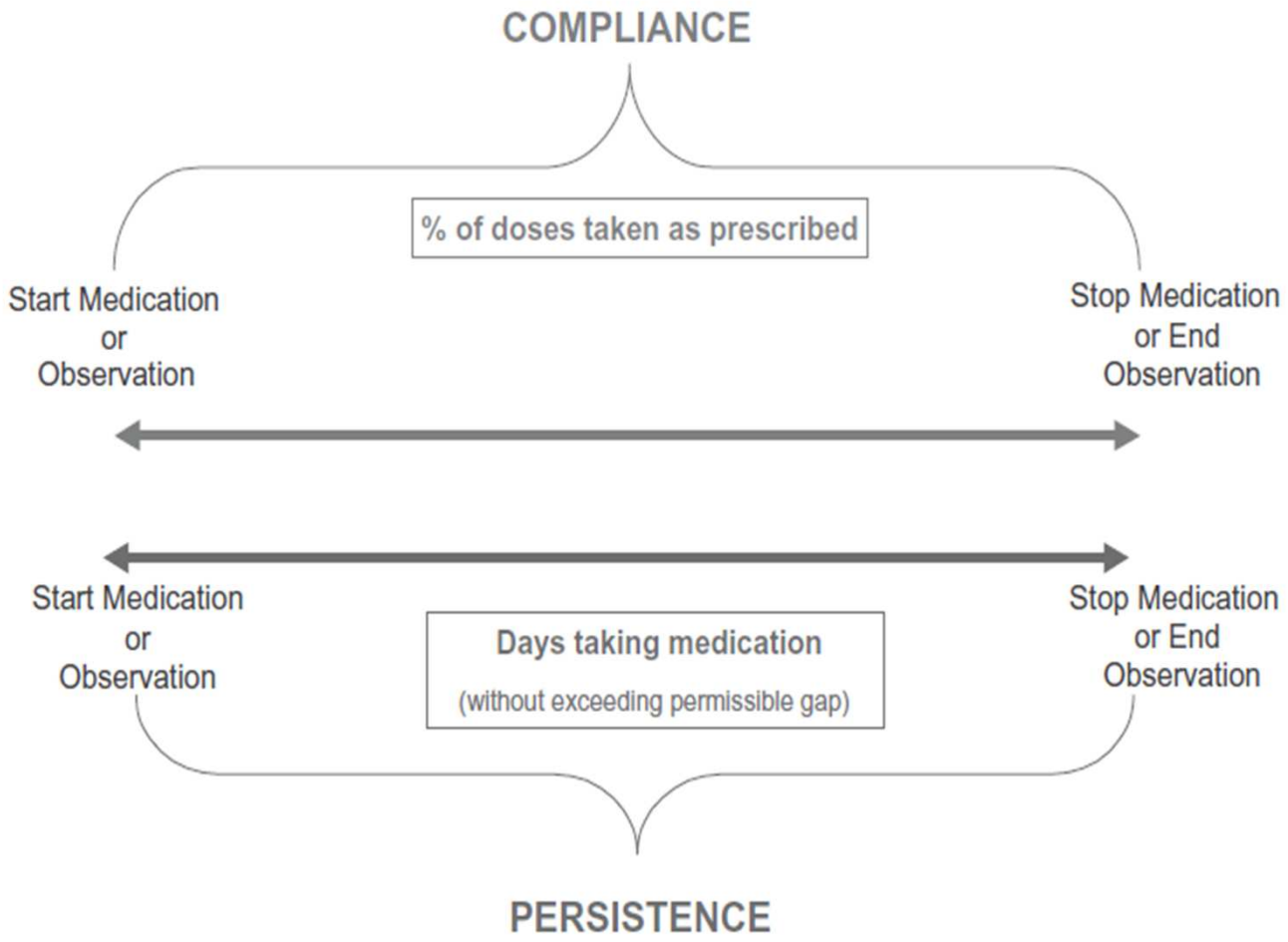
Definitions and measurement

Compliance (synonym 'adherence'): *"the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen"*

Persistence *"the duration of time from initiation to discontinuation of therapy"*

Cramer et al. Value Health 2008;11:44-47

CAPHRI School for Public Health and Primary Care



Cramer et al. Value Health 2008;11:44-47

- **Medication compliance**

  - MPR (Medical Possession Ratio) = *the number of doses taken divided by the number of doses prescribed*

  - Mean MPR over a period of time ~ Probability of being poorly or highly compliant

  - A threshold of 80% is most commonly used to define high compliance

- **Medication persistence**

  - Continuous variable = *the number of days*

  - Dichotomous variable measured at the end of a predefined time period (e.g. 12 months)

  - Which threshold regarding discontinuation period?

- **Direct assessment methods** (observation, serum drug concentration, biochemical analysis…)

  - High validity but costly and inconvenient

- **Indirect assessment methods** (e.g. retrospective prescription claims databases)

  - Lack the details of daily dosing (e.g. missing doses, wrong timing) => may overestimate adherence

  - Inexpensive

  - Often the only source available to assess compliance

Osterberg et al. N Engl J Med 2005;353:487–97
Cramer et al. Value Health 2008;11:44-47

« The clinical and economic burden of poor adherence with osteoporosis medications in Ireland »

What is already know on this topic

- Compliance and persistence with osteoporosis medications are poor and suboptimal
- Poor therapeutic adherence results in increased fracture rates

Objectives

- To assess compliance and persistence to OP medications in Ireland
- To quantify the clinical and economic effects of poor adherence
- To estimate the potential cost-effectiveness of hypothetical adherence-enhancing interventions

1. Compliance and persistence data

- Irish HSE-PCRS pharmacy claims database
- Years 2006-2009
- Aged over 55 years
- New users of anti-osteoporosis medications

	Men	Women
55-64 y	1,864	10,075
65-69 y	1,410	8,092
70-74 y	2,667	16,124
75+ y	6,672	36,378
Total	12,613	70,669

Table Persistence and compliance data in Irish women and men

Follow-up	6 month	1 year	1.5 years	2 years	2.5 years	3 years
Women						
Non-persistence	26.2%	35.7%	41.9%	47.3%	51.9%	55.0%
Poor compliance	13.1%	7.7%	5.9%	4.7%	4.1%	3.5%
High compliance	60.8%	56.6%	52.2%	48.0%	43.9%	41.5%
N persistent cases	52,192	42,819	35,925	30,051	24,983	20,781
Men						
Non-persistence	40.0%	51.8%	58.9%	64.0%	68.1%	70.6%
Poor compliance	10.0%	5.1%	3.4%	2.6%	2.3%	2.1%
High compliance	50.0%	43.2%	37.7%	33.5%	29.6%	27.3%
N persistent cases	7,569	5,557	4,246	3,323	2,567	1,991

**Refill gap period of 9 weeks; MPR ≥80% to define high compliance, <80% to define poor adherence*

Table Non-persistent patients according to different refill gap periods

Follow-up	6 month	1 year	1.5 years	2 years	2.5 years	3 years
Women						
5 weeks	31.4%	43.2%	51.1%	59.2%	64.6%	67.8%
9 weeks (BC)	26.2%	35.7%	41.9%	47.3%	51.9%	55.0%
13 weeks	22.5%	31.0%	36.7%	41.5%	45.8%	48.8%
Men						
5 weeks	45.4%	58.2%	66.1%	72.3%	76.5%	78.9%
9 weeks (BC)	40.0%	51.8%	58.9%	64.0%	68.1%	70.6%
13 weeks	36.7%	47.7%	54.9%	59.9%	64.1%	66.7%

BC base-case

Table Compliance data according to MPR thresholds*

Follow-up	6 month	1 year	1.5 years	2 years	2.5 years	3 years
Women						
MPR 70%	91.1%	93.5%	94.4%	95.0%	95.3%	95.6%
MPR 80% (BC)	82.3%	88.1%	89.9%	91.1%	91.2%	92.2%
MPR 90%	76.2%	73.3%	75.1%	75.5%	76.4%	77.5%
Men						
MPR 70%	91.9%	95.0%	95.8%	95.9%	96.2%	96.6%
MPR 80% (BC)	83.3%	89.5%	91.7%	92.7%	92.7%	93.0%
MPR 90%	75.8%	74.1%	76.2%	76.8%	77.4%	78.6%

* *Percentage of compliant patients among those who are persistent*

BC base-case

2. Simulation modelling

- Hiligsmann et al. Value in Health 2009;12:687-96
- Updated version: Hiligsmann et al. Pharmacoeconomics, 2011

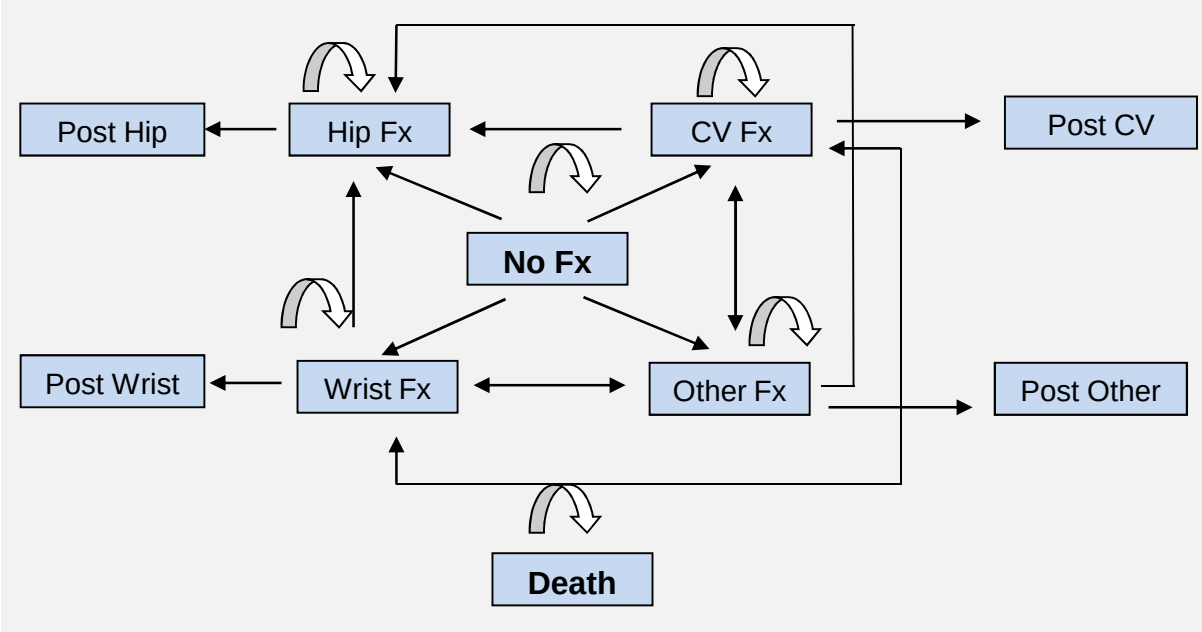
Outcomes

- Fracture events, costs and QALYs

Three adherence scenarios

- No treatment
- Real-world adherence
- Full adherence (over 3 years)

Markov microsimulation model *(TreeAge Pro 2011)*



Lifetime horizon

6-month cycle length

Post-fracture states

Tracker variables

CV clinical vertebral. Transitions to death and from post-fracture states to any fractures states, 'Death' and 'No Fx' were excluded from the graph for simplicity

Table Incidence (rate/1000) of the fracture at the sites shown by age in Ireland

Age range (years)	Hip	Clinical vertebral	Wrist	Other fractures
Women				
55-59	0.76	2.18	6.30	3.68
60-64	1.12	1.75	3.28	2.55
65-69	1.99	2.81	4.42	4.98
70-74	4.73	6.67	7.75	6.77
75-79	9.80	8.32	7.73	13.07
80-84	17.47	9.42	9.78	15.40
+ 85	32.97	14.63	12.36	35.10
Men				
55-59	0.39	0.55	0.69	4.40
60-64	0.62	1.97	1.22	2.31
65-69	1.51	1.81	2.11	5.56
70-74	2.02	3.38	0.60	5.18
75-79	5.68	5.61	1.59	6.91
80-84	10.69	6.56	1.82	22.47
+ 85	20.01	14.13	3.82	28.67

Hip fractures (Health Atlas Ireland, 2008)

Non-hip fractures

Increased risk with osteoporosis

Increased risk when new fractures occur during the simulation

Mortality rates (Central Statistics office in Ireland)

Excess mortality after hip and CV fractures

Table Cost (€2008) of fractures at the sites shown by age in Ireland

Age range (years)	Hip	Clinical vertebral	Wrist	Other fractures
Women				
50-54	10,920	1899	1582	1896
55-59	11,215	1950	1624	1947
60-64	11,421	1986	1654	1983
65-69	12,168	2116	1762	2112
70-74	12,607	2193	1826	2189
75-79	12,710	2210	1841	2206
80-84	13,140	2285	1903	2281
+ 85	13,099	2278	1897	2274
Men				
50-54	10,788	1876	1562	1873
55-59	12,053	2096	1746	2093
60-64	12,890	2242	1867	2238
65-69	14,043	2442	2034	2438
70-74	13,182	2293	1909	2288
75-79	13,460	2341	1949	2337
80-84	13,384	2328	1938	2324
+ 85	13,396	2330	1940	2326

Healthcare payer

Hip fractures
(Hospitalisation cost: Health Atlas Ireland, 2008)

Non-hip fractures

Long-term cost for hip fractures

- Admissions to nursing home
- Probabilities + cost
- Adjustment

Table Health states utility values

Parameter	Data
Reference values	
Women	0.83 (60-69 y), 0.77 (70-79 y) and 0.72 (80-105 y)
Men	0.84 (60-69 y), 0.78 (70-79 y) and 0.71 (80-105 y)
Multipliers for the proportionate effect of a fracture on utility	
Hip (1st year / subs years)	0.80 / 0.90
CV (1st year / subs years)	0.72 / 0.93
Wrist (1st year / subs years)	0.94 / 1.00
Other (1st year / subs years)	0.91 / 1.00

Systematic literature review

Subsequent fractures

Hiligsmann et al. Calcif Tissue Int 2008;82:288-92

Drug therapy

- Oral bisphosphonates (>80%)

Efficacy

- NICE meta-analysis
- Hip (-29%), Vertebral (-42%), Wrist and Other (-22%)
- Linear decrease after stopping therapy

Costs

- Mean drug cost for patients taking OP medications: €422 (Women) & €417 (Men) HSE-PCRS database
- Monitoring cost: one yearly physician visit (€65) & one densitometry every second year (€90) Irish Osteoporosis Society

No adverse events

Incoporating persistence and compliance in modelling

Persistence

- At risk of discontinuation within 3 years
- Treatment effect reduced by half in the dropout cycle
- For those who early discontinued, no treatment effect + specific cost
- Patients who discontinued therapy can restart therapy after one cycle without treatment (re-initiation rates at one year: 25.4% women and 21.5% in men)

Compliance

- Relative risks from the NICE meta-analysis for compliant patients
- Lower efficacy for poorly compliance (RR=1.17) (Huybrechts et al. 2007)
- Drug costs adjusted by mean MPR in the group

Analyses and simulation

- Patients stratified into groups according to sex (female/male) and age (55–64 years, 65–69 years, 70–74 years, and 75+ years)
- Monte-Carlo microsimulations: 200,000 trials and 10 samples

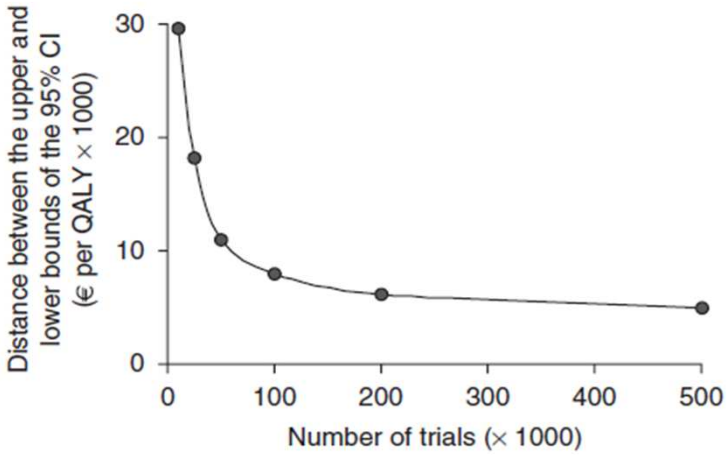


Fig. 2. Model validation: distance between the upper and lower bounds of the 95% CI of the cost effectiveness of denosumab compared with generic alendronate for a varying number of trials run ten times (in women aged 70 years with bone mineral density T-score –2.5 or less).

Model validation

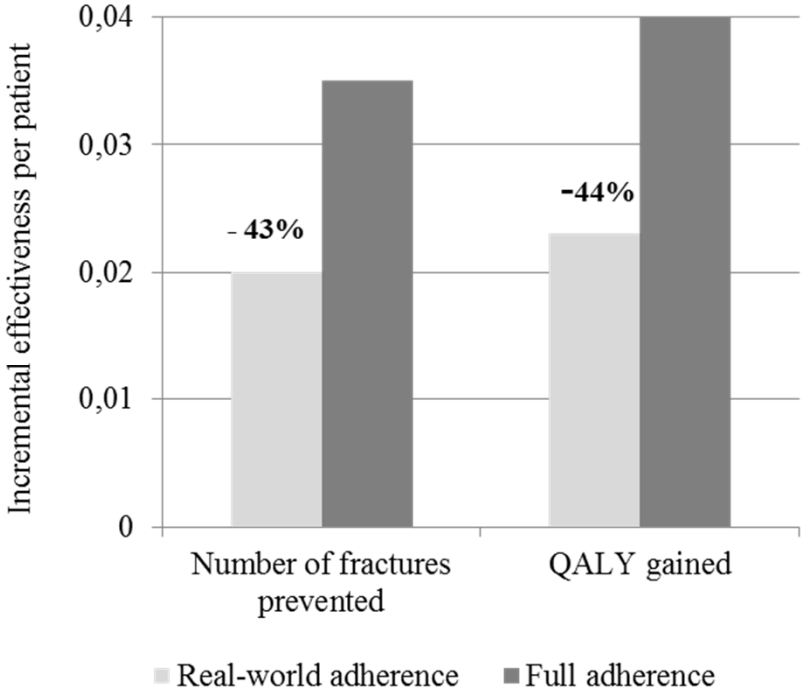
- Absolute lifetime risks of fractures
- Tests on parameters

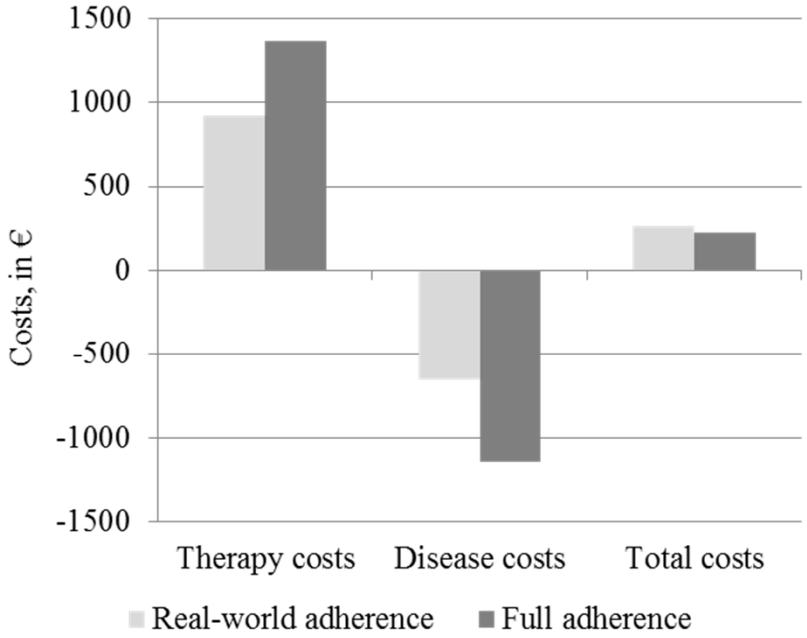
Hiligsmann et al. Pharmacoeconomics, 2011

Results Base-case analysis

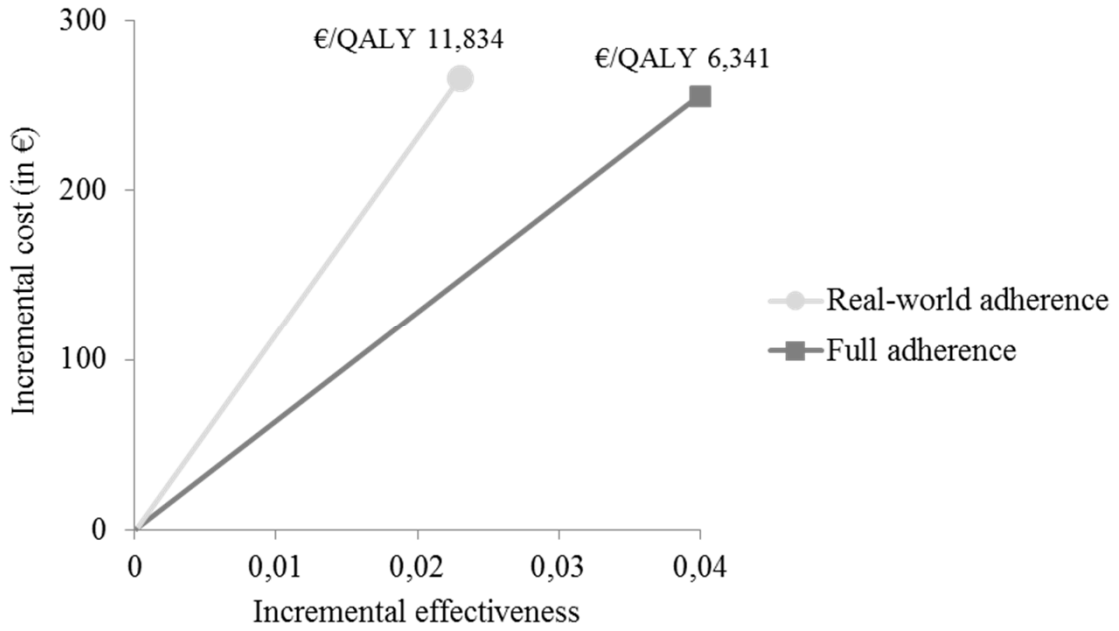
Follow-up	Adherence scenario			Incremental values		
	No Treat	RW	Full	RW vs No Treat	Full vs No Treat	Full vs RW
Patient cost over lifetime						
Treatment cost	0	922	1395	922	1395	473
Disease cost	11,425	10,769	10,284	-656	-1140	-485
Total cost	11,425	11,691	11,679	266	255	-12
Lifetime number of fractures per patient						
Hip	0.495	0.475	0.460	-0.020	-0.035	0.015
Overall	1.320	1.269	1.229	-0.052	-0.092	-0.040
QALYs per patient	6.638	6,661	6.678	0.023	0.040	0.017
ICER (cost per QALY gained)				**11,834**	**6,341**	**-659**
(95% CI)				*(11,197-12,470)*	*(5,944-6,739)*	*(-1,488 - 171)*

Results Impact of poor adherence on effectiveness and costs





Results Cost-effectiveness plane. The incremental cost-effectiveness ratio is represented by the slope of the line from the origin



Results Number (95% confidence interval) of hip and of all osteoporotic fractures due to poor adherence, according to sex and age groups

	55-64 y	65-69 y	70-74 y	+ 75y	Total
Hip fractures					
Women	41 (36-46)	71 (67-74)	231 (221-242)	752 (722-781)	1094 (1064-1125)
Men	8 (7-9)	10 (9-11)	37 (36-38)	121 (117-126)	177 (172-181)
Total	49 (44-53)	81 (77-84)	268 (258-279)	873 (842-904)	**1271** (1238-1304)
All osteoporotic fractures					
Women	149 (141-156)	236 (230-242)	655 (638-671)	1774 (1735-1831)	2814 (2771-2856)
Men	32 (30-33)	34 (33-35)	95 (93-96)	366 (359-374)	527 (519-535)
Total	180 (173-188)	270 (263-277)	749 (732-767)	2140 (2100-2181)	**3340 (3295-3386)**

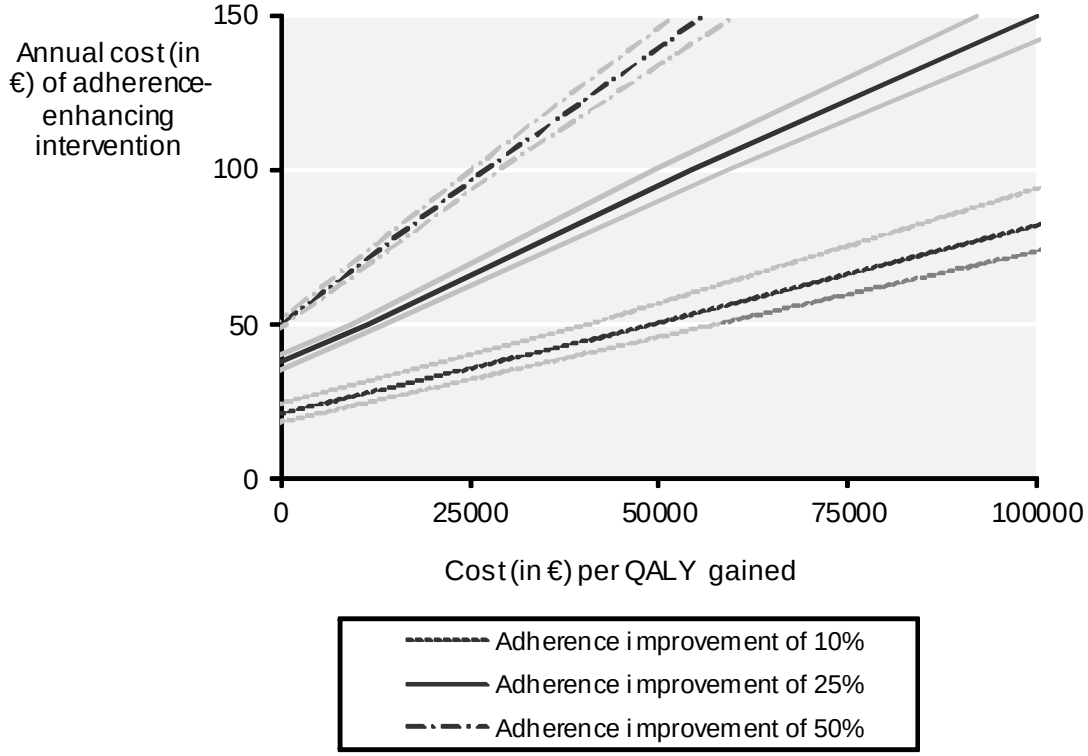
Results Sensitivity analyses on the clinical burden (expressed in % of QALY gain and in number of osteoporotic fractures) of poor adherence with osteoporosis medications

	% of QALY gain	Number of fractures
Base-case analysis	56.3 (54.5-57.5)	3,340 (3,295-3,386)
Women	57.6 (56.2-59.1)	2,814 (2,771-2,856)
Men	44.7 (42.6-46.8)	527 (519-535)
5-week refill gap	50.9 (49.1-52.7)	3,779 (3,741-3,818)
13-week refill gap	59.9 (58.2-61.6)	3,062 (3,033-3,092)
Full compliance	59.7 (58.2-61.2)	3,191 (3,152-3,229)
MPR of 90%	54.7 (53.3-56.1)	3,612 (3,579-3,645)
MPR of 70%	58.0 (56.9-59.2)	3,266 (3,239-3,294)
Treatment efficacy +20%	58.0 (56.9-59.1)	3,985 (3,952-4,017)
Fracture risk +25%	54.5 (52.7-56.3)	4,342 (4,295-4,388)
Fracture risk -25%	57.4 (56.1-58.5)	2,405 (2,375-2,435)

Results Cost-effectiveness (expressed in cost (in €) per QALY gained) between adherence scenarios according to age and sex

	RW vs No Treat	Full vs No Treat	Full vs RW
Women			
55-64 y	69,704	57,033	40,574
65-69 y	29,127	18,579	5,465
70-74 y	10,221	4,313	-3,635
+ 75 y	1,823	-2,111	-7,587
Total	10,253	4,878	-2,437
Men			
55-64 y	78,409	56,438	38,899
65-69 y	46,183	35,013	25,514
70-74 y	27,921	15,750	6,514
+ 75 y	15,661	8,932	3,393
Total	26,159	16,625	8,916

Results Cost-effectiveness (expressed in cost (in €) per QALY gained) of hypothetical adherence-enhancing interventions according to their cost and effect on adherence. The cost-effectiveness is graphically presented by the black lines and the grey lines represent the lower and upper limits of the 95% confidence interval



A 25% adherence improvement:

- *50€ per year:* €11,511/QALY (95% CI €9,238-€13,784)
- *100€ per year:* €54,182/QALY €50 and

Results Sensitivity analyses on the cost-effectiveness (expressed in cost (in €) per QALY gained) of adherence-enhancing interventions

	Adherence improvement		
	10%	25%	50%
€100 per year of treatment			
Base-case	128,621	54,182	26,999
Men	128,898	60,914	35,509
Women	128,574	52,951	25,482
+75 years	110,509	41,859	18,549
One-shot cost			
€100	32,906	-5,686	-15,571
€200	95,245	19,790	-4,394
€300	157,565	45,266	7,445
€400	216,894	70,741	18,953

Discussion – Key findings

- Approximately 50% of the benefits of osteoporosis medications are lost due to poor compliance and persistence
- More than 90% resulting from non-persistence
- Poor adherence with osteoporosis medications results in a doubling of the cost per QALY gained from these medications
- Impact of definitions for persistence and compliance
- Programs to improve adherence have the potential to be an attractive approach to improve the allocation of resources

Discussion – Limitations

- Underestimation of the burden of poor adherence (prescription refill rates + primary adherence not included)
- Highly compliant patients achieved reductions in fracture risk based on meta-analysis from published clinical trials
- Modelling assumptions (non-hip fracture data)
- Impact of poor compliance on fracture efficacy not available in Ireland

Discussion – Implications

- Poor adherence = the critical hurdle to osteoporosis management
- Improving adherence is urgently needed BUT complex
- Systematic review (ISPOR special interest group): most effective interventions are the monitoring of patients by nursing staff and patient education
- New therapies with longer dosing regimens

⇒ Importance of understanding patient's preferences for osteoporosis treatments and of developing strategies to improve adherence (e.g. involving patients into clinical decision-making) – Postdoctoral project

Discussion – Implications

- Persistence and compliance = important determinants of cost-effectiveness analyses
- Not only in osteoporosis but many chronic diseases

⇒ Persistence and compliance should be an integral part of pharmacoeconomic analyses

- Lack of inclusion could bias the results and lead to suboptimal allocation of resources (Hiligsmann et al. Pharmacoeconomics, 2011)

Discussion – Implications

- Some challenges: improving definitions and measurement, epidemiologic survey (treatment-specific), efficacy and effectiveness data for high compliance, real-life effectiveness and adherence data…
- To assess the cost-effectiveness of specific adherence-enhancing programs

Thank you for your attention