The future of modeling and simulation as the engine for strategic decision-making in pharma development, economics, and therapeutics

Jonathan French, Sc.D.
Marc R. Gastonguay, Ph.D.

METRUM
RESEARCH GROUP

Outline

1 Introductory remarks

2 Decision-making survey

3 Small group decision-making exercise

4 Decision-making psychology

5 Status quo for decision-making in pharma

6 Some (not so) big ideas

7 Critique of big ideas

8 Next steps

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Decision-Making Survey

Link sent to each of you via e-mail

https://www.surveymonkey.com/r/WQSBYGX

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Lost at Sea: Survival Items

B Bottle of rum

C Can of petrol

C Chocolate Bars

E Emergency rations

F Fishing rod

F Floating seat/cushion

M Mosquito net

P Plastic sheet

R Radio

R Rope

S Sea chart

S Sextant

S Shark repellant

S Shaving mirror

**W** Water container

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Assignment

1   Each individual to rank the survival items (consider one survival fact): 10 min

2   As a group, rank the survival items (consider all 5 survival facts): 10 min

3   Review simulation outcomes as a group

4   Create a revised group ranking of items

5   Compare to Coast Guard survival items ranking

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Lost at Sea: Facts

1. In 2002, a group lost at sea in the Atlantic was rescued when they made radio contact with a passing cargo ship

2. Time to rescue is the most important determinant of shipwreck survival

3. In 1945, the USS Indianapolis was sunk by two Japanese torpedos in one of the most devastating naval losses of World War II. About 900 out of the 1196-man crew made it into the water alive. It is estimated that up to 150 of those crew members died from shark attacks. A total of 317 survived.

4. Rum is useful as a wound antiseptic.

5. Death due to dehydration can occur in 3 days (or less in hot weather) and no one normally lives more than about 5-6 days without water.
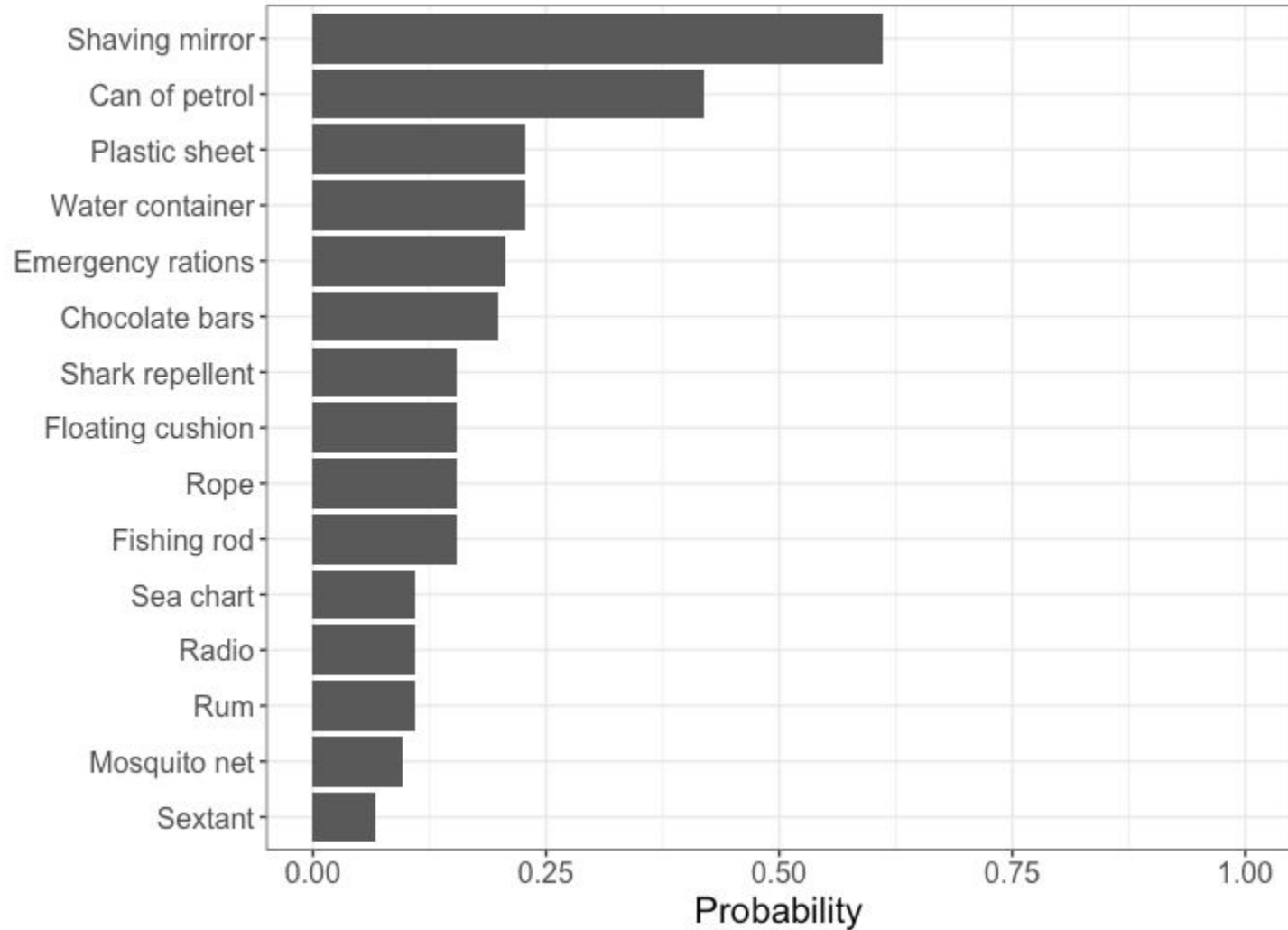
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Probability of rescue with one item
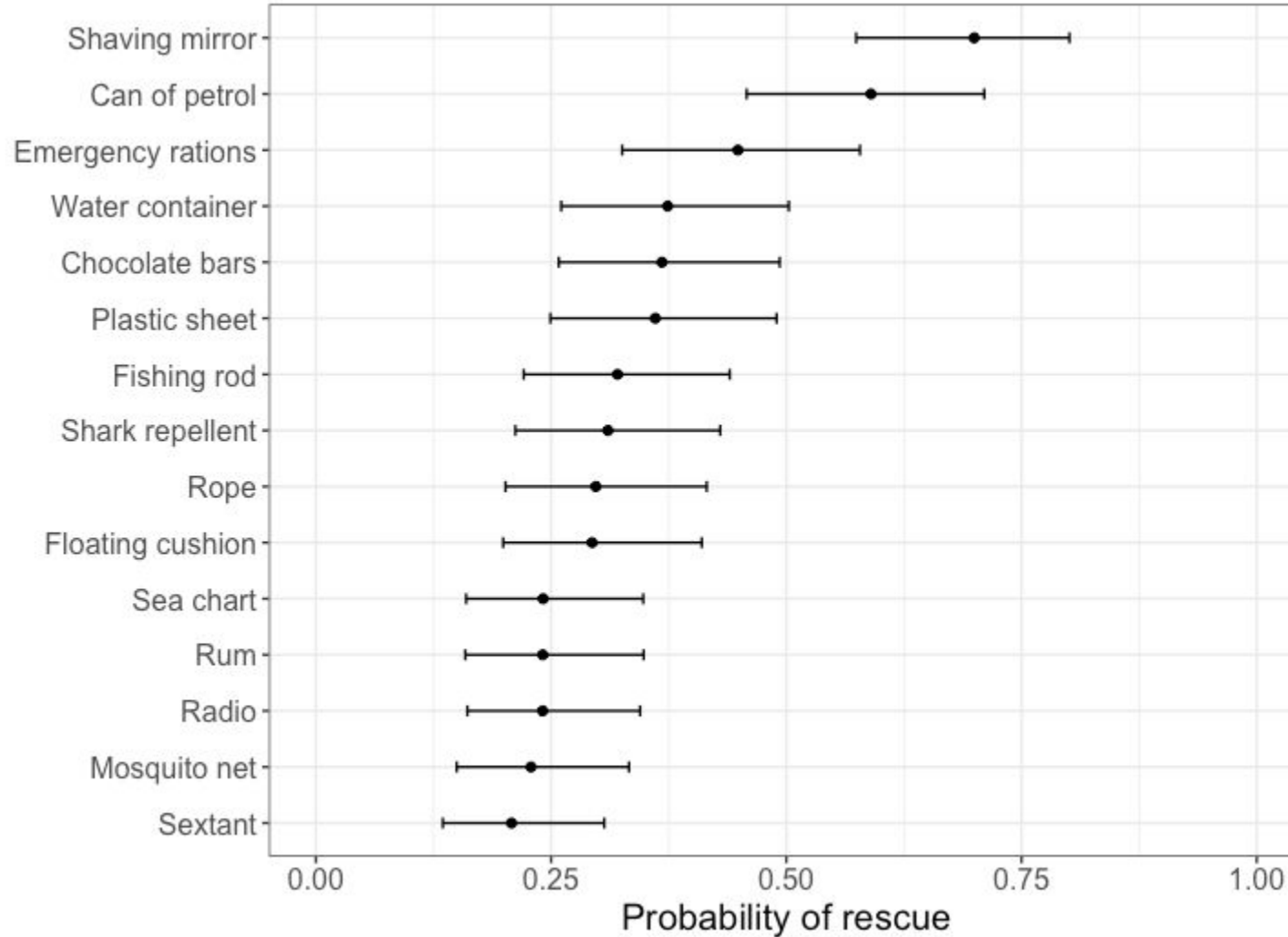
Three items: mean (range) probability of rescue
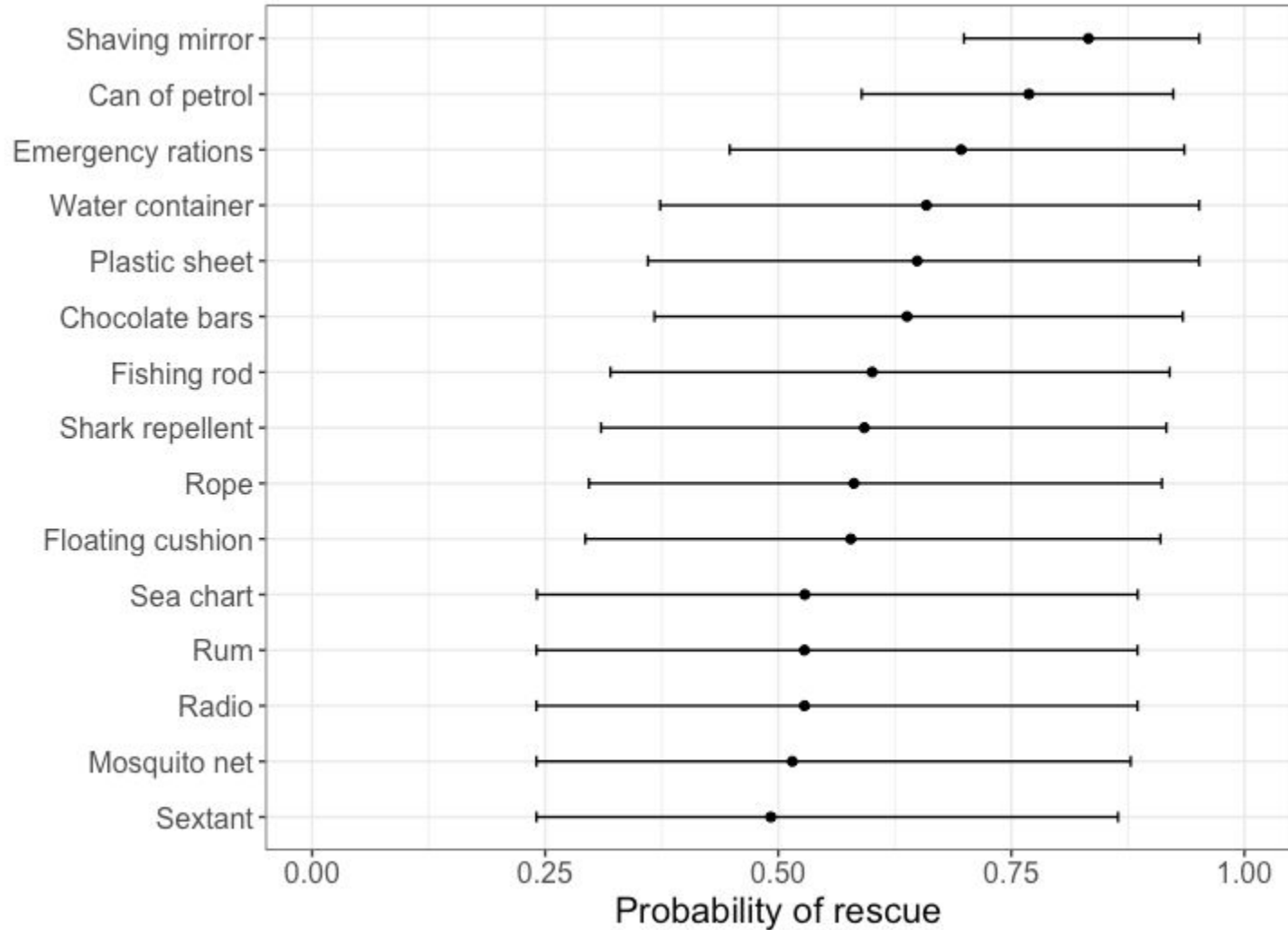
Among sets with high probability, which items are included?

Lost at Sea: Survival Importance by Coast Guard

1. Shaving mirror

2. Can of petrol

3. Water container

4. Emergency rations

5. Plastic sheet

6. Chocolate bars

7. Fishing rod

8. Rope

9. Floating seat/cushion

10. Shark repellant

11. Bottle of rum

12. Radio

13. Sea chart

14. Mosquito net

15. Sextant

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Psychology of Decision-Making (References 1)

"Decision Making in Your Organization: Cutting through the Clutter." n.d. Accessed March 10, 2019. https://www.mckinsey.com/business-functions/organization/our-insights/decision-making-in-your-organization-cutting-through-the-clutter.

Kahneman, Daniel, and Patrick Egan. 2011. Thinking, Fast and Slow. Vol. 1. Farrar, Straus and Giroux New York.

Kahneman, Daniel, Dan Lovallo, and Olivier Sibony. n.d. "A Structured Approach to Strategic Decisions | MIT Sloan Management Review." MIT Sloan Management Review. Accessed March 9, 2019. https://sloanreview.mit.edu/article/a-structured-approach-to-strategic-decisions/.

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McGregor, Jena. 2019. "Analysis." The Washington Post, March 4, 2019. https://www.washingtonpost.com/business/2019/03/04/nobel-prize-winning-psychologist-ceos-dont-be-so-quick-go-with-your-gut/.

Psychology of Decision-Making (References 2)

Nathan Matias, J. 2017. "Bias and Noise: Daniel Kahneman on Errors in Decision-Making." Medium. Medium. October 17, 2017. https://medium.com/@natematias/bias-and-noise-daniel-kahneman-onerrors-in-decision-making-6bc844ff5 194.

Newell, Ben R., David A. Lagnado, and David R. Shanks. 2015. Straight Choices: The Psychology of Decision Making. Psychology Press.
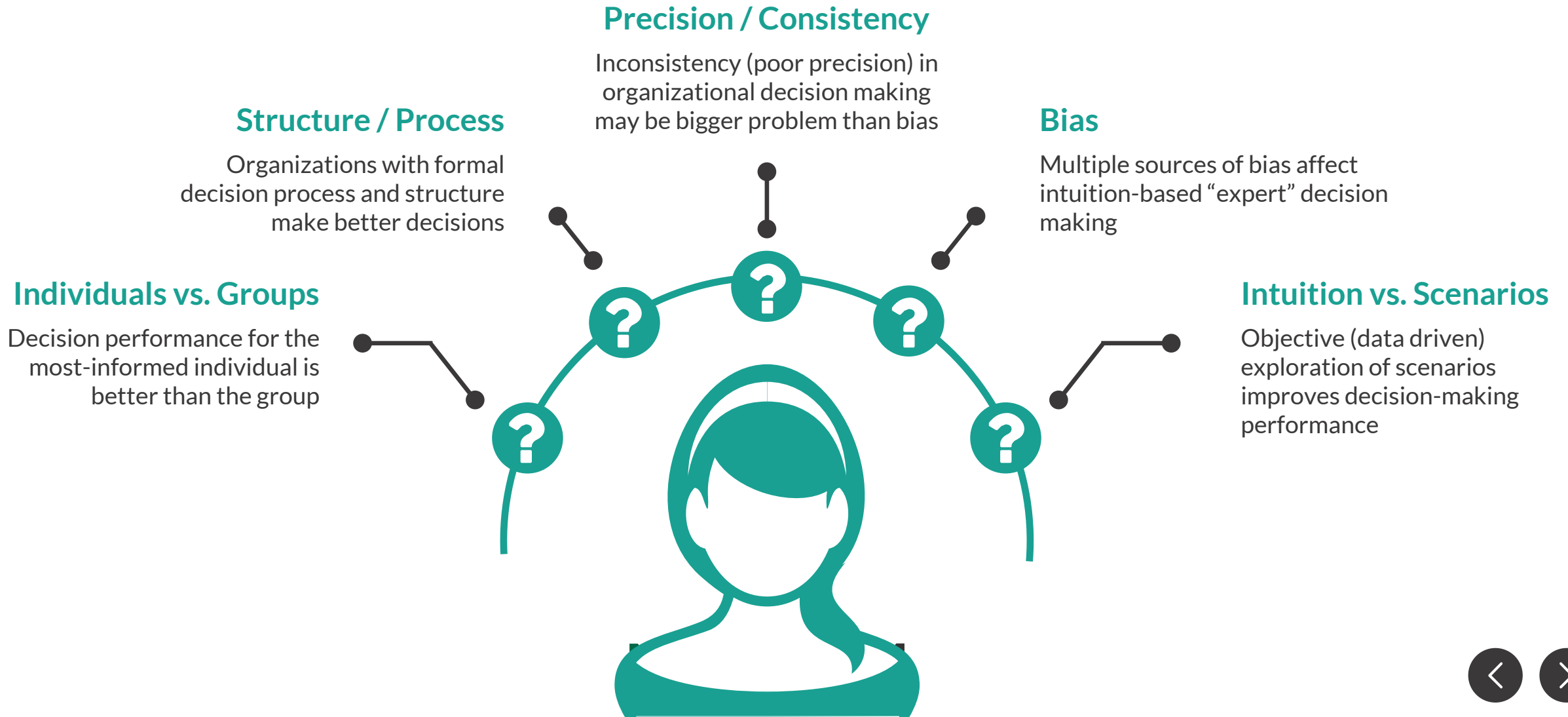
Pettigrew, Andrew M. 2014. The Politics of Organizational Decision-Making. Routledge.

Teirlinck, Peter. 2017. "Configurations of Strategic R&D Decisions and Financial Performance in Small-Sized and Medium-Sized Firms." Journal of Business Research 74 (May): 55–65.

Tenney, Elizabeth R., Nathan Meikle, and David Hunsaker. 2018. "Research: When Overconfidence Is an Asset, and When It's a Liability." Harvard Business Review, December 11, 2018. https://hbr.org/2018/12/research-when-overconfidence-is-an-asset-and-when-its-a-liability.

Psychology of Decision-Making: Themes

Precision / Consistency

Inconsistency (poor precision) in organizational decision making may be bigger problem than bias

Structure / Process

Organizations with formal decision process and structure make better decisions

Bias

Multiple sources of bias affect intuition-based "expert" decision making

Individuals vs. Groups

Decision performance for the most-informed individual is better than the group

Intuition vs. Scenarios

Objective (data driven) exploration of scenarios improves decision-making performance

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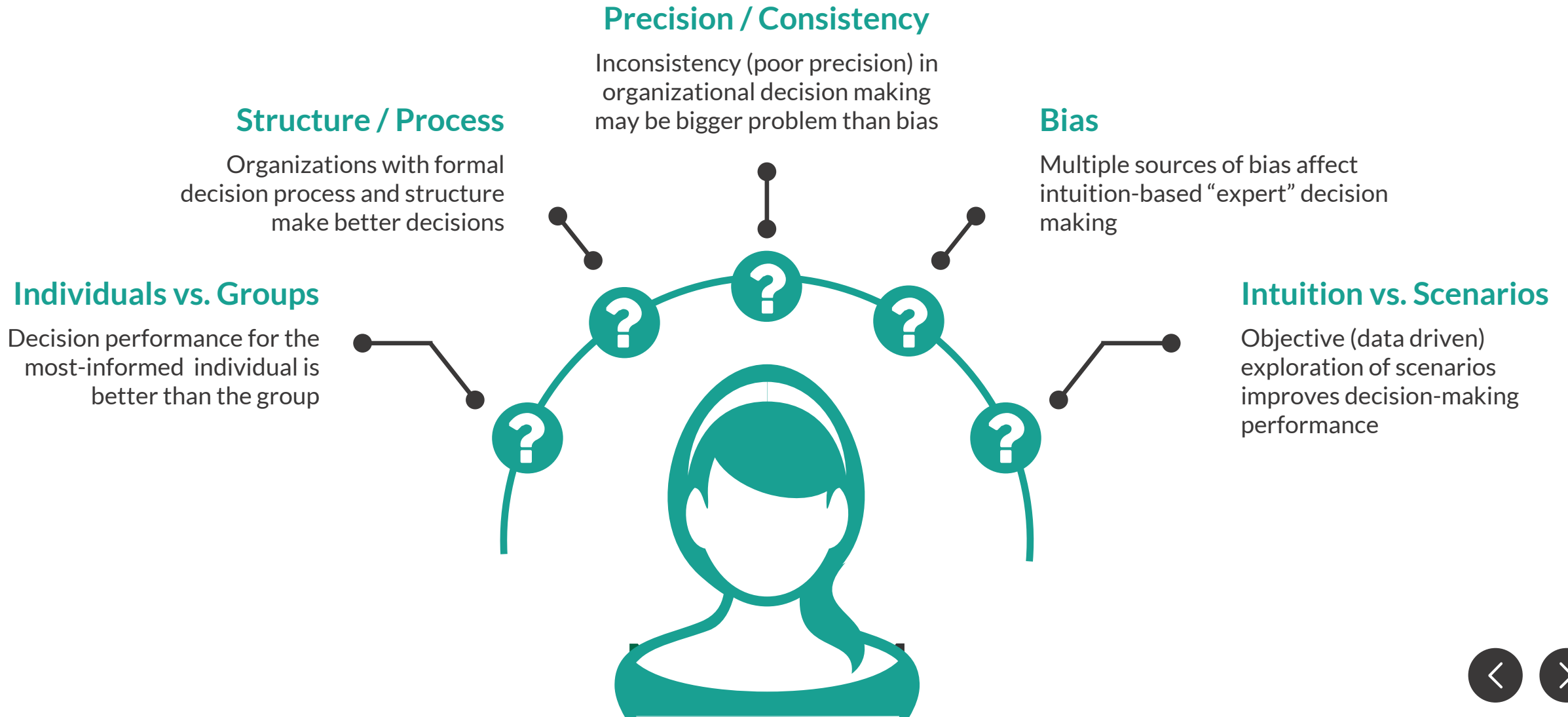5 **Status quo for decision-making in pharma**

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Psychology of Decision-Making: Relevant to Pharma?

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Decision-Making Survey

Your responses

https://www.surveymonkey.com/

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1. Opportunity @ the Intersection

- Extensive domain expertise

- Siloed decision-making

- Opportunity to improve?

Quantitative Disciplines

**Clinical / TA**

Regulatory

Translational Research

Opportunity

Health Economics

Portfolio

Epidemiology & RWE

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Taylor & Francis
Taylor & Francis Group

Check for updates

ORIGINAL RESEARCH

A cost-effectiveness analysis of denosumab for the prevention of skeletal-related events in patients with multiple myeloma in the United States of America

Noopur Raje[a], Garson David Roodman[b], Wolfgang Willenbacher[c], Kazuyuki Shimizu[d], Ramón García-Sanz[e], Evangelos Terpos[f], Lisa Kennedy[g], Lorenzo Sabatelli[h], Michele Intorcia[h] and Guy Hechmati[i]
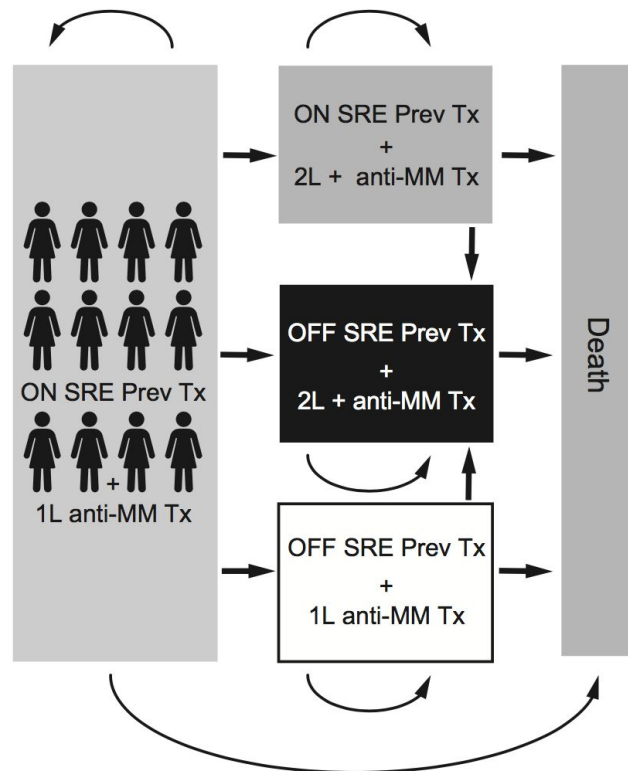
Figure 1. Depiction of model health states. 1L, first line; 2L+, second line or later; Abbreviations. MM, multiple myeloma; OFF SRE Prev Tx, patients not receiving treatment to prevent SREs; ON SRE Prev Tx, patients receiving treatment to prevent SREs; SRE, skeletal-related event; Tx, treatment.

23
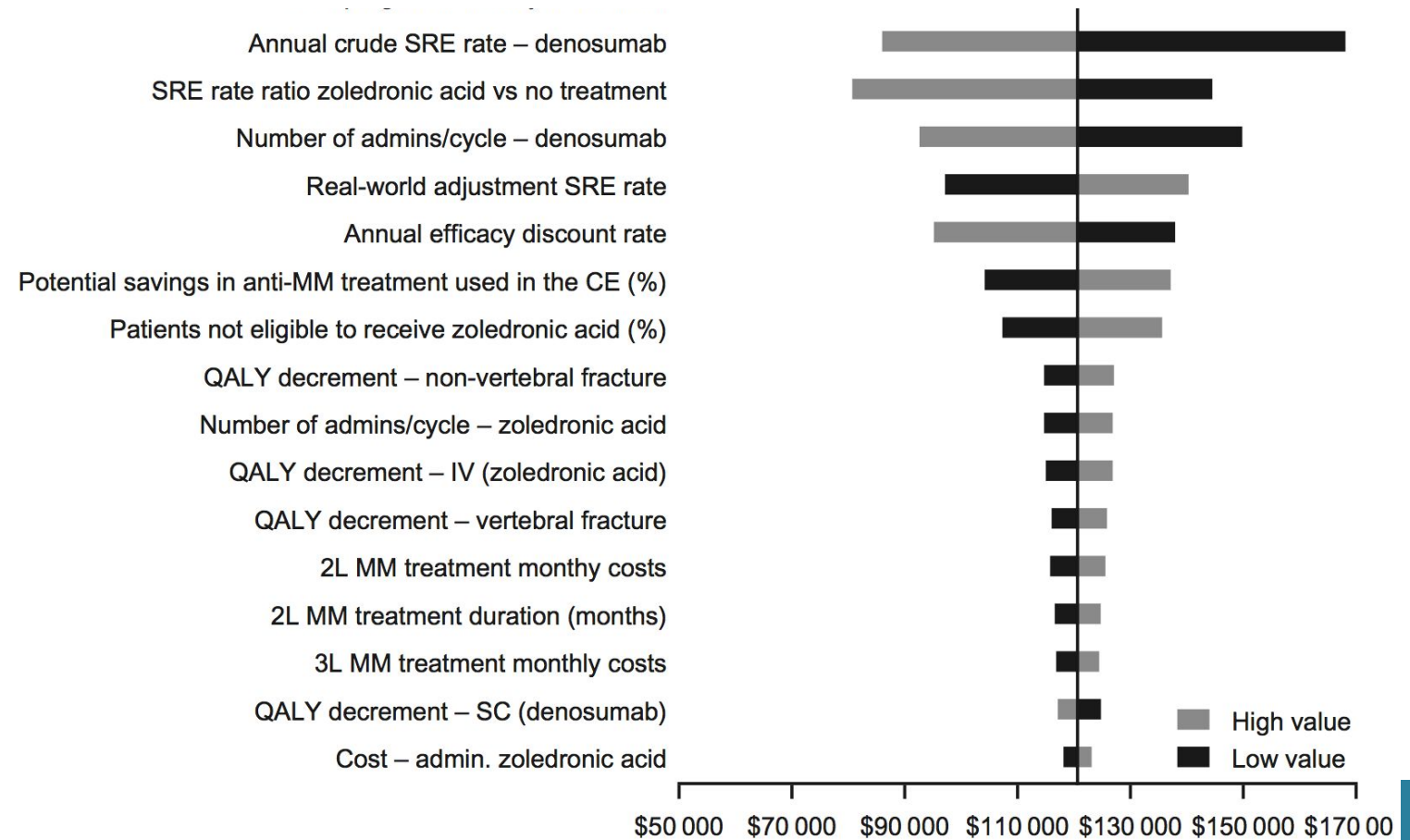
Linking MSSP/Fracture Model & Pharmacoeconomics
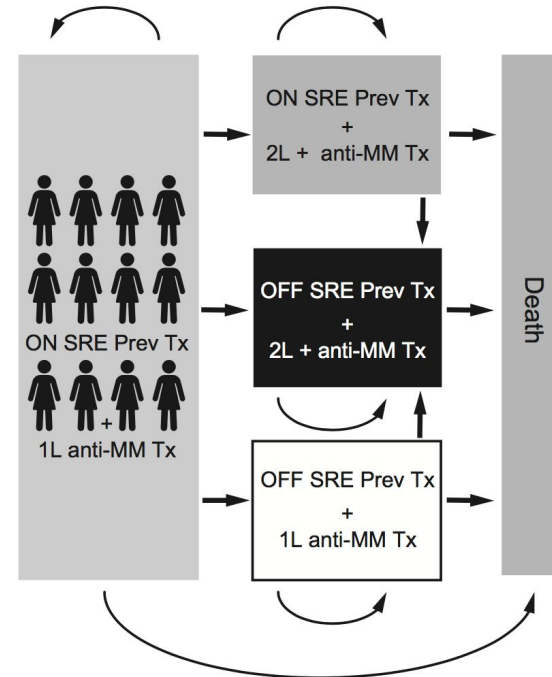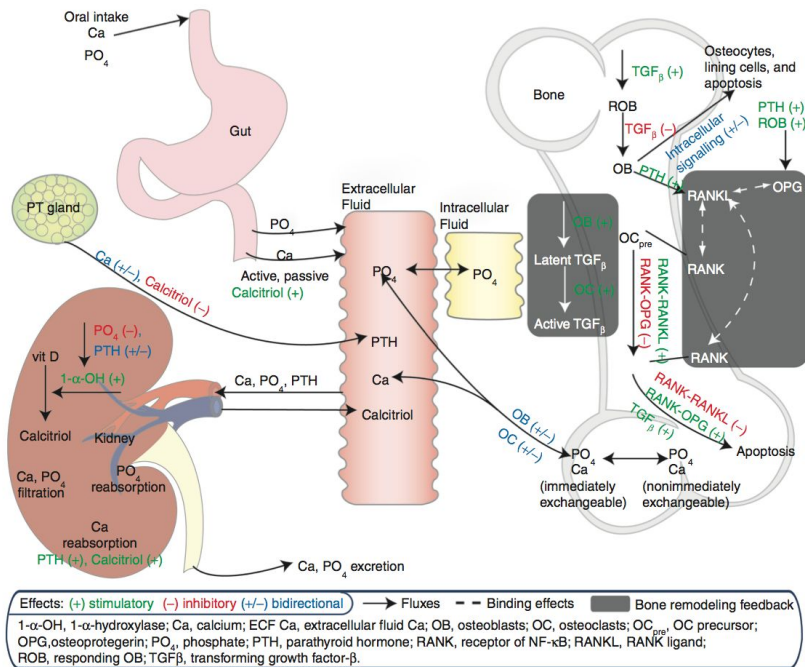
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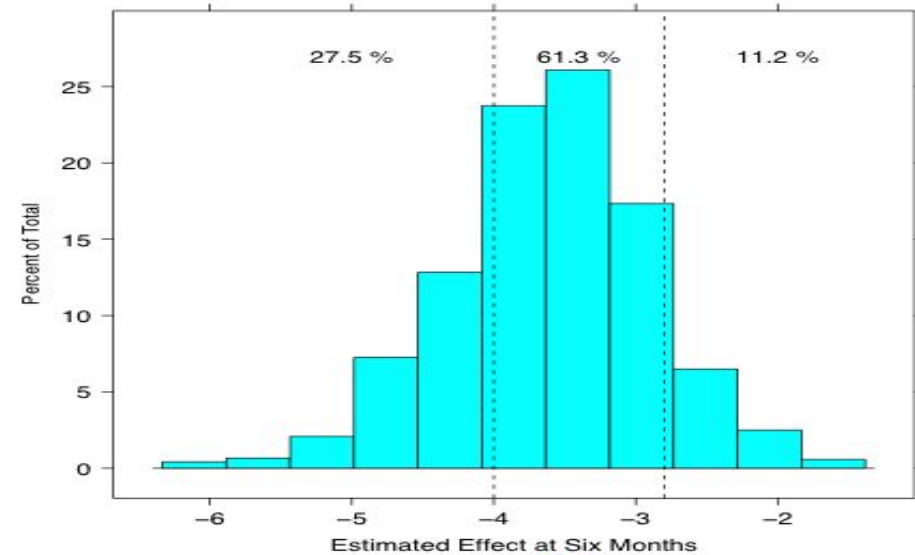
Early Development ICER ($/QALY) Predictions
● New drugs
● New dose/regimen
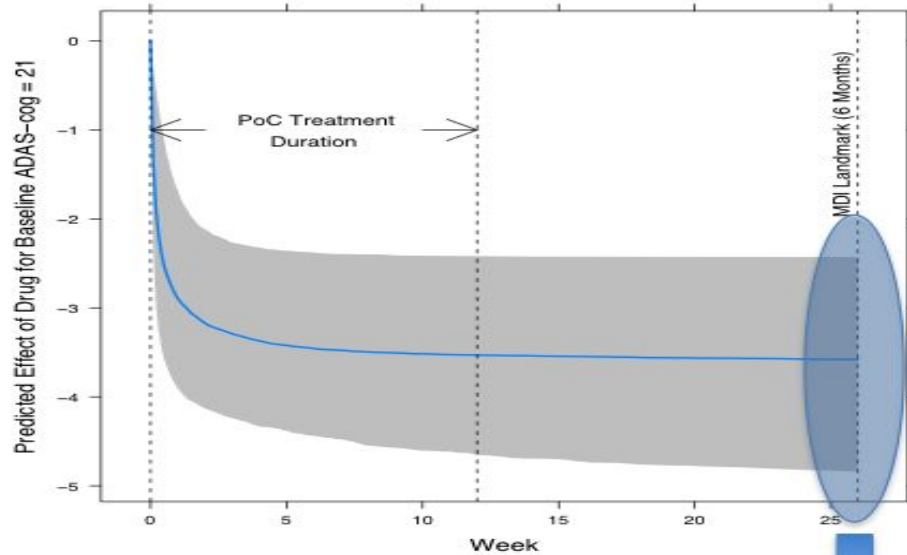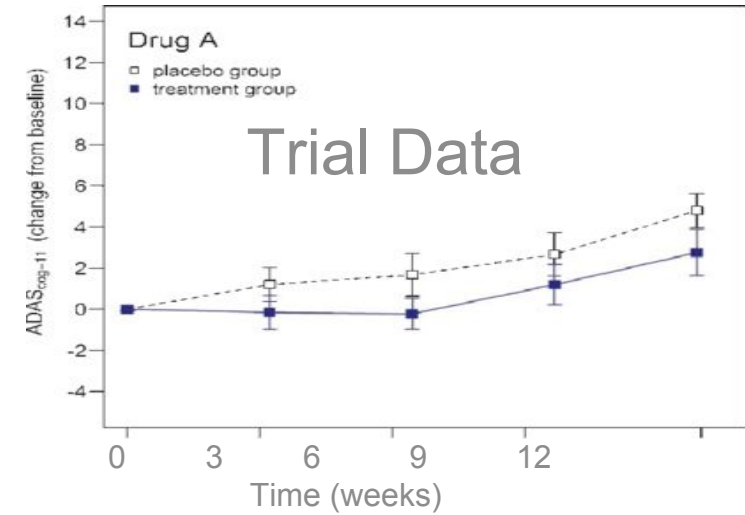● Combination therapies
● New indications
● Adverse Events

$$g(\theta_{ipk}) = \eta_{pk} + \alpha_{pk}t_{ipk} + E_{\mathrm{PBO}}(t_{ipk}) + E_{\mathrm{DRG}}(t_{ipk}, D_{ipk})$$

Prior Model

+

Trial Data

Model Based Projection of Decision Criteria

3. Simulate **All Trials**

Quantitative Systems Pharmacology, Biomarker Exposure-Response

PK, PK-PD, Early Probability of Technical Success, Biomarkers

Model Based POC, Pop PK-PD, Trial Design, Dose Selection, Endpoints, Surrogates

Trial Simulation, Confirmatory Efficacy, Safety, Pop PKPD Filing and Label

Comparative Effectiveness, Real World Evidence

Translational

Phase I

Phase II

Phase III

Post Marketing
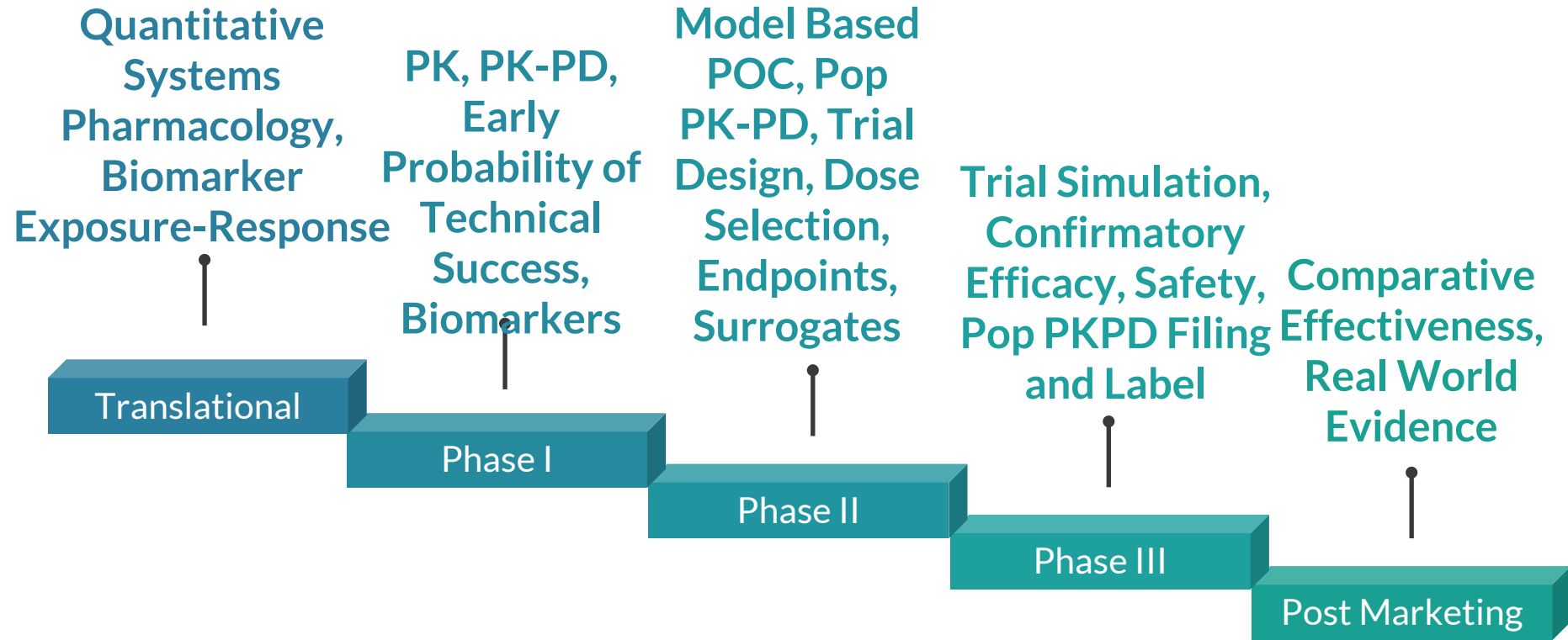
Off-The-Shelf Disease Area Platform Content: Disease Progression, Quantitative Systems Pharmacology, Competitor Model-Based Meta-Analysis, Trial Simulation Tools

3. Simulate **All Trials**

Goals for the Future:
- Simulate all trials at time of protocol development
- Plan and implement all modeling & simulation activities in anticipation of the data to be collected in the next trial
- Update simulations and analyses, given interim and final data

Development Team, Decision Makers

Define Questions, Decision Criteria, Constraints, Scenarios

M&S Scientist

Quantitative M&S Strategy

Explore Results & Alternative Scenarios: Real-Time Simulation

M&S Based Decision

Analyze Results, Prepare Web App & Supporting EC2 Cluster

User 1 EC2 Cluster

User 2 EC2 Cluster

User 3 EC2 Cluster

Other M&S Projects

Implement Estimation Models & Simulations

Cloud-Based Clusters

Assess M&S Results: Satisfactory?

yes

no

Refine Models & Simulations

RWE Simulator   Data Sources   Demographics   Lantus / SOC   Toujeo   Simulation Summary ▾   Advanced

Population Specification

Weight for each data source

Edition3

0 — 5 — 10

0 1 2 3 4 5 6 7 8 9 10

MGH Baseline HbA1c 8 to 11

0 — 5 — 10

0 1 2 3 4 5 6 7 8 9 10

MGH

0 — 5 — 10

0 1 2 3 4 5 6 7 8 9 10
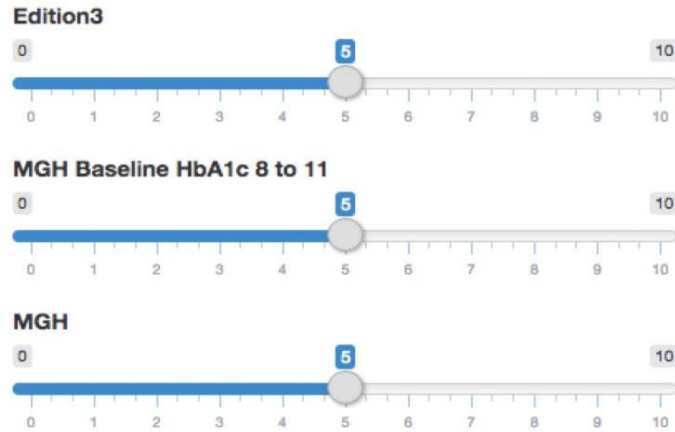
Summary of relative weights

Population
- Edition3
- MGH
- MGH Baseline HbA1c 8 to 11

Relative weighting of populations
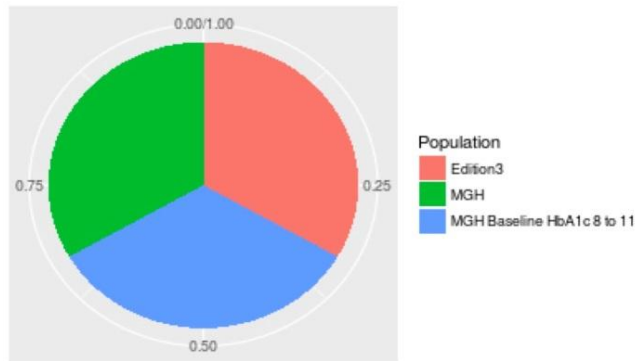
Summary of Specified Population

%	BL ≥ 9 No SU	BL ≥ 9 SU	BL < 9 No SU	BL < 9 SU	Marginal Total
Target=7	20.7	13.8	16.8	11.2	62.5
Target=8	10.1	7.8	11.8	7.9	37.5
Marg. Tot.	30.8	21.6	28.6	19.1	100.0

● ● ● | M Dashboard × | R RStudio - git-SAN0101F × | RWE Simulator × | James ⚠

← → C | 🔒 https://i-e7be0648.metworx.com/envision/rwe_simulator/ | ☆ ••• G 🗂 △ ≡

⊞ Apps ★ Bookmarks 📁 News 📁 metrum office 📁 general ref 📁 comp ref 📁 stats 📁 googlecode 📁 tmp 📁 R 📁 metrum public 🗋 rogerskatee@gmail.c » 📁 Other Bookmarks

RWE Simulator   Data Sources   Demographics   Lantus / SOC   Toujeo   Simulation Summary ▾   Advanced

Probability of Success

Dashed line represents (Bayesian prior) mean powe
Solid line is fixed at 90%

Difference in Composite Event Rates

Treatment difference (U300-Comparator) in Composite Endpoi

### Current Scenario Statistics

	Estimate (%)
Toujeo Composite Endpoint Rate	38.96
Lantus / SOC Composite Endpoint Rate	34.38
Expected Treatment Difference (U300-Comparator)	4.57
Average (Bayesian Predictive) Power	69.70

EDITION 3

Save Scenario

Saved scenarios can be reviewed by toggling to "Multi-scenario Summary" on the Navigation Bar

5. Cross-Discipline Decision Informatics Platform
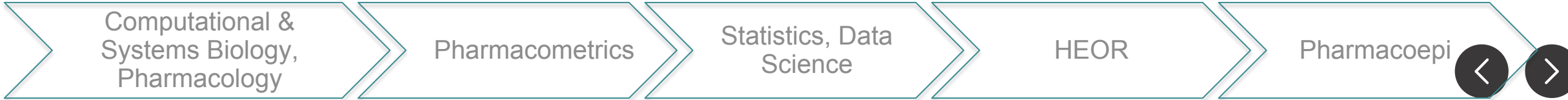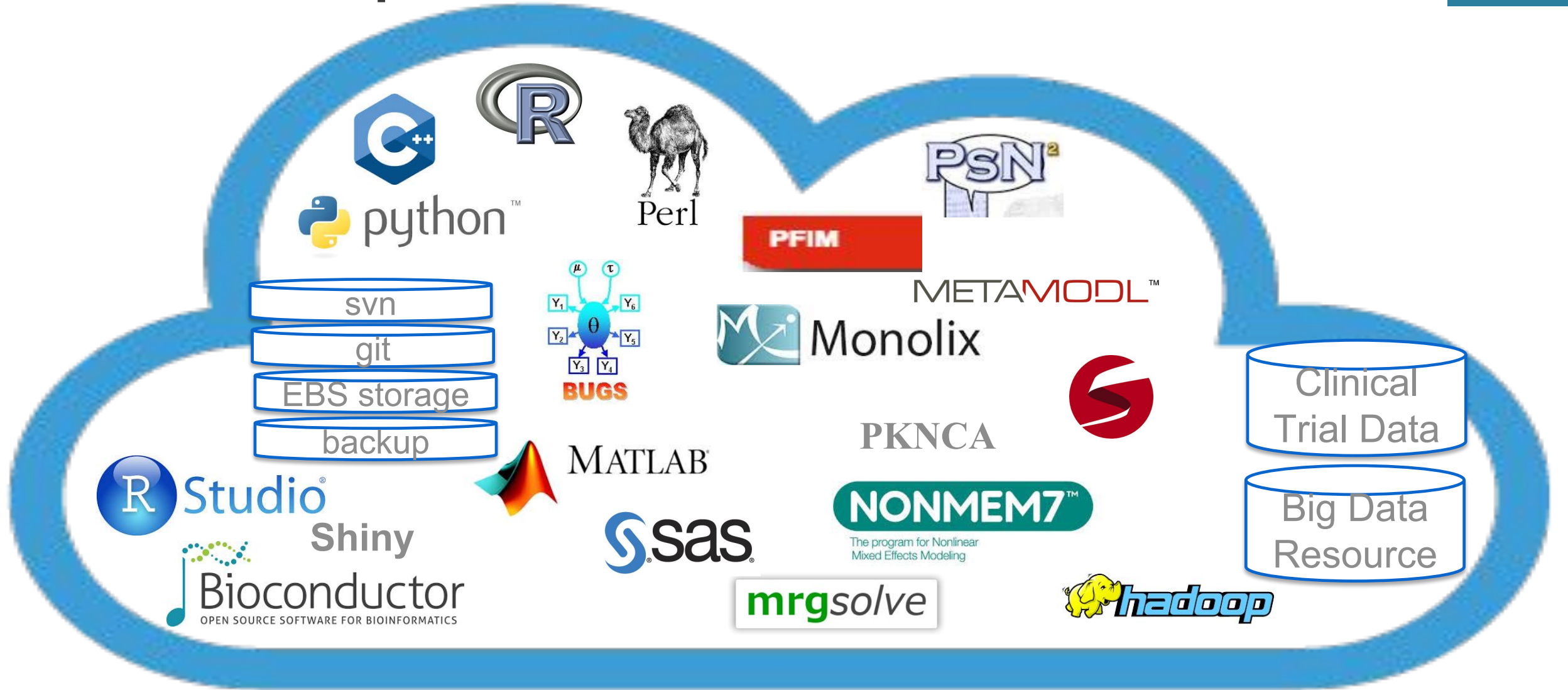
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SWOT

S
Strengths
What makes this big idea a game-changer?

W
Weaknesses
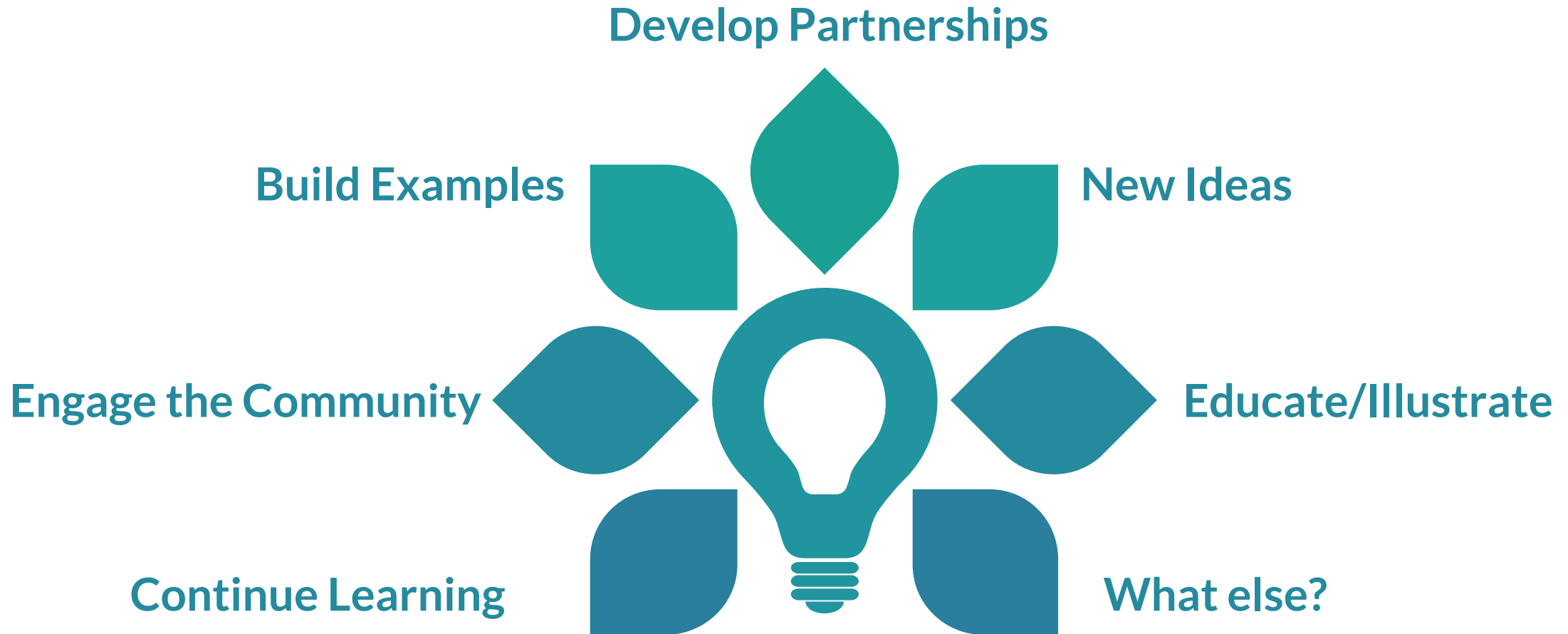Which characteristics of the big idea leave room for improvement?

O
Opportunities
What are the early points of entry, low hanging fruit?

T
Threats
What challenges to adoption/implementation do you anticipate?

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S	**W**	**O**	**T**
Strengths	**Weaknesses**	**Opportunities**	**Threats**
What makes this big idea a game-changer?	Which characteristics of the big idea leave room for improvement?	What are the early points of entry, low hanging fruit?	What challenges to adoption/implementation do you anticipate?

1. Opportunity at the intersections

2. Model-based decision criteria

3. Simulate all trials

4. Interactive scenario evaluation

5. Cross-discipline decision informatics platform

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Next Steps

Develop Partnerships

Build Examples

New Ideas

Engage the Community

Educate/Illustrate

Continue Learning

What else?

Reception

Thank you for your participation.

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