From Model to Medical Device

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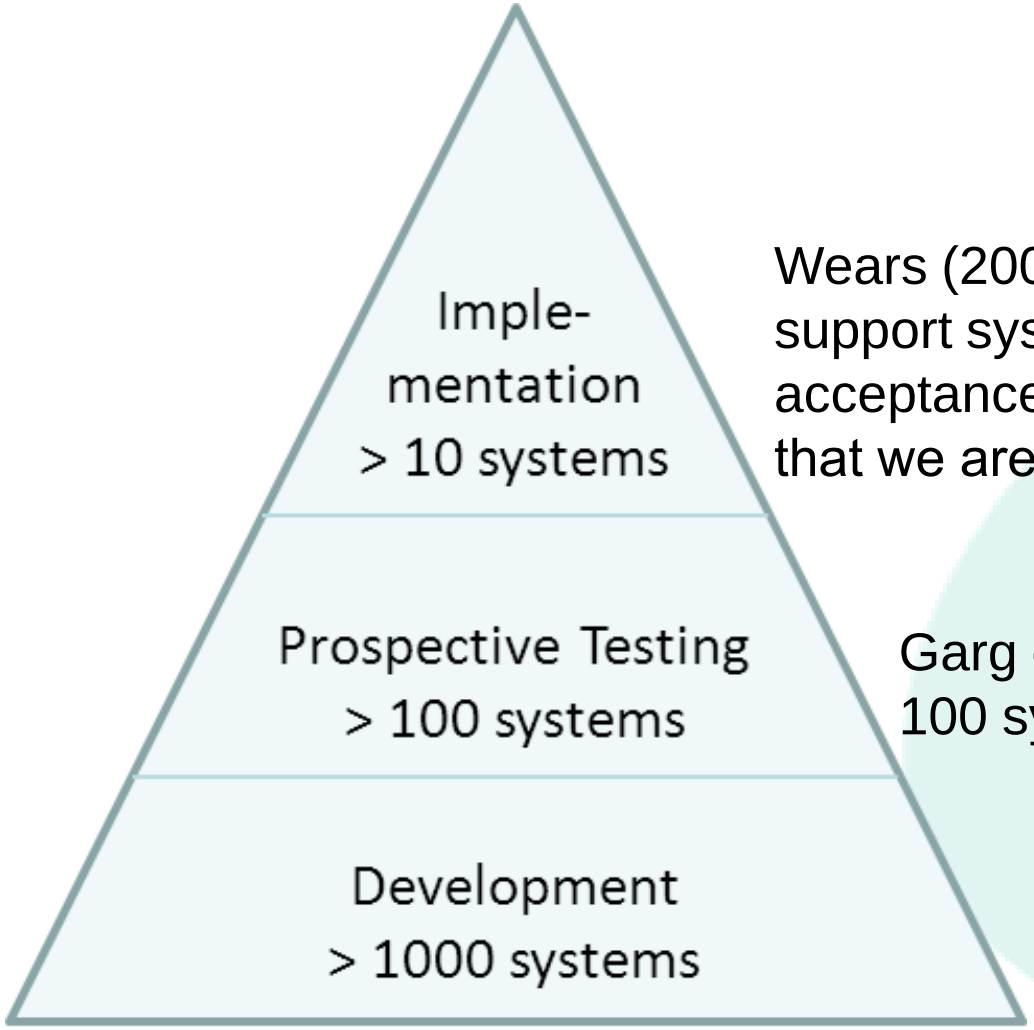
The Phases in the Life Cycle of Medical Decision Support Systems



Wears (2005) complained that decision support systems with widespread clinical acceptance are few and far between and that we are in effect “still waiting for Godot”

Garg et al. (2005) identified trials of 100 systems between 1973 and 2004

Treat – a Case Story

- The life cycle will be illustrated with examples drawn from Treat, a model-based decision support system, which is now in the Implementation phase.
- Treat advises on the choice of antibiotics for treatment of severe acute bacterial infections
- It contains models of the development of sepsis and other signs and symptoms of bacterial infection and models of the interaction between bacteria, antibiotics and the infected host.

Prospective Testing

- The logistics of prospective testing
- Is a prospective trial worth the trouble?
- The chances of a positive test result?

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The logistics of a prospective study

- A prospective study requires clinical collaborators, capable and willing to mount a rigorous clinical trial
  - more demanding than collection of a case database for retrospective testing of a decision support system
- The design of the prospective study is difficult
  - effectively trials of decision support systems can not be blinded
  - clinicians learn from the system and from each other – in particular when being studied
  - before/after design (historical control) is a solution – but non-randomised studies are rarely published in top journals
  - cluster randomization is another solution – but requires participation of many clinical partners and a larger patient population
- For further frustration – read the book Evaluation Methods in Medical Informatics (Friedman and Wyatt 2006)

The case of Treat

- Treat received substantial research funding from the European Commission.

- This made a cluster randomized trial possible
  - 14 participating departments from three countries.
  - 2326 patients included (Paul et al. 2006a, 2006b)

- Subsequent trials have been with a before/after design

Prospective Testing

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Is a prospective trial worth the trouble?

The questions:

- **Relevance**
  - is my decision support system addressing a real clinical problem?
  - does the clinical problem substantially affects a substantial number of patients?
- **Efficiency:**
  - is it likely that my system will efficiently address this clinical problem?
  - you need numbers for this anyhow to make a power calculation for the trial
- **Transferability:**
  - **c**an my system be adapted to different clinical traditions?
  - if not, widespread acceptance will not happen

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The case of Treat: relevance

- **A real clinical problem…**

  About 40% of patients hospitalized with an infection receive inappropriate treatment, i.e. antibiotic treatment, which cannot eradicate the infection (Paul et al. 2006a)

- **which substantially affects…**

  Mortality is high, typically 10-20% and inappropriate treatment approximately doubles the odds ratio for death (Fraser et al. 2006)

- **a substantial number of patients.**

  Annually about 1% of the population is hospitalized with a severe infection making acute infections one of the leading causes of death

- **A secondary problem**

  Many patients receive treatment with broad-spectrum antibiotics, which promotes bacterial resistance.

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The case of Treat: efficiency

- The belief that Treat reduces inappropriate treatment and the consumption of broad-spectrum antibiotics was based on a previous retrospective trial (Andreassen et al. 1999)
- This trial made it possible to do a power calculation to determine the necessary number of participating wards and patients in the prospective trial

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The case of Treat: transferability

Transferability was designed into Treat:

- Treat allows for local calibration of bacterial resistance
- as well as local calibration of the prevalence of different infections
- Adaptation to local antibiotic policies was accomplished by local calibration of “penalties”, allowing clinicians to express preferences for certain antibiotics.

Prospective Testing

- The logistics of prospective testing
- The motivation for prospective testing
- The chances of a positive test result?

The chances of a positive test result?

The odds for success before you start the prospective trial:

- Out of 100 systems in controlled clinical trials (Garg et al. 2005) 64% improved practitioner performance
- only 52% of the studies measured patient outcomes
- out of those only 13% (7 systems) reported improvements.
- The link between the use of a decision support system and improvement in patient outcomes thus seems fairly weak.

How can you improve your odds?

- Out of 70 systems in RCTs, 68% improved practitioner performance (Kawamoto et al. 2005) (agrees well with 64% by Garg et al. (2005).
- Few studies included indicators of patient outcome.
- Four features predict improvement of practitioner performance:
  a) decision support provided automatically as part of clinician workflow,
  b) decision support delivered at the time and location of decision making,
  c) actionable recommendations provided, and
  d) computer based advice
- Of the systems including all four features 94% improved practitioner performance (substantially above the average of 68%).
- Only 46% of systems including none of these improved practitioner performance.

Further ways to improve your odds

- Direct experimental evidence (Kawamoto et al. 2005) was found for the positive effect of four additional features:
  - e) integration with charting or order entry system to support workflow integration
  - f) request documentation of the reason for not following the systems recommendations
  - g) provision of decision support to patients as well as providers
  - h) system accompanied by periodic performance feedback

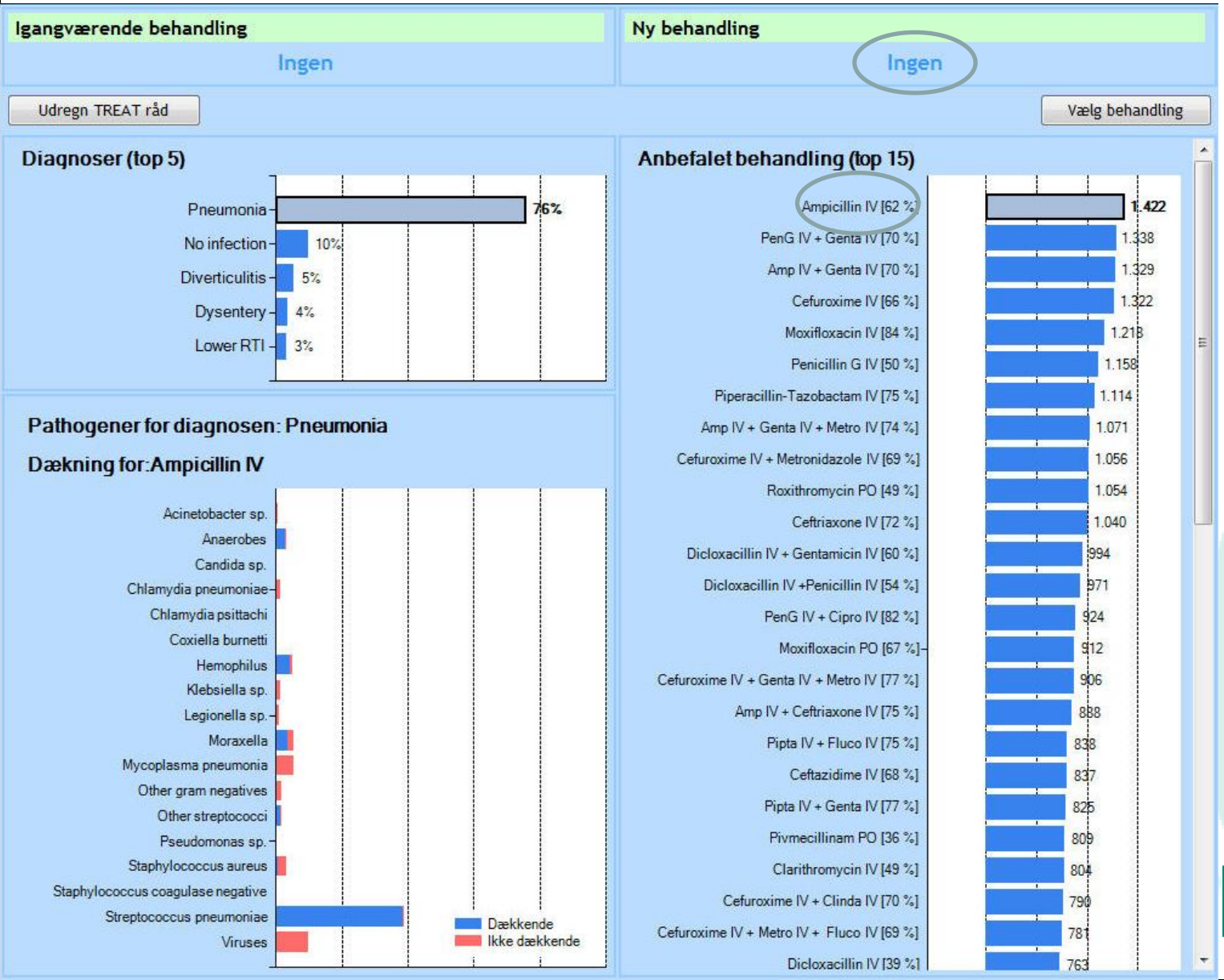
- Other studies have indicated the importance of the features:
  - i) a clear and intuitive user interface
  - j) the system is fast and/or saves time
  - k) active involvement of clinical opinion leaders

- These features form a checklist for developers to predict positive impact on clinical practice

The case of Treat: functionality of Treat

TREAT, patient 010525-0000 (86 yr.) Female								Episode 1 of 1		Encounter 1 of 1
Demography		Admission date:	16-02-2012 14:25	Encounter time:	16-02-2012 14:25	Department:				
Background		Place of acquisition:	Community	MRSA exposure:	?					
Sepsis Presentation		Temperature:	37.6 °C	SBP:	114 mmHg	DBP:	73 mmHg			
Heart rate:	102 bpm	Mental status:	Unknown	Respiratory rate:	?	Dyspnea:	Yes			
CURB65-Score:	1	SaO2:	94.0 %							
Clinical chemistry results		WBC:	10.3 x 10^9/l	ANC:	8.3 x 10^9/l	Platelets:	232 x 10^9/l			
CRP:	106 mg/l	Creatinine:	83 µmol/l	Albumin:	28 g/l					
Local Findings		Cough:	Productive	Auscultation:	Nonspecific	Diarrhea:	Watery			
Abdominal tenderness :	RUQ									
Not examined:	CNS, Tissue and Urinary Tract			Not pathological:						

Treatment: Clinically and by Treat



Clinically:
no treatment

Treat:
appropriate
treatment

Mortality reduced
from ca. 20% to
ca. 12%

Features in Treat predicting success

a) decision support provided automatically as part of clinician workflow
b) decision support delivered at the time and location of decision making
c) actionable recommendations provided
d) computer based advice
e) integration with charting or order entry system to support workflow integration
f) request documentation of the reason for not following the systems recommendations
g) provision of decision support to patients as well as providers
h) system accompanied by periodic performance feedback
i) a clear and intuitive user interface
j) the system is fast and/or saves time (from 50 s to 5 s)
k) active involvement of clinical opinion leaders

Features not present at the prospective trial

Features provided at the prospective trial

Treat actually improved performance

- Treat reduced the percentage of patients receiving inappropriate antibiotic treatment from 36% to 27%
- It significantly reduced the number of bed-days
- It approximately reduced the consumption of broad-spectrum antibiotics to half
- A reduction in mortality was also seen, although the study was not powered to give a statistically significant reduction in mortality.

Surprise: But a successful prospective trial does not ensure clinical acceptance !

[1]Paul, Andreassen, Tacconelli et al. Improving empirical antibiotic treatment using TREAT, a computerized decision support system: cluster randomized trial. J Antimicrob Chemother. 2006; 58:1238-45.

Implementation – a new set of skills

You need:

- an interesting business case
- funding for product development and patents
- compliance with regulatory authorities
- To overcome obstacles to implementation

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Treat: a business case

- A hospital (population 400.000) will annually see about **5600** (1.4%) infections.
- If Treat increases covering antibiotic treatment by 15%[1,2] then annually an additional 5600* 15% = **840** additional patients will receive covering empirical treatment.
- If covering antibiotic treatment reduces mortality by 8.3%[3], then 840 * 8.3% = **70** additional patients/year will survive, or about 5 * 70 = **350** life-years/year.
- With a €110.000/year Treat license, the cost of a saved life-year is: € 110.000 / 350 = **€ 314/life-year** (100 times less than the € 35000/life-year considered cost effective[4])
- Similarly, savings on bed-days[3] pays for the Treat license 6 times/year.
- Conclusion: the case for acquisition of Treat by a hospital is clinically and economically sound.

Paul et al. 2006b[1]; Kofoed et al. 2009[2]; Fraser et al. 2006[3];
UK National Institute for Health and Clinical Excellence 2012[4];

Compliance with regulatory authorities

- In Europe CE marking of a Medical Device is regulated by the European Commission
- In the USA the Food and Drug Administration (FDA) controls the approvals required for Medical Devices
- The rules in Europe and the USA are similar, but the FDA may require additional documentation that patients the will actually benefit from the Medical Device.

CE marking of Medical Devices

The European story goes to the tune of:

Yesterday – that was such an easy game to play

where yesterday is any date before 6. January 2012.

The Medical Devices Directive
Council of the European Communities 1993

- Software is not mentioned and thus not a Medical Device

Amended Medical Devices Directive
The European Parliament and the Council of the European Union 2007

- Amendment takes effect March 2010
- Administrative software (including lab. information software) is not a Medical Device.
- Status of the Electronic Patient Record and Medical Decision Support is unclear.

Medical Devices Guidance Document
The European Commission 6. Jan 2012

- The Electronic Patient Record is not a Medical Device.
- Medical Decision Support Systems are Medical Devices.
- Only software modules which are Medical Devices need to conform.

The regulatory consequences

- A “Notified Body” must verify that the Medical Decision Support System conforms with the “essential requirements” of the Medical Directive.
- The company producing the software must have a Quality Assurance System, which conforms with the rules of the standard: Medical Devices - Quality Management Systems – Requirements for Regulatory Purposes[1]
- The software must be documented according to the international standards document: Medical Devices - Software Lifecycles Process[2]
- A risk assessment must be made in compliance with the standard: Application of Risk Management to Medical Devices[3]

[1] International Organization for Standardization 2003

[2] Association for the Advancement of Medical Instrumentation 2006

[3] International Organization for Standardization 2000

The case of Treat: CE marking

- About half a man-year has been invested in designing and introducing the Quality Assurance system
- The investment in the documentation of the system and the risk assessment amounts to another couple of man-years.

Obstacles to implementation

The obstacles to implementation may take many forms:

- Technical
  - The IT environment of the hospital, including computers, servers, intranet or the decision support software itself may be unstable, outdated or slow. Perceived response time will influence clinical acceptance of the system. Kawamoto et al. (2005)
- Organizational or logistic
  - The workflow in the department clashes with the workflow anticipated in the decision support system
  - A staff group (department management, nurses....) hesitates to collaborate
- Psychological
  - Doctors may have a general distrust (maybe justified) of computer generated advice or may feel that a decision support system infringes on their territory.

The case of Treat: Obstacles to implementation

- Psychological factors turned out to be important.
  - Some microbiologists and infectious disease specialists see Treat as an effective way of making sure that the hospital's antibiotic policy is followed in the actual treatment of patients. Others chose to distrust the system, even in the face of the evidence collected in the clinical trials.
  - Presently no systematic data has been collected on the mechanisms behind acceptance/non-acceptance of Treat, but it will be a priority in connection with future Treat installations to use questionnaires to collect data to uncover these mechanisms.

Discussion and conclusions

- Few systems make it through a prospective clinical trial.
  - Logistics are complex, it requires clinical collaborators and lots of funding
  - The trial should be worth while: the system should have a fair chance of successfully addressing an important clinical question
  - The system should contain the features which predict a successful trial
- Even fewer systems obtain widespread clinical implementation.
  - An attractive business case is required to attract funding for development and patents
  - The system must be certified as a medical device
  - And the technical, organizational, logistic and psychological obstacles to implementation must be overcome

A university setting is usually not optimal for solving these problems. An industrial approach is required and fortunately many universities collaborate with business or science parks, which can help solve these problem, either by helping the developers with access to seed- and venture capital or with connections to companies with the required expertise.

Discussion and conclusions

So now we have seen that over a 40 year period out of thousands of systems developed, no more than a good handful of systems have made it to the Implementation phase.

Is the obvious conclusion: Find a different career?

No, the business plan for Treat says that before the end of 2014, Treat should have saved a thousand lives. And that number will grow exponentially for the next many years.

Even though a business plan is nothing more than a piece of paper where you can write numbers, it is difficult to think of another line of work that hold such potential.

And incidentally – a system which can save thousands of lives every year is likely to make you:

rich and famous

Acknowledgements

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[1]Tel Aviv University
[2]Aalborg University
[3]Treat Systems

- and thank you for your attention