

Compliance and Persistence: Capturing the Economic Benefits

Amgen Symposium at ISPOR 2009
Tuesday, 27th October
07:00 – 08:00
Amphithéâtre Bordeaux

Agenda

Welcome & Introduction

Chair: Rob Horne

Understanding Poor Adherence: Causes and Solutions

Rob Horne

Measuring Adherence in the Real World

Tjeerd-Pieter van Staa

The Economic Value of Improved Adherence

Oskar Ström

Q&A session

Summary & Conclusion

Chair: Rob Horne

Compliance and Persistence: Capturing the Economic Benefits

Welcome & Introduction

Rob Horne

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Behaviour as the Rate Limiting Step Between Effective Treatments and Health Gain



Neanderthal creativity

Effective treatments



BEHAVIOUR

PRESCRIBER

PATIENT - adherence



Optimum outcomes

Poor Adherence to Medicines



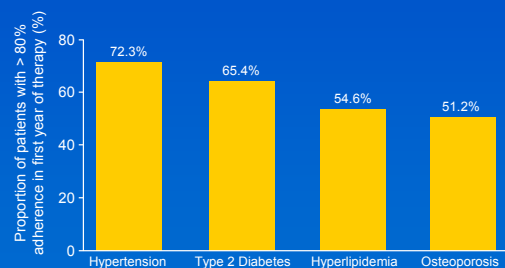
WHO REPORTS, NIHR POINTS:

- Estimated that between 30–50% medicines prescribed for long-term conditions are not taken as directed¹.
- If prescription was appropriate, then this represents a loss for patients, the NHS and pharma industries².
- Effective interventions are elusive^{3,4}.

“Poor medication adherence is the primary reason for suboptimal clinical benefit of therapy.”¹

1. World Health Organization Report, 2003. 2. Horne R, et al. National Co-ordinating Centre for NHS Service Delivery and Organisation R&D, London, 2005. 3. Haynes RB, et al. *Lancet* 1996. 4. Haynes RB, et al. *Cochrane Database Syst Rev* 2002.

Poor Adherence is Common in Chronic Conditions



Lekkerkerker F, et al. *Osteoporos Int* 2007.
Briesacher BA, et al. *Pharmacotherapy* 2008.

Understanding Poor Adherence: Causes and Solutions

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Interventions to Improve Adherence: Series of Cochrane Systematic Reviews

- A series of 10 Cochrane Reviews reported interventions to improve adherence in 10 disease settings in the last five years¹.
- **GOOD NEWS:** Adherence can be improved – it is a changeable behaviour.
- **BAD NEWS:** Previous interventions have had disappointing effects – even the best achieve only small and short-lived improvements.
- Comprehensive review for NIHR² identified why and what we should do about it:
 - Limitations in the design of interventions and the way they were tested.
 - Failure to understand and address the real causes of poor adherence with content often based on myths.
- We need to dispel these...

1. Cochrane Database of Systematic Reviews: Gray, 2009; Halpern, 2006; Haynes, 2007; Renz, 2007; Bosch-Capblanch, 2007; Jordan, 2006; Ruzick, 2006; Vermeire, 2005; Schedlbauer, 2004; Schroeder, 2004.
 2. Horne, National Co-ordinating Centre for NHS Service Delivery and Organisation R&D, London, 2005.

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Myth 1: Poor Adherence is a Feature of the Disease

- Poor adherence is not linked to the type of disease.
- Low adherence rates are problematic in most chronic diseases, e.g.
 - HIV¹
 - Cancer²
 - Heart disease³

1. Friedland, AIDS 1999. 2. Lilleyman, BMJ 1996. 3. Horwitz, Lancet 1990.

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Myth 2: The 'Non-Compliant' (Deviant) Patient




- No clear and consistent links between adherence and age, gender, intelligence, marital status etc.
- Findings are inconsistent, e.g. poor adherence linked to older age in some studies and to younger age in others.

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Adherence Rates Vary

Between patients Within the same patient over time and across treatments



Most of us are non-adherent some of the time!

Horne, National Co-ordinating Centre for NHS Service Delivery and Organisation R&D, London, 2005.

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Myth 3: Simplifying the Regimen and Reducing 'Pill-Burden' Solves the Problem of Poor Adherence

- Simplifying the regimen can be helpful for some patients¹.
- **BUT...** this alone will not solve the adherence problem.
- Complexity *per se* is not the key issue, but how well the treatment fits in with the individual patient's routine, expectations and preferences.

1. Claxton, Clin Ther 2001.

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Myth 4: Providing Clear Instructions/Information is Enough

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The Information-Action Gap

Information **X** Action

Information is essential to enable adherence, BUT... giving more information does not guarantee adherence

Beliefs

This is a common problem in healthcare – we have an information-action gap

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Information and Beliefs: a Thought Experiment

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Information and Beliefs: a Thought Experiment

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Perceptions & Practicalities Model of Adherence

UNINTENTIONAL poor adherence

Capacity & resources

Practical barriers

INTENTIONAL poor adherence

Motivational Beliefs/preferences

Perceptual barriers

Horne, In: Taylor & Harding (Eds.), *Pharmacy Practice*. London, 2001.

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What are the Salient Beliefs Influencing Medication-Taking Behaviour?

We need a simple framework that can explain poor adherence across illnesses and groups (e.g. defined by ethnicity, sociodemographics etc.).

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Beliefs about Medicines Questionnaire (BMQ)

SPECIFIC BELIEFS
about medicines prescribed for a particular illness

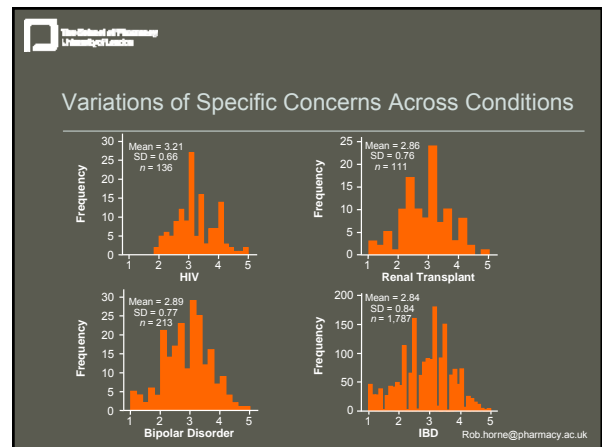
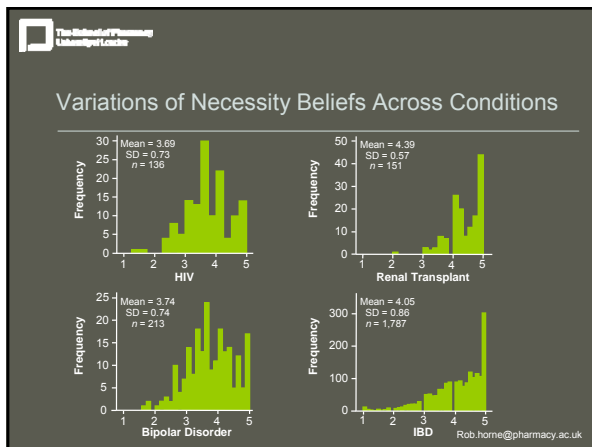
GENERAL BELIEFS
about medicines as a whole – pharmaceuticals as a class of treatment

Home, *Psychology and Health* 1999. Rob.horne@pharmacy.ac.uk

SPECIFIC BELIEFS
Views about prescribed medication

Necessity
Beliefs about personal need for medication to maintain/improve current and future health

Concerns
Arising from beliefs about potential negative effects



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The Necessity-Concerns Framework

Studies across range of illnesses, countries and cultures indicate that the **Necessity-Concerns Framework** is useful for explaining poor adherence.

Poor adherence

Doubts about personal NECESSITY of medication

CONCERNS
About potential adverse effects

- Renal dialysis¹
- HIV/Aids⁶
- Renal transplantation²
- Haemophilia⁷
- Asthma³
- Depression⁸
- Cancer⁴
- Bipolar disorder⁹
- Coronary heart disease⁴
- Rheumatoid arthritis¹⁰
- Hypertension⁵
- General practice – new medicines¹¹

1. Horne, *Int J Pharm Pract* 2001. 2. Butler, *Nephrol Dial Transplant* 2004. 3. Horne, *Psychol Health* 2002. 4. Horne, *J Psychosom Res* 1999. 5. Ross, *J Hum Hypertens* 2004. 6. Horne, *J AIDS* 2007. 7. Llewellyn, *Psychol Health* 2003. 8. Alkens, *Ann Fam Med* 2005. 9. Clatworthy, *Bipolar Disord* 2007. 10. Neame, *Rheumatology* 2005. 11. Clifford, *J Psychosom Res* 2008.

Home, in: Petrie & Weinman (Eds.), *Perceptions of Health and Illness: Current Research and Applications*. London, 1997; Horne, in: Cameron & Leventhal (Eds.), *The Self-regulation of Health and Illness Behaviour*. London, 2003; Horne, in: Halligan & Aylard (Eds.), *The Power of Belief*. Oxford, UK, 2006. Rob.horne@pharmacy.ac.uk

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Segmentation: Belief Groups and Adherence

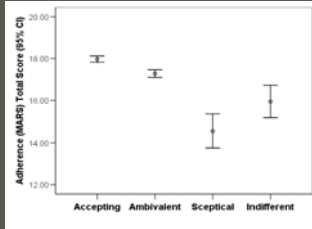
N = 1871 (A survey of 1 in 10 members of the National Association of Crohn's and Colitis)

	Low Necessity	High Necessity
High Concerns	Sceptical n = 110 (6%)	Ambivalent n = 746 (42%)
Low Concerns	Indifferent n = 75 (4%)	Accepting n = 847 (48%)

Home, *Inflamm Bowel Dis* 2009. Rob.horne@pharmacy.ac.uk

N = 1871 (A survey of 1 in 10 members of the National Association of Crohn's and Colitis (NACC))

Accepting group had higher adherence than all others
($F(3,210.44) = 36.99, p < 0.001$):



Accepting group > Ambivalent group ($p < 0.001$) > Sceptical ($p < 0.001$) and Indifferent groups ($p < 0.01$).

Telephone-Based Advice by Pharmacist Improves Adherence



- Pharmacist follow-up from centralised telephone service 10 days after new prescription from community pharmacy.
- 500 patients entered were randomised to intervention vs. care as normal.
- 12 minute call from pharmacist resulted in significantly:
 - More positive beliefs about medicines (necessity-concerns)
 - Higher adherence
 - Fewer patients reporting medication-related problems

Need to First Consider How Our Messages are Likely to be Received by the Patient: They are not a Blank Canvas



Common-Sense Perceptions of Illness and Treatment – a Question of Fit



Judging Personal Need for Maintenance Treatment without Symptoms

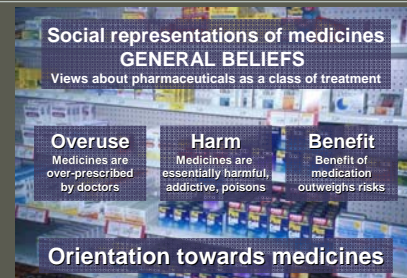
Taking maintenance treatment does not make you feel better (contrast with 'as needed' medicines)

Missing doses may not immediately make you feel worse

Potentially reinforcing perception that maintenance treatment does not matter to me

- Many patients do not have a clear 'common-sense' rationale for why maintenance treatment is necessary... 'no symptoms, no problem'
- Contrast between short- vs. long-term consequences

Common-Sense Origins of Medication Concerns



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Common-Sense Origins of Medication Concerns

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Need to 'Translate' PIL Lists of All Possible Side-Effects into Relative Risk Assessments

PIL package insert label.
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The Perceptions & Practicalities Approach

Home, In: Cameron & Leventhal (Eds.), *The Selfregulation of Health and Illness Behaviour*. London, 2003. Home, National Co-ordinating Centre for NHS Service Delivery and Organisation R&D, London, 2005.
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Perceptions & Practicalities Approach to Facilitate Informed Adherence

Perceptual

- Provide a 'common-sense' rationale for NECESSITY that is consistent with patients' symptom experiences and expectations – short- vs. long-term effects
- Elicit and address individual CONCERNS about potential adverse effects

Practical

- Tailor a convenient regimen and address practical barriers

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Product PLUS Beyond Medicines to Facilitated Self-Management

- Support to help patients understand relative risk and benefits
- Communication aids and support initiatives to help busy practitioners identify and meet individual patient needs
- Phase 4 studies including patient perspectives and experiences
- We need methods to target support to those who need it – we need to measure adherence

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Measuring Adherence in the Real World

Tjeerd-Pieter van Staa^{1,2}

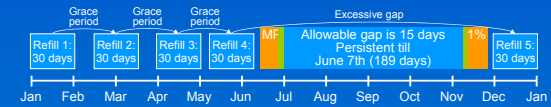
¹General Practice Research Database, London, United Kingdom
²Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, the Netherlands

Introduction

- Compliance: adherence to dosage instructions (e.g. once daily) – quality aspect
- Persistence: duration of treatment – quantity aspect
 - Persistent compliant patients
 - Non-persistent compliant patients
 - Persistent non-compliant patients
 - Non-persistent non-compliant patients
- Measuring compliance and persistence is challenging.
 - Focus on database
- Economic modelling requires data on drug effect, event rates, patient population, and costs.
- Observational studies can provide valuable information for economic modelling.

Possible Approaches to the Classification of Patients Based on Prescription Data

- Adherence can be calculated based on:
 - Medication Possession Ratio (MPR)
 - Medication possession at a fixed point in time
- Persistence can be calculated based on:
 - Gaps between refills
- Classification of patients will vary depending on the approach used.



- Painting the most accurate picture of an individual's adherence to medication may require multiple different measures and techniques.

Sikka R, et al. *Am J Manag Care* 2005;11:449-57.

Methodological Issues Faced in Measuring Adherence in Database Studies

- Prescription does not equal drug intake by patients – 'patient with a plastic bag'.
- Investigator needs to define grace periods and allowable gaps.
- Data gaps in records – e.g. hospitalisation.
- Confounding – less compliant patients are not the same as compliant patients.

Methodological Considerations in the Assessment of Effectiveness in Observational Studies

Good Research Practices for Comparative Effectiveness Research: Approaches to Mitigate Bias and Confounding in the Design of Nonrandomized Studies of Treatment Effects Using Secondary Data Sources: The International Society for Pharmacoeconomics and Outcomes Research Good Research Practices for Retrospective Database Analysis Task Force Report—Part II

Emily Cox, PhD,¹ Bradley C. Martin, PharmD, PhD,² Tjeerd Van Staa, PhD, MD, MSc, MA,³ Edeltraut Garbe, MD, PhD,⁴ Uwe Siebert, MD, MPH, MSc, ScD,⁵ Michael L. Johnson, PhD⁶

Cox E, et al. *Value Health* 2009; doi:10.1111/j.1524-4733.2009.00601.x.

RCTs versus Observational Studies: a Spurious Debate?

Which clinical studies provide the best evidence?

The best RCT still trumps the best observational study

Barton S. *BMJ* 2000;321:255-256.

Cost-Efficacy versus Cost-Effectiveness Models: Ideal Data Requirements

	Efficacy models	Effectiveness models
Drug effects	Phase III RCT	Pragmatic RCT
Event rates	Phase III RCT (averages)	Observational data (individual patient data)
Costs	Phase III RCT (single)	Observational data (heterogeneous)
Patient characteristics	Licensed indication (Phase III RCT)	Observational data (all likely indications)
Exposure characteristics	100% compliant and persistent	Observational data (exposure 'as is')

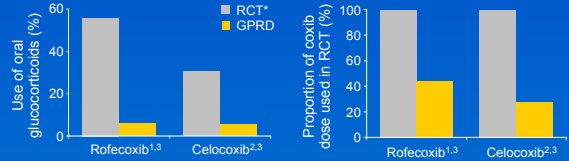
Cost-Efficacy versus Cost-Effectiveness Models: an Example of Cox-2 Inhibitors versus Traditional NSAIDs

- Guidelines and NICE¹ recommend preferential use of RCT data for modelling.
- 33 published studies evaluated the cost-effectiveness of coxibs:
 - All studies (except 4 old ones) only used RCT data for drug effect, event rates, and patient and exposure characteristics.
 - Studies evaluated long-term daily use at high dosage in patients with rheumatoid arthritis (RA)/osteoarthritis (OA) → similar to phase III RCTs.

1. NICE Guide to the methods of technology appraisal, issue date June 2008; available at <http://www.nice.org.uk/medial/B52/A7/TAMethodsGuideUpdatedJune2008.pdf>.

Patients in RCTs versus Actual Clinical Practice: Coxib Users in GPRD

- Study population in GPRD:
 - 971,426 conventional NSAID users (23.0% had history of RA/OA)
 - 148,592 coxib users (45.9% had history of RA/OA)



Patients in RCTs are different from those in the real world.

* VIGOR trial for rofecoxib; CLASS trial for celecoxib.

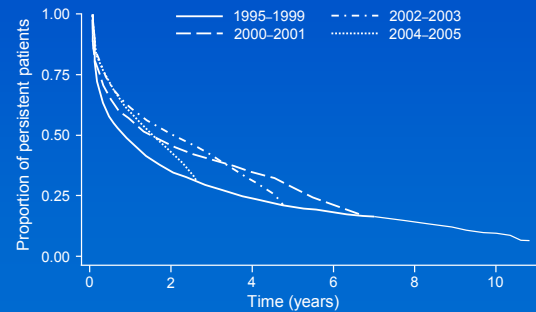
1. Bombardier C, et al. *N Engl J Med* 2000;343:1520-28. 2. Silverstein FE, et al. *J Am Med Assoc* 2000;284:1247-55. 3. GPRD database, available at <http://www.gprd.com>.

Patients in RCTs versus Actual Clinical Practice: Coxib Users in GPRD

	% of Rx	OA or RA (%)	Repeat NSAID Rx within 3 months
First-time	2.7%	22.2%	39.7%
Long gap	10.1%	42.8%	44.4%
MPR			
Very low	8.5%	53.2%	65.4%
Low	13.2%	57.7%	84.2%
Moderate	9.9%	58.0%	87.5%
High			
Short-term use	11.5%	47.2%	78.9%
Medium-term use	19.2%	59.2%	92.6%
Long-term use	25.0%	63.9%	97.3%

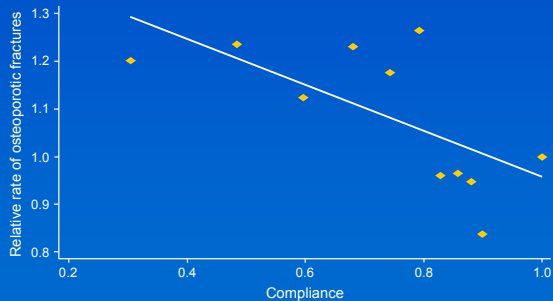
GPRD database, available at <http://www.gprd.com>.

Persistence over Time with Oral Bisphosphonates is Suboptimal



GPRD database, available at <http://www.gprd.com>.

Poor Adherence is Associated with Increased Risk of Fracture



Gallagher AM, et al. *J Bone Miner Res* 2008;23:1569-75.

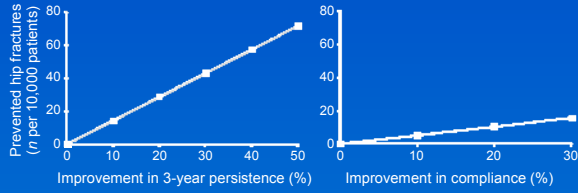
The Impact of Treatment Duration on the Relative Rates of Hip Fracture in Bisphosphonate Users in GPRD

	Fully adjusted relative rate*
Past use	Reference
Current use	0.78 (0.64–0.94)
Past use: 6 + months after discontinuation	Reference
0–6 months after discontinuation	1.26 (0.9–1.75)
Current use: 0–6 months after starting	1.23 (0.95–1.59)
6 + months after starting	0.77 (0.61–0.98)

*Adjusted for important co-variables known to impact on fracture rates.

Gallagher AM, et al. *J Bone Miner Res* 2008;23:1569-75.

Improved Adherence can Prevent More Fractures



Reference scenario is based on weekly bisphosphonates, with compliance and persistence as observed in GPRD:
 * Compliance (MPR > 90%): 72% of patients 80–89 years old; 62% of patients < 60 years old.
 * Persistence: 56.7% at 12 months; 35.3% at 3 years.

Rietbrock S, et al. *QJM* 2009;102:35-42.

Summary

- Adherence is a complex phenomenon – definitions used need to be explicit.
- Data from RCTs and observational studies are complementary and can be used to determine the value of improved adherence.
- There is a need to capture imperfect persistence and compliance in the real world.
 - The effects of a drug with lower persistence and compliance and residual effect are often unknown.
 - It is challenging to measure these concepts in databases.
- Observational studies can provide useful data on actual levels of persistence and compliance, as well as on event rates and costs to be used in modelling.

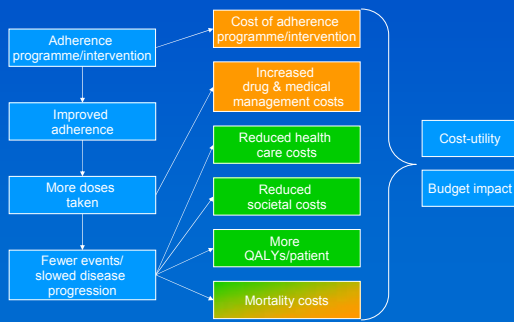
The Economic Value of Improved Adherence

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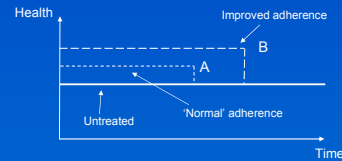
Introduction

- Medication compliance and persistence is a problem in many disease areas:
 - Blood pressure
 - Cholesterol
 - Blood glucose
 - Fracture prevention
- It is fair to say that improved adherence will improve health outcomes, but what is the relation to costs?
- Health economic value of adherence is a complex topic:
 - Adherence often improves when you measure it.
 - The exact link between adherence and outcomes can be difficult to establish, and can have a marked impact on the results.
 - Changes in adherence will interact with other variables: drug prices, time horizon, time-dependent differences, etc.

Overview of the Causal Relationships



Example 1: Neutral Effect of Improved Persistence and Compliance

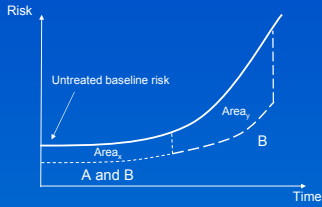


- Treatment could be for e.g. psoriasis or pain.
- Both regimens A and B are based on the same drug.
- Increased medication adherence is proportional to the increase in effect.
- The adherence programme is not associated with a cost.

	A vs. untreated	B vs. untreated	A vs. B
Drug cost	1,000	2,000	1,000
Reduced morbidity cost	-100	-200	-100
Incremental QALYs	0.05	0.10	0.05
ICER	18,000	18,000	18,000

- The ICER will always be the same.
- If we were willing to pay for A in the first place, we should also invest in B.

Example 2: Positive Effect of Increased Persistence

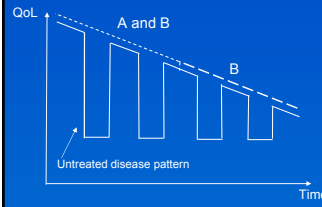


- Treatment could be prevention of events with increasing risk (e.g. CV events).
- RRR is constant over time and both treatments have the same effect.
- Risk immediately returns to baseline after treatment discontinuation.
- Patients on B stay on average twice as long on treatment as patients on A.
- The two treatments have the same drug cost/unit of time.

	A vs. untreated	B vs. untreated	A vs. B
Drug cost	1,000	2,000	1,000
Reduced morbidity cost	-100	-300	-200
Incremental QALYs	0.05	0.15	0.10
ICER	18,000	11,300	8,000

- We will get more 'bang for the buck' in the later time period because $area_A > area_B$.
- We get more QALYs, but also at a reduced cost/QALY.

Example 3: Diminishing Value of Increased Persistence



- Treatment could be reduction of relapses in a chronic progressive disease (e.g. multiple sclerosis).
- Both A and B have the same effect on reduction of relapses.
- Risk of relapse immediately returns to baseline after treatment discontinuation.
- Patients on B stay on average twice as long on treatment as patients on A.
- The two treatments have the same drug cost/unit of time.

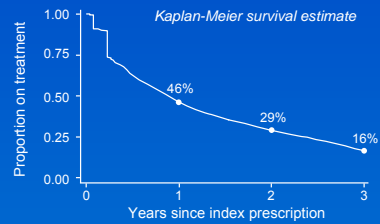
	A vs. untreated	B vs. untreated	A vs. B
Drug cost	1,000	2,000	1,000
Reduced morbidity cost	-100	-150	-50
Incremental QALYs	0.05	0.075	0.025
ICER	18,000	24,667	38,000

- Improving persistence will generate more QALYs, but at a higher cost/QALY in the later time period.
- There are thus diminishing returns of treatment in this example.
- Treatment B should only be implemented if we are prepared to pay > 38,000/QALY.

The Economic Value of Improved Adherence is Dependent on Different Factors

- Disease type
 - Baseline risk may change over time
- Time
 - The health economic impact of adherence will be affected by time factors (modelling horizon, study follow-up)
- Drug/health care costs involved
 - Not all clinical improvements are cost-effective.
- Health economic consequences of improved adherence are context-specific.

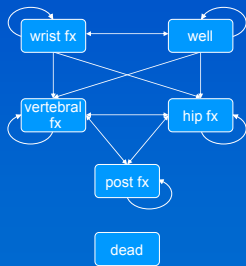
The Case of Osteoporosis



- Based on treatment with bisphosphonates, raloxifene and strontium ranelate in 53,364 Swedish patients between 2005–2008.
- A two-month 'grace period' was used to define discontinuation.
- What are the costs and benefits of improving this situation?

Landfeldt E. et al. ISPOR 12th Annual European Conference 2009.

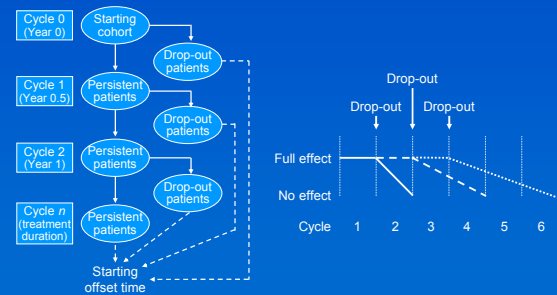
Health Economic Model



Basic Model Info	
Model type	Monte Carlo
Cycle length	6 months
Simulation horizon	Life-time
Perspective	Societal
Discount rates	3%
Data	Swedish

Ström O, et al. *Osteoporos Int* 2009;20:23-34.

Modelling Discontinuation and Residual Effect



Adapted from Ström O, et al. *Osteoporos Int* 2009;20:23-34.

The Economic Value of Improved Adherence in the Swedish Setting

	No treatment	Partial adherence	Full adherence	Difference	
				Partial vs. no treatment	Full vs. partial
Treatment costs (€)	0	1,101	3,434	1,101	2,333
Fracture costs (€)	14,626	14,022	12,401	-604	-1,621
Total costs (€)	14,626	15,123	15,835	497	712
Hip fractures	0.298	0.292	0.272	-0.006	-0.020
Life years	15.3965	15.4076	15.4289	0.009	0.021
QALYs	7.7588	7.7739	7.8118	0.0151	0.0379
NNT to avoid a hip fracture		167	38		
Cost per QALY gained (€)				32,914	18,786

Partial adherence: there is a defined chance for every patient in every cycle of dropping out of treatment, and the patient has only a fraction of the treatment benefit that a fully compliant patient has. Full adherence: treatment duration as planned, 100% compliant.

Ström O, et al. *Osteoporos Int* 2009;20:23-34.

Summary

- Improving adherence will usually improve health outcomes, but this needs to be put in relation to the associated costs and savings.
- The benefit of improved adherence will increase with the baseline risk of disease-related events.
- Health economics of improved adherence is situation-specific and will vary between diseases and treatments.
- Investing to improve adherence can be worthwhile even if the cost/QALY becomes higher.

Compliance and Persistence: Capturing the Economic Benefits

Q & A

Compliance and Persistence: Capturing the Economic Benefits

Summary & Conclusion

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Summary & Conclusion

- Non-adherence is the rate-limiting step between effective treatments and optimum outcomes.
- Doing nothing is costly.
- We need to capture non-adherence in the real world, and advances in methodology help us to do this.

Summary & Conclusion

- The development of effective interventions to support adherence is a priority for patients, healthcare providers and the pharmaceutical industry.
- Interventions will be more effective if they are tailored to address the perceptual and practical barriers for each patient.

Compliance and Persistence:
Capturing the Economic Benefits

Amgen Symposium at ISPOR 2009
Tuesday, 27th October
07:00 – 08:00
Amphithéâtre Bordeaux