

Escher 3.2: Exploratory Software Development

Gert van Valkenhoef

7 September, 2009

Outline

- 1 Introduction
- 2 Work so Far
 - Project Characteristics
 - Our Approach
 - Outputs
- 3 The Future
 - Work in Progress
 - Research Directions

Introduction: Who Am I?

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Introduction: Project Escher

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 - Evidence Based (in context)
 - Personalized
 - Transparent

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- There is a need for regulatory reform
 - More transparent
 - More predictable
 - More collaborative (with drug companies)
- Call for automation of information access (WP 3.2)
 - Clinical trials are delivered to regulators as huge document
 - Research results (summary) are published to journals
 - Data are not (formally) structured

What is wrong with current decision making?

Some slides by Hans Hillege

Escher 3.2: Stated Goals

- Build a comprehensive information system
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 - Identify benefits and risks, trade-offs

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 - Identify benefits and risks, trade-offs
- Support everyone involved in
 - Drug development
 - Drug approval
 - Drug marketing
 - Drug prescription

This Presentation

- 'Work so Far' focusses on Software Development
- Because that is what we've done since I joined
- And because it provides my research context
- Then, in 'The Future' I will extrapolate to research topics
- I hope to get your input there!

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Enabling Reform

- The ultimate goal: enable new, better ways of working
- No-one has clear vision of how any of this could/should be done
- Limited usefulness of “talking it through”
- I.e., up-front requirements analysis difficult or impossible

Target Audience

Our target audience includes:

- 1 regulatory authorities,
- 2 physicians (or their organizations),
- 3 pharmacists (or their organizations),
- 4 patient organizations,
- 5 health care consumers,
- 6 academic (pharmaceutical) researchers,
- 7 opinion leaders and consensus leaders, media, and politicians,
- 8 pharmaceutical companies,
- 9 insurance companies

Up-Front Analysis: Problems

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- Requirements are largely unknown
 - Stakeholders do not have a coherent vision
 - Will change upon seeing any actual implementation
 - Hence, requirements are inherently uncertain/unknown

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- We could spend the next 4 years talking and specifying, but
 - We need to show feasibility
 - We need to generate interest
 - We need to discover (rather than elicit) requirements

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 - We need to show feasibility
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 - We need to discover (rather than elicit) requirements
- **We need working software**

Resource Constraints

- Development being done by 1 post doc, 1 phd student
- Project is Software Development, but
- We should spend more time “doing science” than “coding”

Characteristics Summary

- Huge system to be developed
- Very limited resources
- Many unknowns, uncertainties about goal (desired features)
- Many stakeholders, some unwilling to get (deeply) involved
- Need to align research and software development

Exploratory Software Development

Taken from “Agile” Software Development

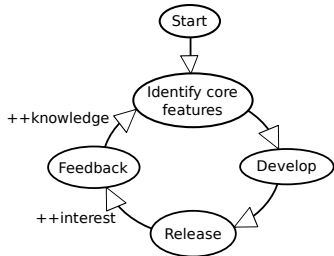
- No big, up-front design or requirements analysis
- Instead, start by identifying core features to start with
- Be ready for change
 - In requirements
 - In system architecture
- Let further requirements emerge
 - ‘Customer’ as part of development team

Exploratory Software Development

Develop software to find unknowns,
arouse interest

- In small iterations
- Tackle important problems first
- High risk of “getting it wrong”
- But minimal cost of failure

Feature-oriented rather than
phase-oriented or task-oriented planning



Exploratory Software Development

Develop software to find unknowns, arouse interest

- Open Source policy; Allow anyone to
 - Use our software
 - Modify our software
 - Verify our approach and code
- Expose what we are doing

Where To Start?

What features to implement first?

Mike Cohn (2005), "Agile Estimating and Planning"

	Low Value	High Value
Low Risk	Do Last	Do Second
High Risk	Avoid	Do First

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High Risk	Avoid	Do First

Start with high value, high risk features

- Generate value from the start
- Eliminate uncertainty

Extreme Programming (XP)

- Our specific methodology: Extreme Programming (XP)
- Kent Beck (1999), “Extreme Programming Explained: Embrace Change”
- Kent Beck (2004), 2nd Edition

Solution Summary

- Look for opportunities to quickly generate value
 - And reduce uncertainty
- Actively seek feedback (release early, often, Open Source)
- Small steps at a time
- Don't be afraid to "get it wrong" the first time.
 - Investment is low
 - Quickly generate feedback

Implications

- Work closely with “customer”
- Continuously spend a part of our research time on development
- Find research problems in/by system development
- Try not to drive development by research interest too much

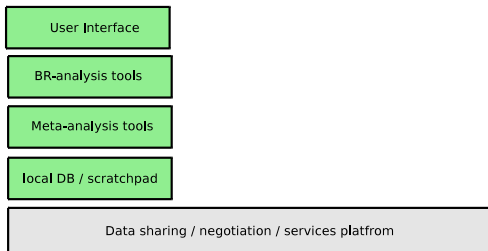
Work So Far (April - July 2009)

- Established a Development Methodology
- Aggregate Data Drug Information System (ADDIS) v0.2
- JSMAA library v0.2 (by Tommi)
- drugis.org website

ADDIS v0.2

- Can store clinical trials data in structured way
- Can do (simple) meta-analyses
 - Meta-Analysis: combining evidence from multiple (similar) studies to answer a specific question with higher confidence
- Can (semi-automatically) construct Benefit-Risk analyses
 - Benefit-Risk analysis: the comparison of the risk of a situation to its related benefits.

ADDIS v0.2



Full top-to-bottom implementation of (a/the) desired application

- Further development is refinement, enhancement, specialization

ADDIS v0.2

ADDIS v0.2

File Edit Add Help

Drugs

- Fluoxetine
- Paroxetine
- Sertraline
- Venlafaxine

Endpoints

- Diarrhea
- Dizziness
- HAM-D
- Headache
- Insomnia
- Nausea

Studies

- Alves et al (1999)
- Bennie et al (1995)
- Boyer et al (1998)
- Chouinard et al (1999)
- De Nayer et al (2002)
- De Wilde et al (1993)
- Dienck et al (1996)
- Drug BR analysis
- Fava et al (1998)
- Fava et al (2002)
- Gargano (1993)
- Hansen et al (2005) - meta ADEs**
- Meta - Fluoxetine vs Paroxetine
- Meta - Fluoxetine vs Sertraline
- Meta - Fluoxetine vs Venlafaxine
- Newhouse et al (2000)
- Rudolph and Faiger (1999)
- Schone and Ludwig (1993)
- Sechter et al (1999)
- Silverstone and Ravindran (1999)
- Tylee et al (1997)

Study ID: Hansen et al (2005) - meta ADEs

Endpoints

- Insomnia Find Studies
- Diarrhea Find Studies
- Dizziness Find Studies
- Headache Find Studies
- Nausea Find Studies

Add Endpoint

Data

	Size	<input type="checkbox"/> Insomnia	<input type="checkbox"/> Diarrhea	<input type="checkbox"/> Dizziness	<input type="checkbox"/> Headache	<input type="checkbox"/> Nausea
Fluoxetine 0.0 mg/day	0	13.7 ± 1.89	11.7 ± 2.5	7.2 ± 1.45	16.6 ± 3.27	18.6 ± 1.79
Paroxetine 0.0 mg/day	0	14.3 ± 2.93	9.2 ± 1.86	10.6 ± 1.86	21.2 ± 5.15	18.3 ± 3.7
Sertraline 0.0 mg/day	0	15.0 ± 3.21	15.4 ± 2.65	7.5 ± 1.48	20.2 ± 3.78	19.5 ± 2.6
Venlafaxine 0.0 mg/day	0	11.2 ± 3.98	5.5 ± 2.32	15.7 ± 4.44	12.8 ± 2.45	31.0 ± 1.68

Add patient group

Analyses

SMAA benefit-risk

ADDIS v0.2

ADDIS v0.2

File Edit Add Help

▼ Drugs
Fluoxetine
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 Meta - Fluoxetine vs Parox
 Meta - Fluoxetine vs Sartr
 Meta - Fluoxetine vs Venla
 Newhouse et al (2000)
 Rudolph and Feiger (1999)
 Schone and Ludwig (1993)
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Endpoint
Name: HAM-D
Description: 50% improvement on the Hamilton Rating Scale for Depression

Studies

Alves et al (1999)
 Bennie et al (1995)
 Boyer et al (1998)
 Chouinard et al (1999)
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Meta-Analysis

Meta Analysis
Endpoint: HAM-D
Fluoxetine

Alves et al (1999)	30/47
Boyer et al (1998)	61/120
Chouinard et al (1999)	67/101
Combined	158/268

Close Save as new study

Meta-Analyze

ADDIS v0.2

ADDIS v0.2

File Edit Add Help

Combined study ID: Drug BR analysis

Endpoints

- Insomnia Find Studies
- HAM-D Find Studies
- Diarrhea Find Studies
- Dizziness Find Studies
- Headache Find Studies
- Nausea Find Studies

Data JSMAA v0.3 - Untitled model* Help

File Results

Drug BR analysis

Criteria

Name	Type	Scale	Ascending
Insomnia	Cardinal	[3.40 - 21.29]	<input type="checkbox"/>
HAM-D	Cardinal	[0.95 - 1.24]	<input checked="" type="checkbox"/>
Diarrhea	Cardinal	[0.95 - 20.59]	<input type="checkbox"/>
Dizziness	Cardinal	[4.36 - 24.40]	<input type="checkbox"/>
Headache	Cardinal	[8.00 - 31.29]	<input type="checkbox"/>
Nausea	Cardinal	[11.05 - 34.29]	<input type="checkbox"/>

Simulation complete.

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What's Next?

- ADDIS v0.4 to be developed September - December 2009
- Expand & make better use of drugis.org
- Several papers:
 - (Rework of Drug Information Systems review?)
 - Knapsack optimization for XP planning
 - Position paper on medical DSS

ADDIS v0.4

- Theme: develop a program for dynamic construction of meta-analyses
- We can do one simple case, but there is much more to do!

My PhD?

I'm still working towards my research proposal.

At present I know that:

- It should be in the context of this project
- I want it to be (somewhat) technical
- It probably shouldn't be on software development methodology

Your ideas are welcome!

- My ideas are on the next slides, though :-)

My PhD?

Some possibilities:

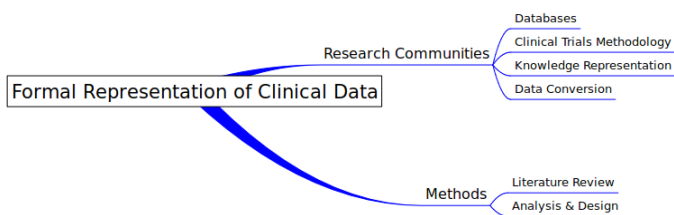
- Formal representation of clinical data
- Identifying relevant data
- Judging quality of (included) studies
- And combining data in useful ways
- Building a SOA around the data sharing aspects
- Building end-user frontends

Formal representation of clinical data

How to represent data from clinical trials

- Different types of output (e.g mortality, blood pressure delta)
- Different protocols: mortality after 6 months, 8 months?
- How to represent the treatment regimen?
- Which study characteristics should be represented?
- How to represent/judge study quality?
- Risks of too complex representation:
 - Elaborate data entry nobody will understand
 - Make other problems worse (data finding, combination)

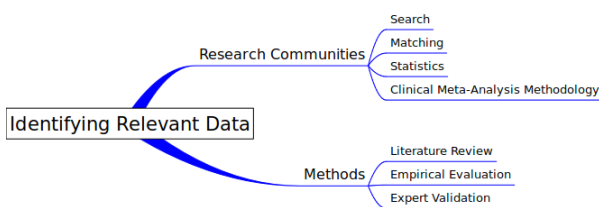
Formal representation of clinical data



Identifying relevant data

- When are studies similar enough to enable comparisons?
- Can different outputs/measures be converted?
- How to collect data on different criteria?
- We want to maximize the number of studies used (recall)
- But we don't want to use data inappropriately (precision)

Identifying relevant data



Study quality

How this is normally done:

- Blinded studies are rated by experts
- Several independent judgments checked for consistency
- For every meta-analysis

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Can we save some time:

- By storing ratings?
- In some sort of reputation system?

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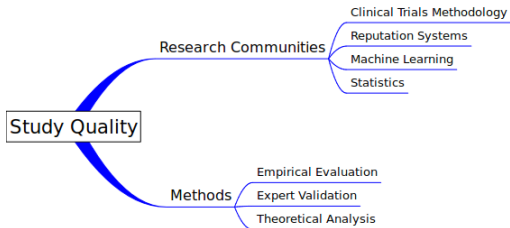
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- By storing ratings?
- In some sort of reputation system?

Can we help find which studies should be rated:

- By having an automated indication of quality?
- Possibly based on machine learning?

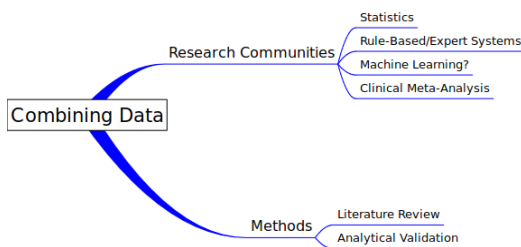
Study quality



Combining data in useful ways

- Overlaps somewhat with previous
- How to combine data on M drugs from a pool of N studies
 - Problems with doing this consistently
 - Get worse with multiple criteria
 - I have slides on this if you are interested
- Can we do more than just meta-analysis?
 - Identify suitable sub-populations?
 - The most suitable dose?
 - Other sorts of data mining?

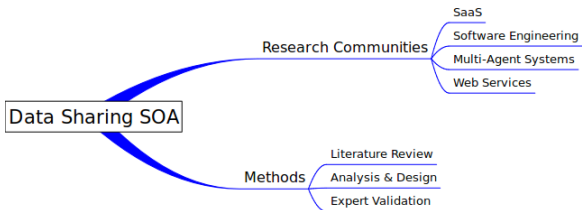
Combining data in useful ways



Building a SOA around the data sharing aspects

- There are many different parties that want to share data
- However, some are (somewhat) antagonistic
 - Pharmaceutical Companies - Regulatory Authorities
 - Competing Pharmaceutical Companies
- They may not want to share with everyone
- They may not want to share for free
- Some of the data is confidential or privacy sensitive
- A central repository for everyone/everything not desired (?)
- A natural fit for Services and Multi-Agent Systems it seems

Building a SOA around the data sharing aspects



Building end-user frontends

Make an optimal interface for

- A clinical practitioner / physician
- A pharmaceutical researcher
- A regulator
- Etc.

To enable them to make informed decisions painlessly

Building end-user frontends

