MedTech IGNITE
Inspiring Growth in New Innovative Technology Enterprises

Addressing the Outcome Studies Challenges for New Medical Technologies

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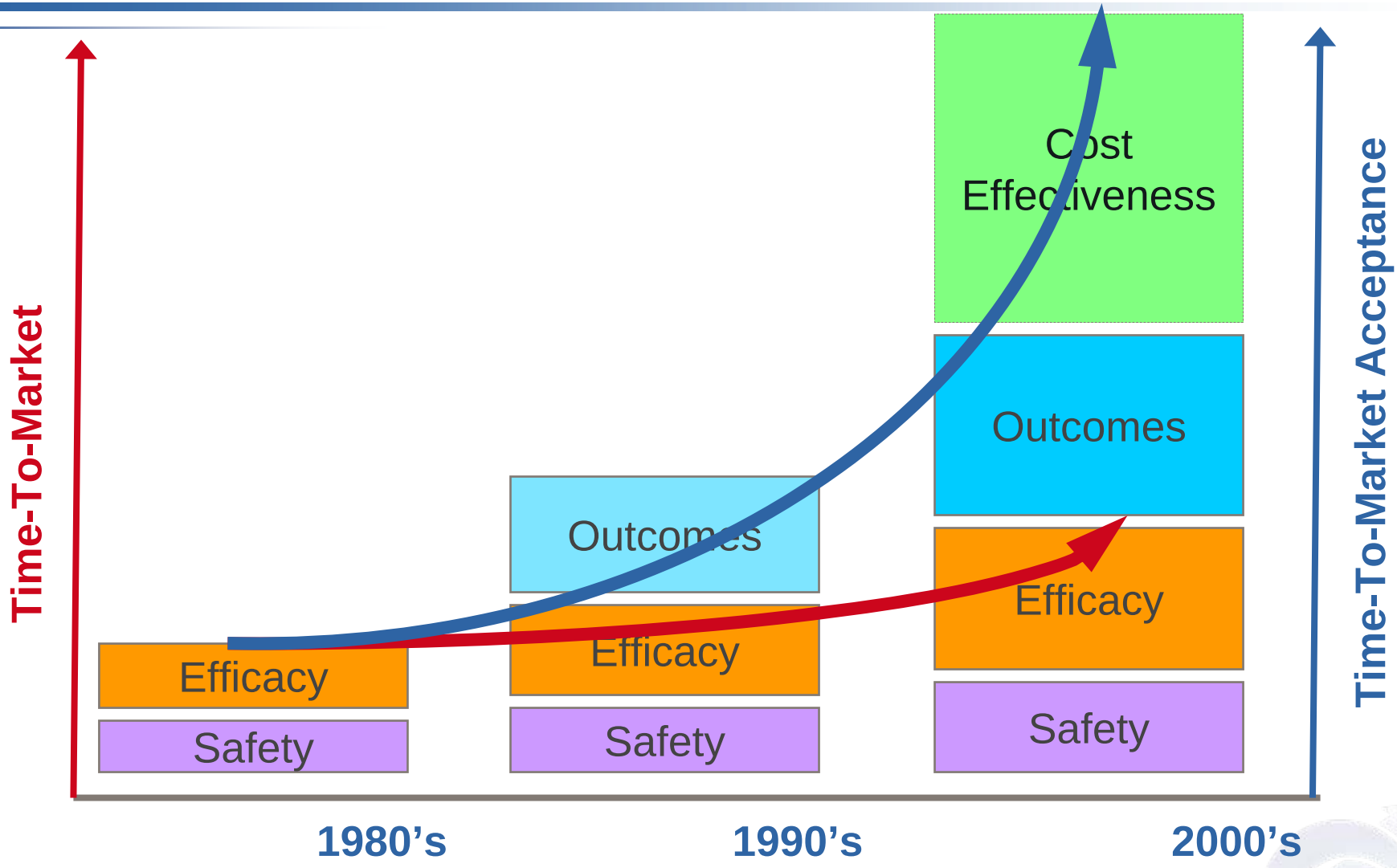
Time to Market and to Market Acceptance



Regulatory Approval and Payers (and Users)

Regulatory Approval

Does the product do what it claims?

- Safety and efficacy
- Data generated in controlled studies
- Intermediate or short-term outcomes
- No cost considerations

Payers (and Users)

Does the product improve outcomes?

- Reasonable and necessary
- Use in “real world”
- Long-term outcomes
  - Mortality
  - Complication rates
- Professional societies input important
- Cost is often key consideration

Medical Technologies

Therapeutic

- Healing of diseases and injuries

- Healing
- Elimination of or relief from symptoms
- Quality of Life
- Prevention

Non therapeutic

- Detection and recognition of diseases and symptoms

- Diagnosis of diseases and injuries
- Monitoring of physiological function
- Prognostication

Assessment of Medical Technologies

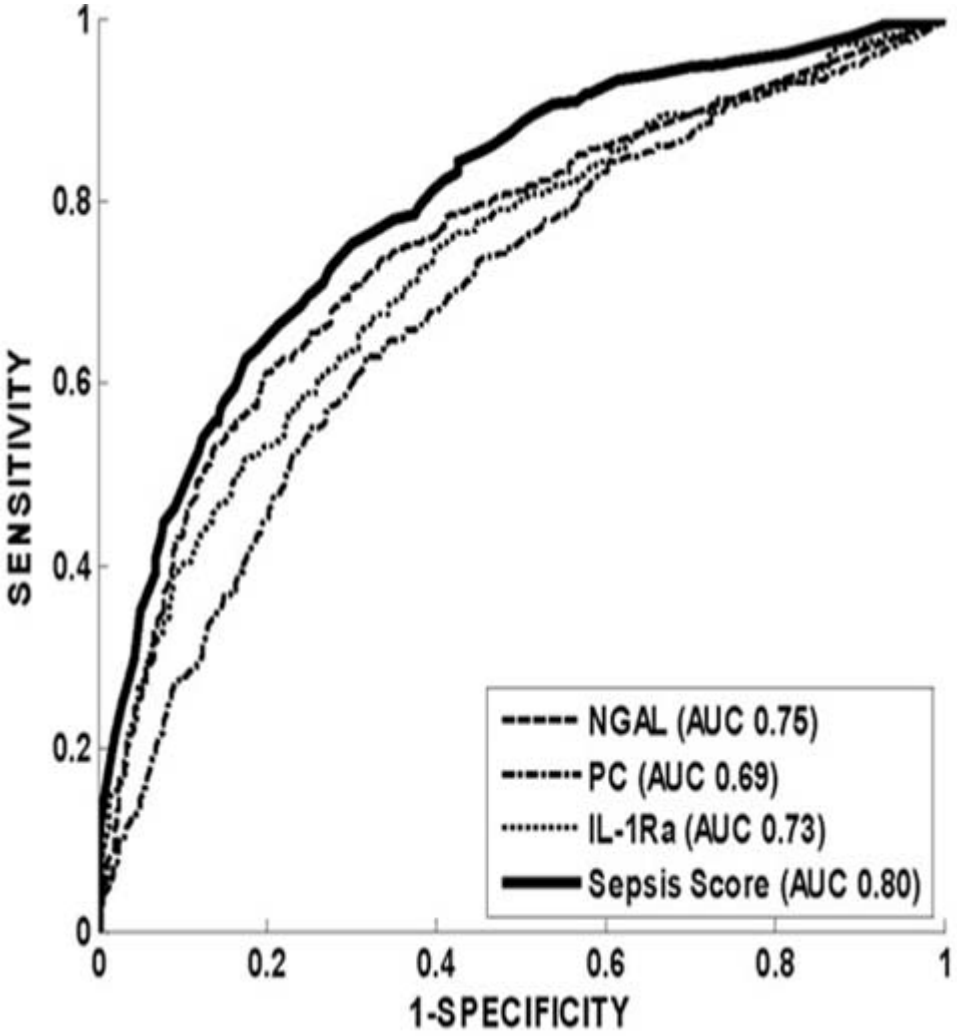
Therapeutic

- Safety
- Effect
  - Physiological effect
  - Pharmacological effect
- Under optimal conditions (efficacy)
- Under real-life conditions (effectiveness)
- Benefit/outcome

Non therapeutic

- Safety
- "Effect"
  - Measurement: precision, accuracy, timeliness
  - Diagnostics: sensitivity, specificity, PPV, NPV, ROC
- Under optimal conditions (efficacy)
- Under real-life conditions (effectiveness)
- Benefit/outcome

Sepsis – Biomarkers



- Two-phase multicenter study
- Phase 1: 250 pts –
  150 circulating biomarkers
- Phase 2: 9 biomarkers selected and tested in 971 pts total
- 3 biomarkers finally selected from 971 ER pts.
  (465 w/o sepsis)
  - NGAL
  - IL1-ra
  - Protein C

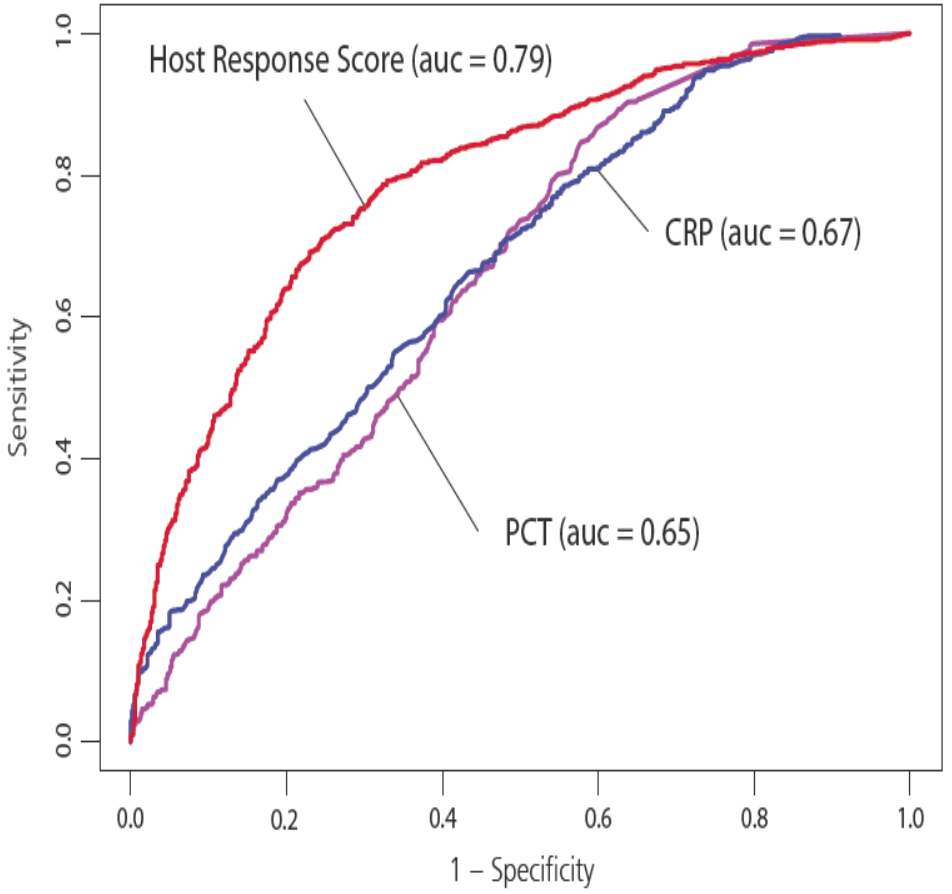
  ➔ Sepsis Score

Shapiro NI, et al., 2009

Sepsis – Host Response

- 364 ICU patients
- Robust gene expression in sepsis
- Differentiation between sepsis and SIRS
- Potentially early initiation of therapy
- Host response score (ROC AUC = 0.79)
- 48 hours before any other markers

Bauer, M et al., 2008



➔ Clinical value can only be shown in outcome study!

Validation vs. Outcomes

Validation

- Technical performance
- Precision, accuracy, sensitivity, specificty, etc.
- Comparison with reference methods
- Measurement of reference samples
- Assessment across entire measurement range
- Inclusion of diverse populations (generalization)
- No potential study benefit for patients/subjects
- Sufficient, when new method shall replace existing

Outcomes

- Technical performance must be established
- Translation into clinically relevant effects
- These are truly therapeutic trials!
- Control group, randomization, follow-up
- Clearly defined, tight inclusion criteria
- There must be potential benefit for patient population
- The therapeutic intervention must be able to generate some benefit

Non-Therapeutic Medical Technologies

Benefits from patient monitoring

- Clinical benefit seems intuitive, but …
- Benefit could not be found
  - Pulmonary artery catheter
  - Pulse oximetry
- Benefit could be found
  - ScvO2 / early goal directed therapy in sepsis
  - Cardiac output / perioperative hemodynamic optimization
- Benefit depends on the translation of monitoring into therapy
- For monitoring/diagnostics with potential side effects the diagnostic benefit must be relevant
  ➔ Therapeutic relevance!

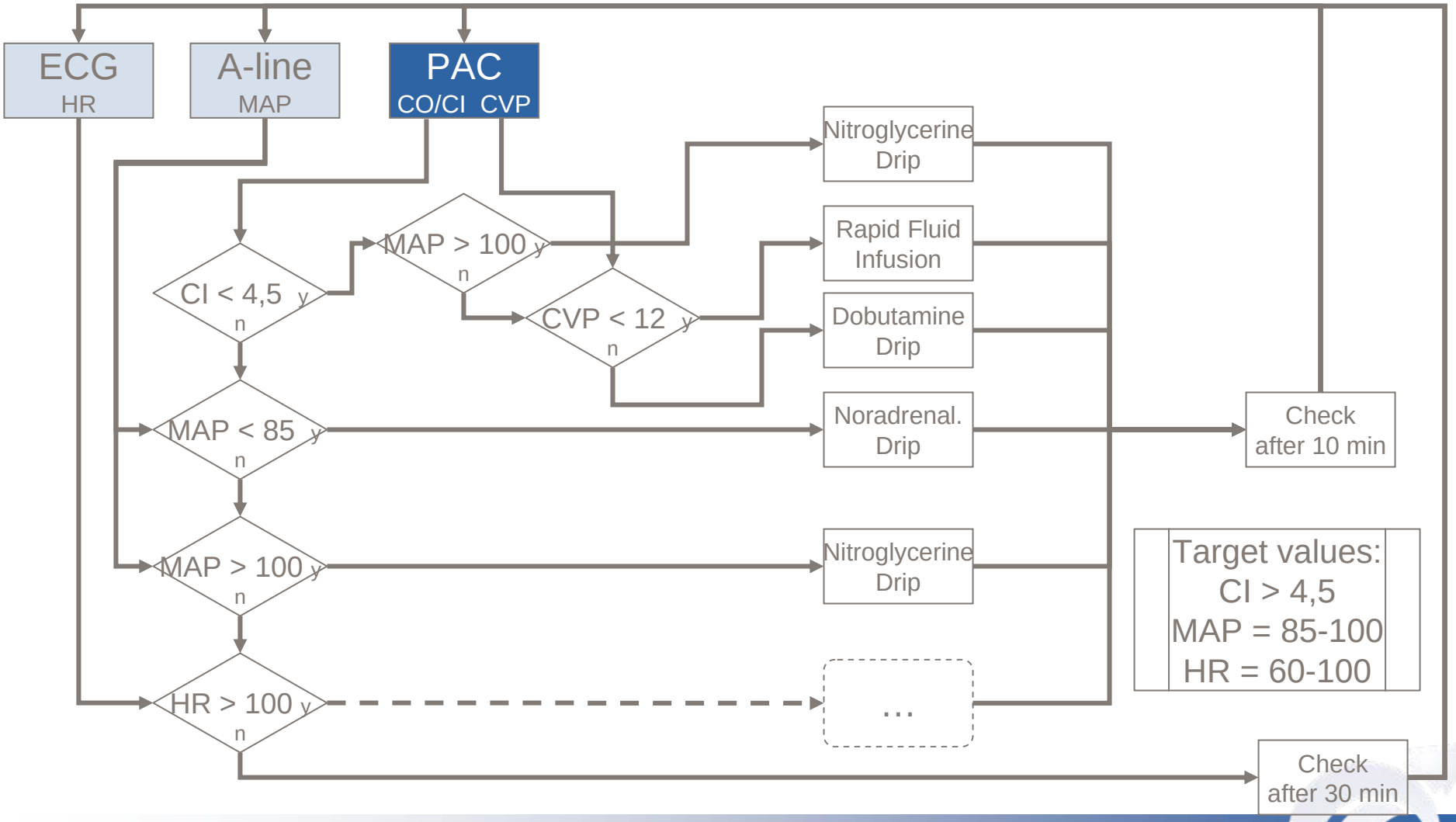
Outcome Studies with Non-Therapeutic Medical Technologies

- Adequate patient populations
- Embedding in therapeutic protocols
  - Explicit and implementable protocols
  - Therapeutic interventions with outcome effects
  - Established therapies
  - Intervention at the right time
- Target variable with therapeutic relevance
  - Appropriate target variable
  - Correct measurement/assessment
  - Adequate timeliness
- Adequate therapeutic endpoints

Pulmonary Artery Catheter

- Clinical reference of (highly) invasive cardio-vascular monitoring (Swan, Ganz, 1970)
  - Diagnostics of cardiac and pulmonary diseases
  - Monitoring in ICU and OR
  - “Gold Standard” for the measurement of cardiac output
- 2 M catheters annually world wide (1990s)
  - USA: 1.4 M
  - RoW: 0.6 M
- Hemodynamic optimization of surgical high-risk patients improves outcomes (Shoemaker, 1990-98; Boyd, 1997)
- Hemodynamic optimization of patients in multi-organ failure has no outcome benefit (Gattinoni, 1997)
- PAC independently associated with mortality (Connors, 1996)

PAC – Clinical Protocol



Implementation/Training/Control

- Explicit and unambiguous formulation of a protocol
- PAC at induction
- Hemodynamic optimization
  - CI = 4,5 l/min/qm
  - MAP = 90-100 mmHg
- Interventions
  - Rapid infusions (Ringers, HAES)
  - Dobutamine
  - Nitroglycerine
- Start of surgery only after target values have been achieved

Implementation/Training/Control

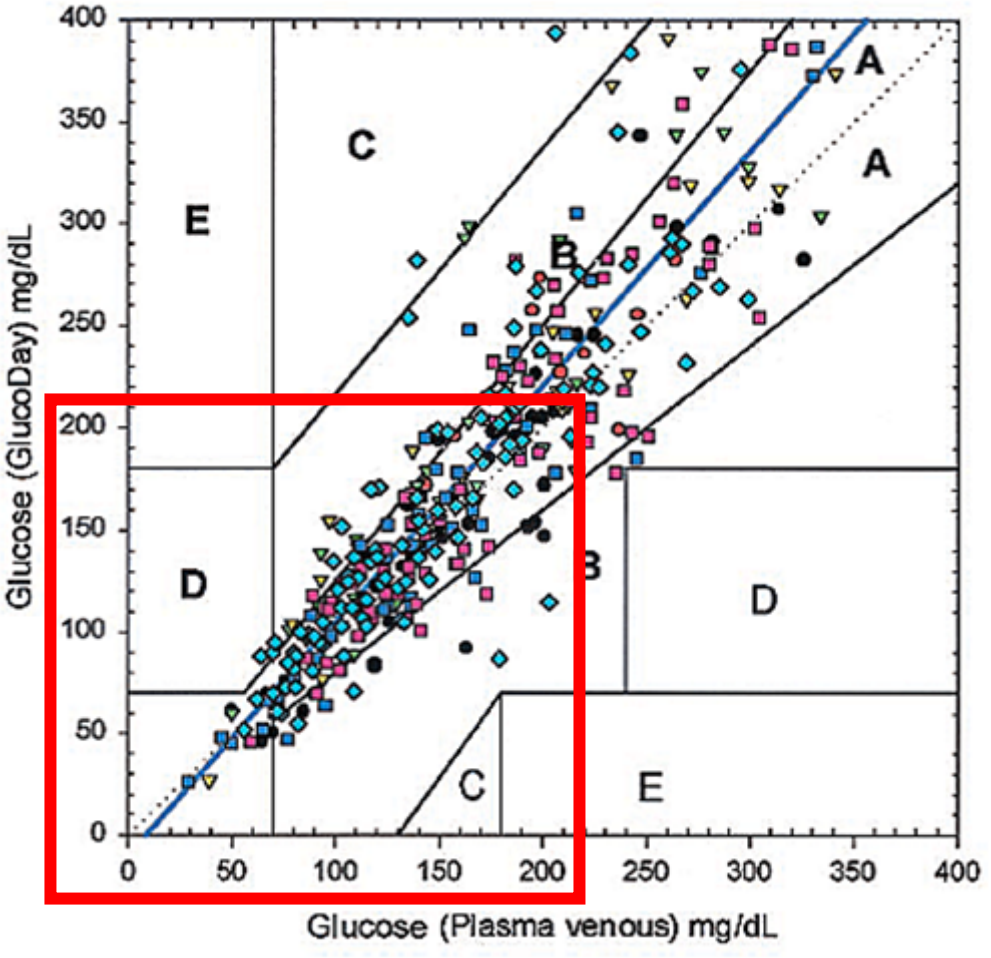
- Coordination between anesthesiologist and surgeon
- Limitation to 2 indications and 2 anesthesiologists

- Continuation of therapy on ICU
- Attending intensivist present for first patients
- Detailed information to nursing staff

- Continuous control
  - Are all patients enrolled?
  - When are the target values reached?
  - Which interventions are required?

Clinical Endpoints
Glucose Monitoring

- Clinical endpoints
  - Hypoglycemia
  - Normoglycemia
  - Hyperglycemia
- Therapeutic decisions
  - Insulin therapy
  - Ambulatory management
  - IIT / TGC
- Populations
  - Ambulatory diabetes control
  - Critical care



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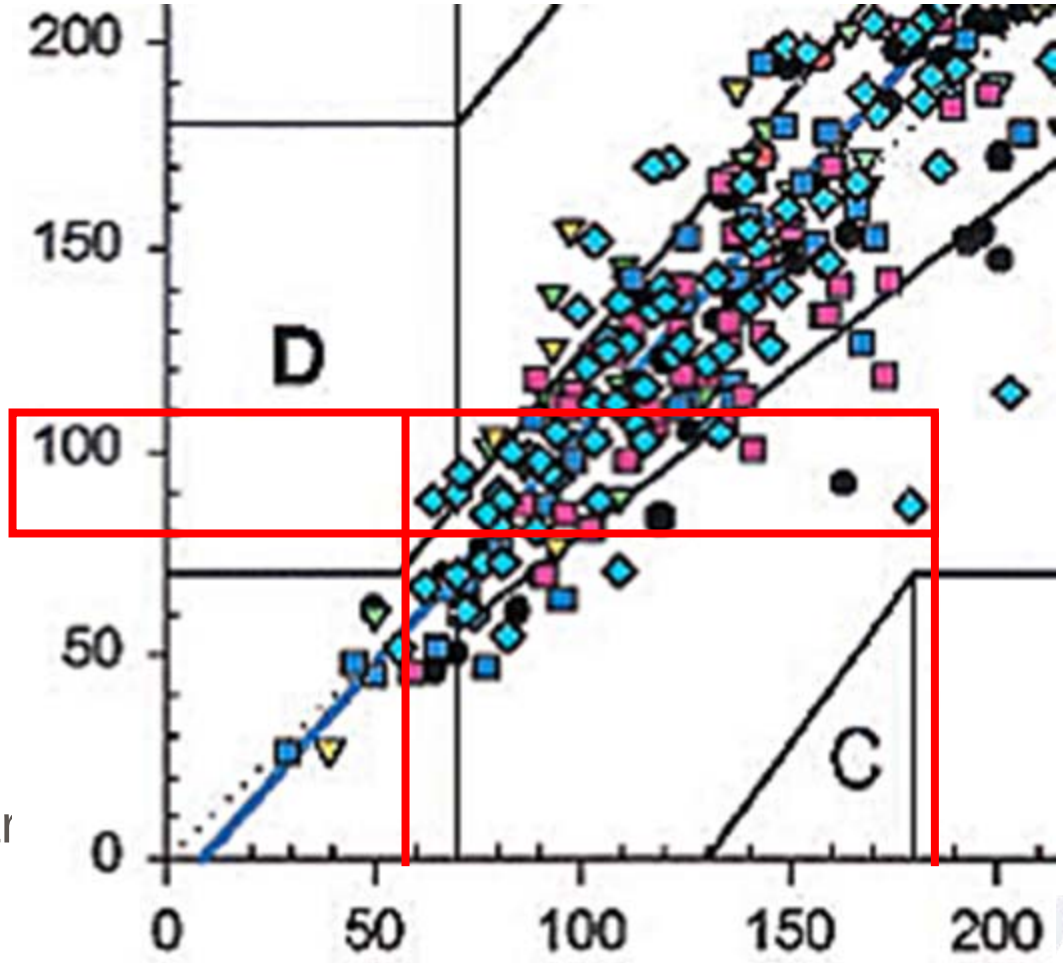
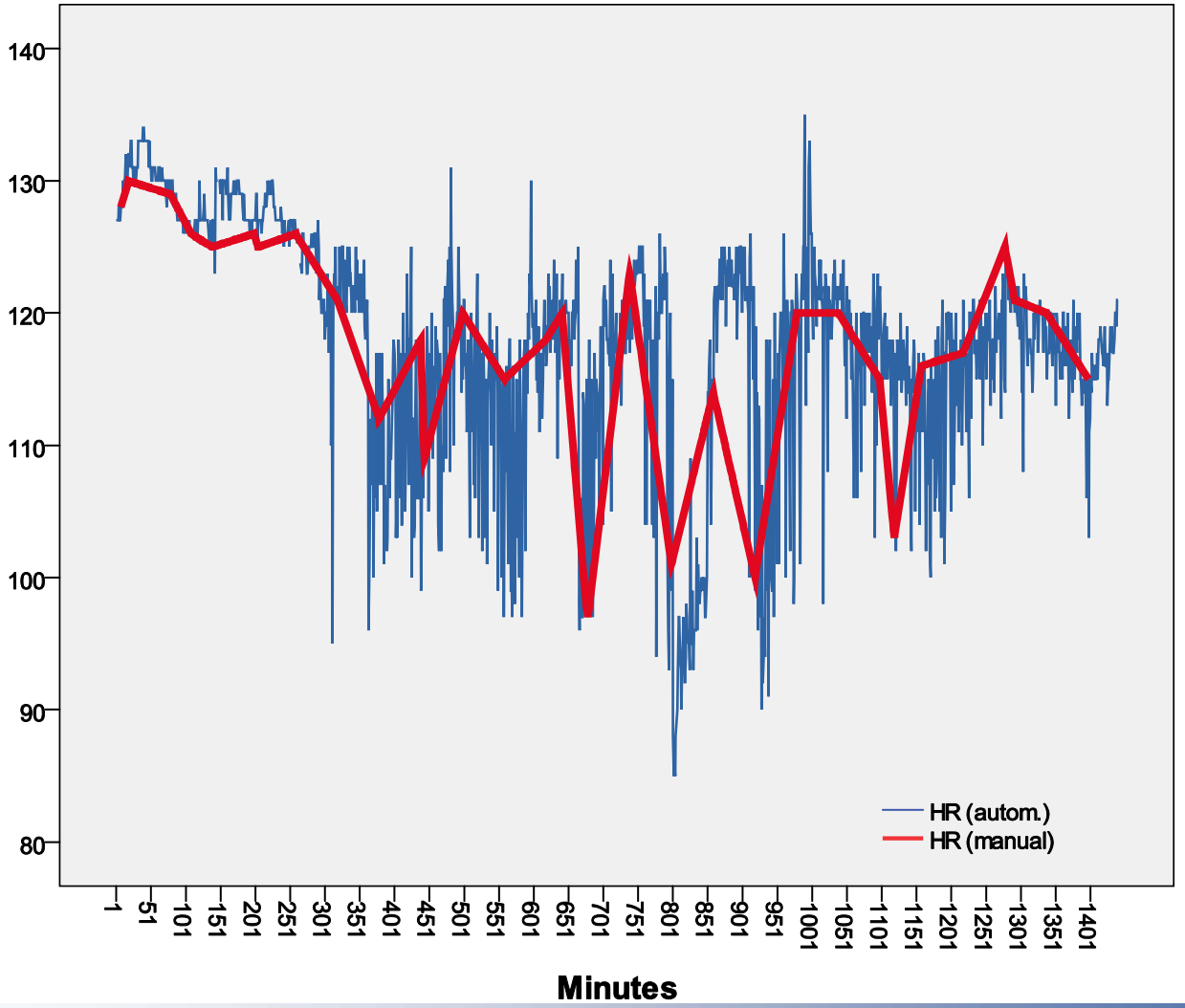


Data Acquisition – Data Reduction



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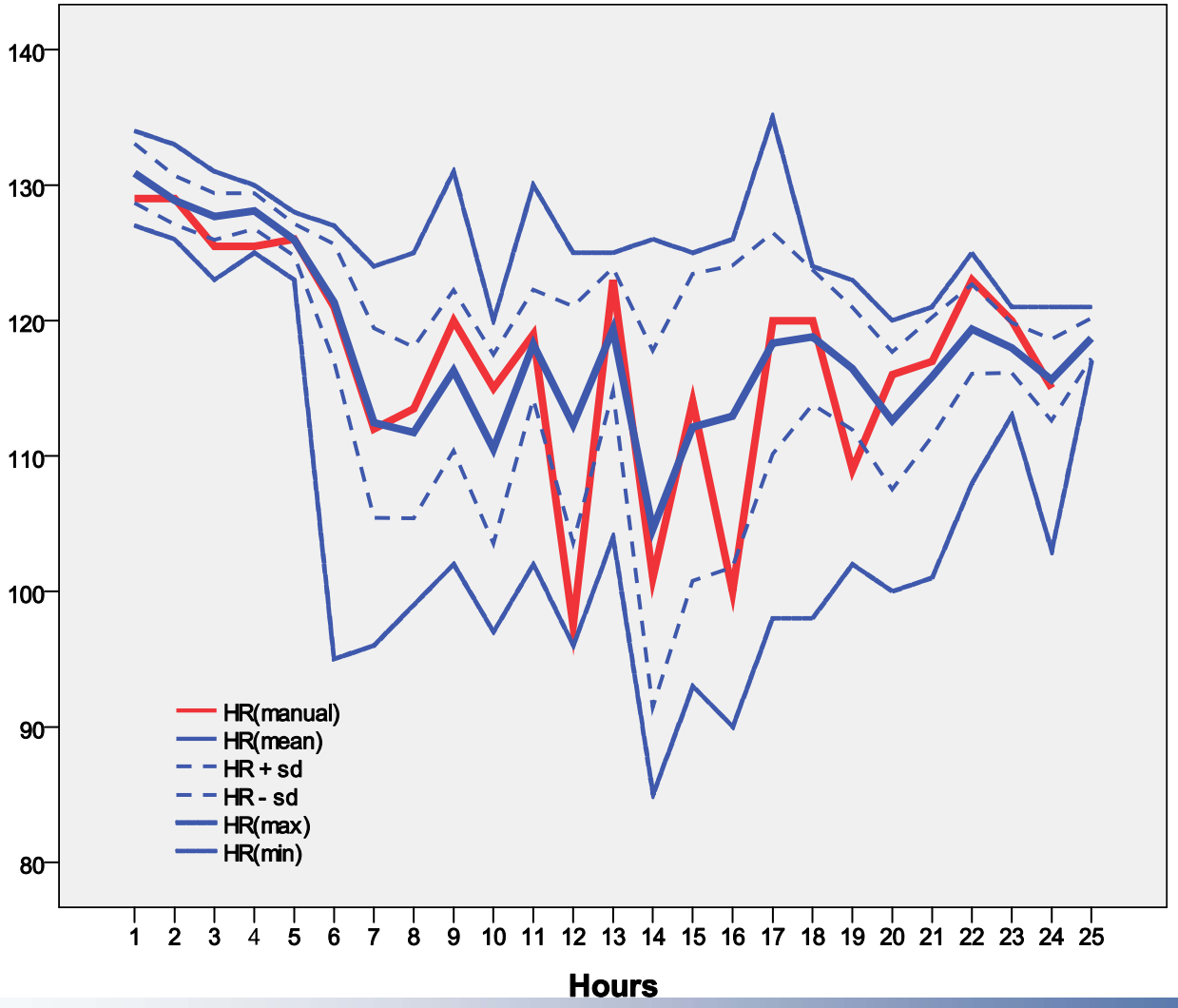
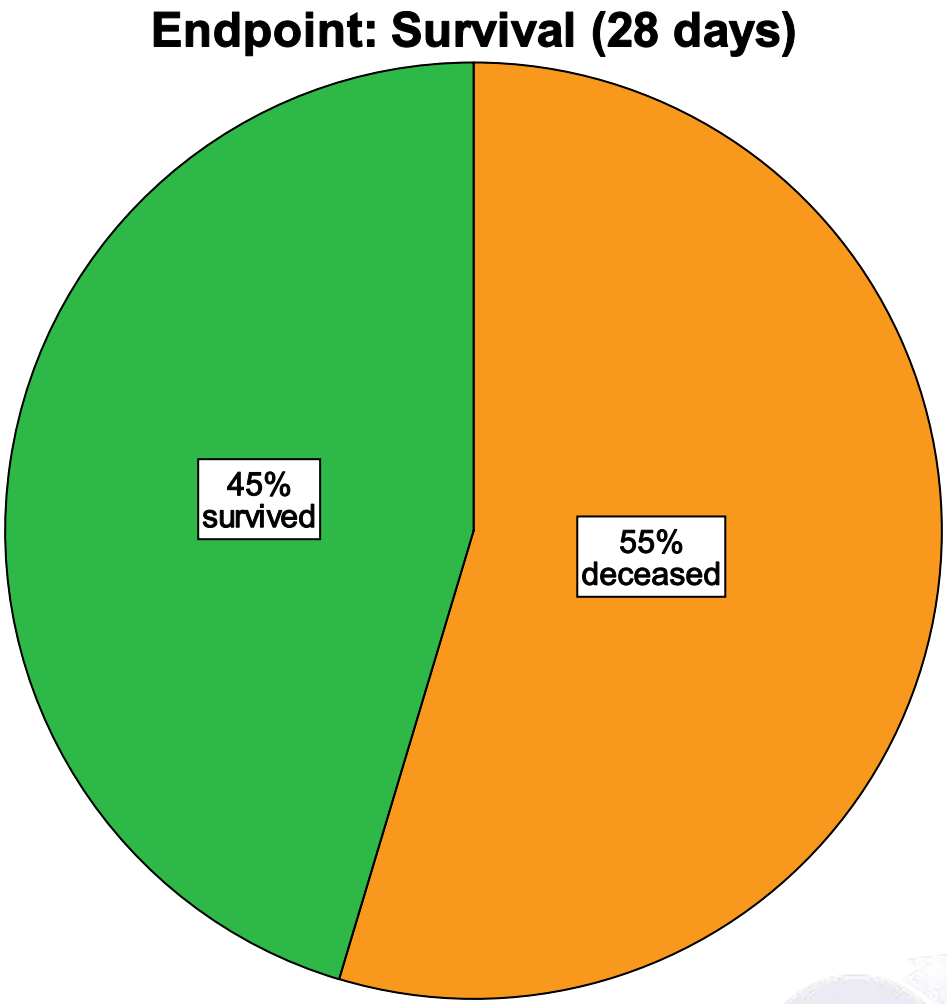


Adequate Therapeutic Endpoints

- Endpoint: ICU mortality
- 28-days mortality frequently used endpoint
- Hospital mortality

- Patients with 2+ organ failure
- Standard therapy



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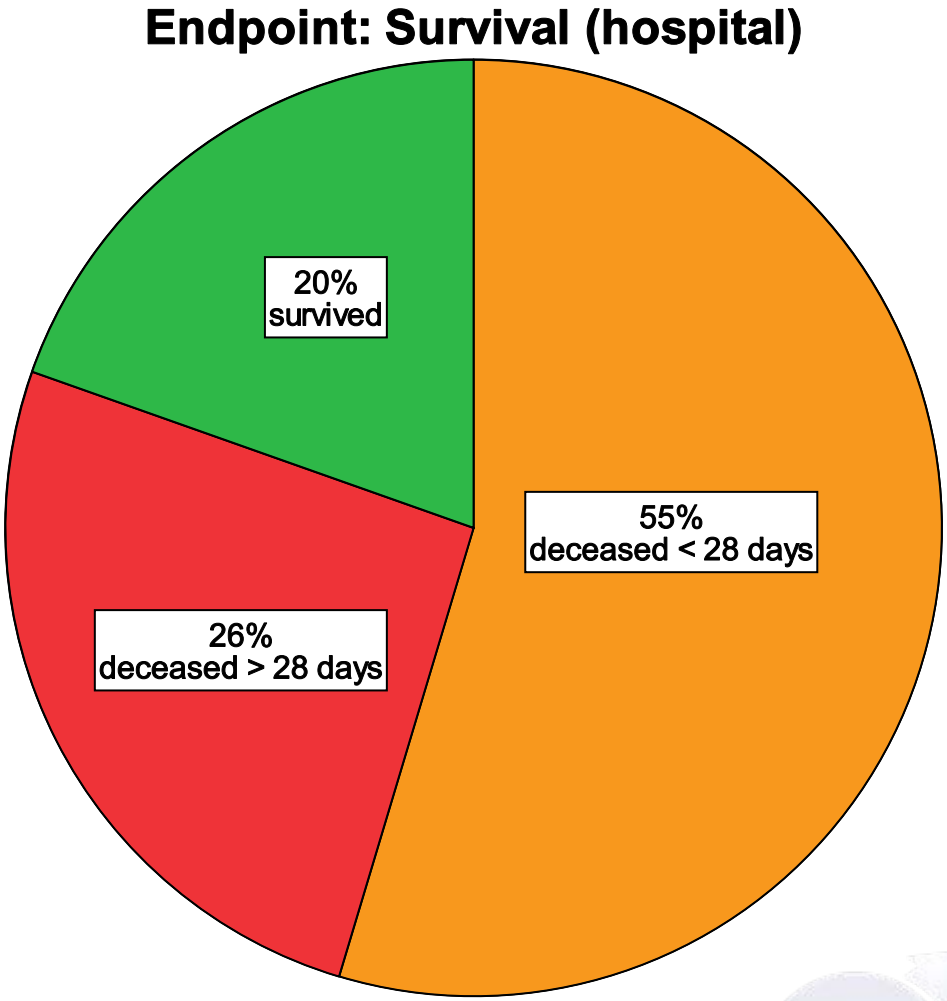

Adequate Therapeutic Endpoints

- Perioperative management of “high-risk” surgeries
  - Esophageal resection and gastric interposition
  - Extended liver resections (60+%)
- “Standard” endpoint mortality
  - Reduction of mortality not very likely (baseline mortality < 5%)
- “Achievable” endpoints
  - Reduction of non-surgical complications
  - Reduction of length of stay (ICU, hospital)

Adequate Therapeutic Endpoints

- Cost is also a potential outcome
- If there is not specific reimbursement for a technology, it must provide a quality and/or cost benefit for the user
- Monitoring/diagnostics can rarely achieve this by and in itself

➔ Improvement of outcomes, reduction of complications thru early detection

➔ Compliance with (external) requirements (JCAHO, Leapfrog, …)

Outcome Studies with Non-Therapeutic Medical Technologies

- Study results influenced by many factors
- Quality of a non-therapeutic technology
  - Quality of measurement
  - Diagnostic quality
- Quality of the therapeutic intervention
- Pathophysiological relevance
- Clinical relevance

Addressing the Outcome Studies Challenges for New Medical Technologies

- Increasing requests for outcome studies
- Outcome studies with non-therapeutic medical technology mostly NOT relevant for regulatory approval (= market entry)
- BUT are often decisive for market acceptance
- They are often relevant to determine clinical utility and value

- Careful, detailed and professional planning
- Relevant risks and costs
- Early consideration in business planning and development

Criteria to Evaluate New Technology*

1. Final regulatory approval
2. Scientific evidence – effect of the technology on health outcomes
3. Must improve the net health outcome
4. Must be as beneficial as any established alternatives
5. The improvement must be attainable outside the investigational settings

BlueCross BlueShield Association

** Technology Evaluation Center (TEC), used by Blue Cross and Blue Shield Association*

Thank You!

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