

## Case Study 2

What evidence at what time? Three evidence case examples:

- A registry case
- A prospective controlled trial case
- A randomized controlled prospective trial case

## The DESDE registry case example - Background and Objectives

Background:

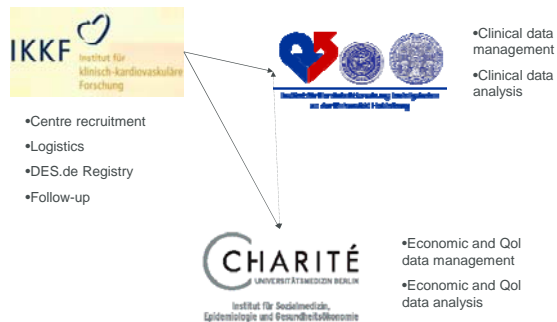
- Significant reduction of coronary re-intervention following drug-eluting stent implantation shown in randomised trials
- Can results of efficacy trials be realised in usual medical practice?
- Insufficient cost effectiveness data for treatment with DES

Objectives:

- Cost effectiveness of drug-eluting stents (DES) compared to bare-metal stents (BMS)
- Major adverse cardiac and cardiovascular events after DES
- Health related quality of life

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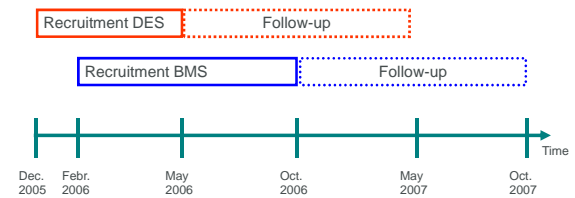
## The DESDE registry case example - Cooperating partners



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## The DESDE registry case example - Study Design



- DES: Indication for drug-eluting stent implantation (Taxis/ Cypher)
- BMS: Indication for BMS implantation - Only BMS implanted
  - Eligible medical conditions:
    - Acute Coronary Syndrome, Diabetes Mellitus, Previous Percutaneous Coronary Intervention/ Coronary Artery Bypass Graft, 3-Vessel Diseases,

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### The DESDE registry case example - Baseline Issues

	BMS (n=457)	DES (n=3516)	p
Gender (male %)	74	75	0.688
Age in years (mean ± SD)	67 ± 11	65 ± 11	<0.001
Smoker (%)	26	22	0.127
Hypertension(%)	84	84	0.681
Hyperlipidemia (%)	76	81	0.017
Diabetes (%)	33	32	0.749
Previous myocardial infarction (%)	26	30	0.064
Previous bypass (%)	16	15	0.326
Lesion type C (%)	27	27	1.0
Stent diameter (mean ± SD)	3.1 ± 0.5	3.0 ± 0.4	<0.001
Stent length (mean ± SD)	16.1 ± 5.7	19.2 ± 7.0	<0.001
3-vessel disease (%)	46	39	0.008
Number of stents (mean ± SD)	1.4 ± 0.7	1.4 ± 0.7	0.543

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### Evidence requirements in medical device development - First Conclusions

- Preliminary 6-month follow-up indicated that
  - DES is clinically superior to BMS
  - DES is associated with higher costs
  - Compared to previous studies, cost effectiveness seems to improve with declining DES surcharges

#### Evidence requirements Issues:

- Control group without statistical power calculation basis
- Even with multivariate adjustment impact of selection bias highly probable
- Generates evidence with regard to device usage characteristics in Germany

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### The GERSHWIN prospective study case example – Background and Objectives

#### Background:

- Significant reduction of coronary re-intervention following sirolimus-eluting stent (SES) implantation shown in randomised trials
- Can results of efficacy trials be realised in usual medical practice?
- Insufficient long-term medical and cost benefit data for treatment with SES

#### Objectives:

- Cost equivalence over the long-term, despite the higher initial cost of SES compared to bare metal stents
- Major adverse cardiac events after SES (death, myocardial infarct, bypass, re-PCI)
- Patient quality of life
- Follow-up medical care

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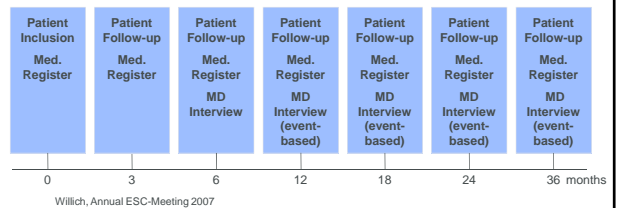
### GERSHWIN Study Concept: German Stent Health Outcome and Economics Within Normal Practice

Control strategy (sequential design, 1:2 ratio)

Bare metal stent

Sirolimus-eluting stent

#### Follow-up timeline



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**The GERSHWIN prospective study case example - Patient Selection**

**Inclusion criteria**

- Diabetics**
- De novo lesion
  - Lesion length  $\leq$  30 mm
- Non diabetics**
- De novo lesion with
  - Lesion length 12-30 mm
- OR
- RVD 2.5-3 mm, proximal lesions 2.25-3 mm

**Exclusion criteria**

- Acute MI
- Lesion length > 30 mm
- In-stent restenosis
- Distal lesion RVD < 2.25 mm
- Lesion in left main or CABG or treated with brachytherapy
- Contraindications

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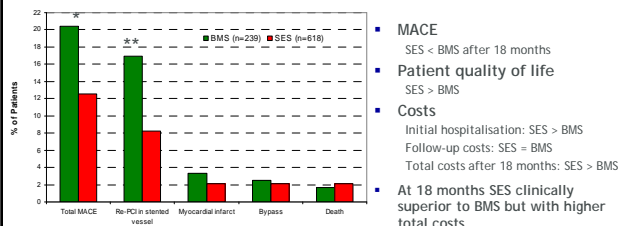
**The GERSHWIN prospective study case example - Baseline Characteristics**

	BMS n=294	p	SES n=658
Gender (male %)	79	0,003	87
Age in years (mean $\pm$ SD)	64 $\pm$ 10	0,122	63 $\pm$ 9
Single-person household (%)	16	0,034	11
Employed(%)	29	ns	33
Smoker (%)	59	ns	63
Hypertension(%)	82	ns	80
Hyperlipidemia (%)	85	ns	86
Diabetes (%)	20	ns	24
Body Mass Index > 30kg/m2 (%)	24	ns	20
Angina pectoris (%)	85	ns	86
Previous myocardial infarct (%)	31	ns	36
Previous bypass (%)	10	ns	12
3-vessel disease (%)	32	0,229	38
Number of stents (mean $\pm$ SD)	1,3 $\pm$ 0,6	<0,001	1,6 $\pm$ 0,9

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**The GERSHWIN prospective study case example - Clinical Events 0 - 18 Months**



\* p<0.01, \*\* p<0.001, adjusted for age, gender, single-person household, 3-vessel disease and number of stents

- **MACE**  
SES < BMS after 18 months
- **Patient quality of life**  
SES > BMS
- **Costs**  
Initial hospitalisation: SES > BMS  
Follow-up costs: SES = BMS  
Total costs after 18 months: SES > BMS
- At 18 months SES clinically superior to BMS but with higher total costs

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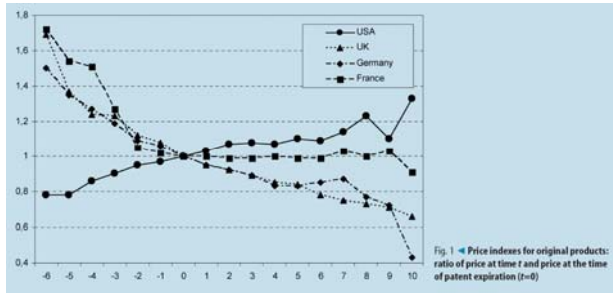
**Evidence requirements in medical device development - Further Conclusions**

- A control design is an essential element for generating evidence
- However, the non-feasibility of introducing a randomization at that time of market launch introduced some selection bias.
- Despite a multi-variate adjustment being performed a remaining selection bias could not be excluded.
- The German IQWiG embarks merely on randomized approaches, even if a feasibility is not given.

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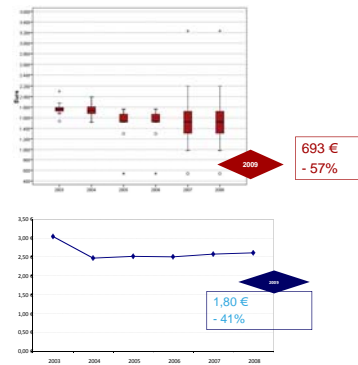
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### Further Issues - Development of Unit Costs in Longitudinal Settings



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### Further Issues - Development of Unit Costs in Longitudinal Study Settings



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### Evidence requirements in medical device development - Further Conclusions

- In longitudinal setting development of cost units is a further issue.
- Simulation of final costing year or publication year reasonable.

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### The OptiLink HF Randomized Study case example

- OptiLink HF Study: Optimization of Heart Failure Management Using Medtronic OptiVol Fluid Status Monitoring and Medtronic CareLink Network (OptiLink-HF)
- Patients suffering from heart failure and a markedly reduced pumping capacity and sometimes desynchronization of the lower chambers of the heart have a higher risk of suffering sudden cardiac death.
- Medtronic ICD- and CRT-D-Systems incorporated with fluid measuring coupled with modern data transmitting technology (CareLink)
  - Automatic information in case of a worsening of the cardiac status can be sent to caregivers.
- The study examines to which extent this new technology prevents potentially adverse cardiac situations and / or hospitalizations and has an influence of the duration of patient's lives. (<http://clinicaltrials.gov/ct2/show/NCT00769457>)

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### The OptiLink HF Randomized Study case example

- **OptiLink HF Study: Optimization of Heart Failure Management Using Medtronic OptiVol Fluid Status Monitoring and Medtronic CareLink Network (OptiLink-HF)**
- **Objective:** Evidence generating whether the use of event-triggered HF-disease management through Medtronic's OptiVol® fluid status monitoring with an automatically generated wireless CareAlert® notification ... can reduce cardiovascular related hospitalizations and the number of deaths ... compared to standard clinical assessment.
- **Primary Outcomes Measure:** All-cause of death or unplanned admission to hospital for cardiovascular reason from day of patient informed consent sign off [ Time Frame: 18 Months ]
- **Study Type:** Interventional Study
- **Allocation:** Randomized
- **Endpoint Classification:** Efficacy Study  
**Intervention Model:** Parallel Assignment
- **Patients to be included: 1000**  
(<http://clinicaltrials.gov/ct2/show/NCT00769457>)

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### Evidence requirements in medical device development - Conclusions

- Medical device assessment ideally part of full process assessment.
- A control design is an essential element for generating evidence. However, despite a multi-variate adjustments selection bias can not be excluded.
- A randomized design is considered even for medical devices as the only way demonstrating causal inference.
- Registries might contribute to resource utilization and cost features understandings.
- France (HAS) also focuses on clinical utility and comparative effectiveness to control costs
- UK (NICE) applies comprehensive reviews in order to obtain cost effectiveness results. So far most transparent international body
- The German IQWiG embarks merely on randomized approaches, even if a feasibility is not given with a strong focus on clinical benefit (not yet mandatory process).

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