Knowledge-Focused Decision-Making

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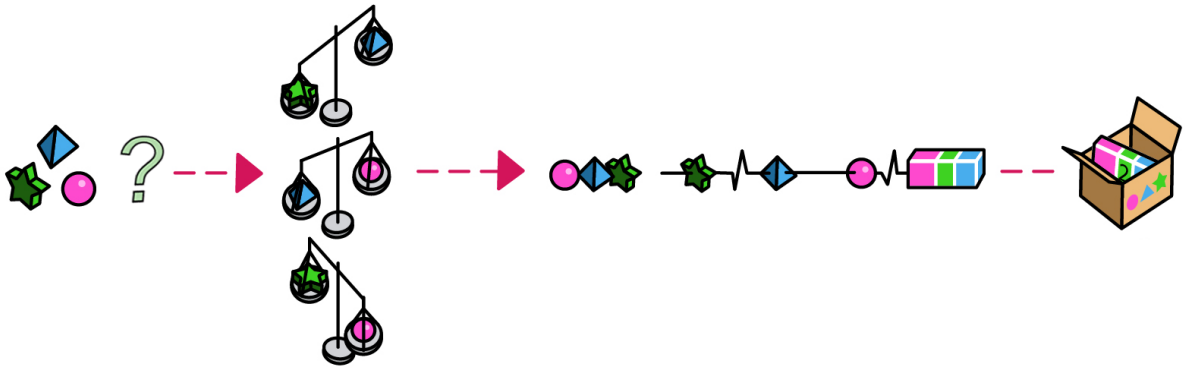

I'd like to share a real story about moving a biopharma team from cross-functional conflict to creative problem-solving. By thoughtfully applying concepts from cognitive science and decision strategy, a team member can focus a group on the knowledge that counts for making sound decisions.

Understanding how the brain naturally comes to conclusions helps you guide R&D groups through contentious decisions. Knowing that you don't see the whole picture keeps you from unproductive conflict. Arraying all the options opens up the team's thinking. Homing in on the key information saves time and money. Using the combined knowledge in the team leads you all to better decisions.

Here's what we recommend for teams facing complex decisions:

1. Observe the way differences in knowledge make people primed to take different actions.
2. Reframe your own ideas as "options I see" instead of "solutions I know."
3. Pool team knowledge to structure decisions as choices between options.
4. Specify the information that the team would find compelling to eliminate options.
5. Efficiently produce robust data.

Should we run a new study?

A Biostats manager asked me for help resolving a team disagreement between her department and the Preclinical group. Applying knowledge-focused decision concepts, she was able to step back and help the team generate a more effective, less costly way to get the data needed for their decision.

I started our work by asking the Biostats lead to describe what was happening.

> I am the Biostatistics lead for a drug development program to increase Factor A in patients with a rare disease. Management instructed the project team to have the first patient dosed in the first quarter of next year, and made it a team goal which impacted our performance review.
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> In the third quarter, we received the results from a study in 12 primates that did not find a statistically significant difference between groups, although there was a trend towards significance (p= 0.08). The

study had only 4 animals in each dose group and there was an outlier in the placebo group. Factor A increased about 15% in the treated group, but also in the placebo group! The dosing schedule in the primate study was slightly different from the first-in-human study plan.

At our team meeting, before I could present my statistical analysis, the Preclinical lead (P) proposed a new, larger primate study. This surprised me because the company was in a cash crunch, trying to conserve funding for another, higher priority drug, and it would be a large unexpected cost.

Here's our conversation.

Preclinical: To get a more definitive answer on the drug effect, I'd like to propose that we conduct a new primate study that would have 9 animals per group and would dose the animals on the same schedule planned for humans. The study will cost approximately $250,000.

Biostats (Me): What are we hoping to get out of this study?

Preclinical: A few things. It will help give us confidence around there being a drug effect. It will help to refine the selection of the doses to be tested and justify the dosing regimen to the FDA. Also, we will add in a competitor drug as a control, in addition to placebo, so we can have a head to head comparison with the competitor. And, the data will be used to feed into the PK/PD modelling we are doing on the drug.

Biostats: Will the results be available prior to starting the dosing in humans?

Preclinical: It would read out about a month before the planned first dose in humans.

Biostats: Would it be possible that if there is not a significant difference between the drug and placebo in this study that we would decide not to pursue dosing in humans?

Preclinical: No, I don't think so.

Biostats: Why not? If we can't show an effect preclinically, why continue to pursue development?

Preclinical: Well, primates are not the most sensitive model for this effect. The competitor only found a 15% increase in Factor A in primates, but 25% in humans. Mice are a more sensitive model.

Biostats: Then why are we studying the primates? Shouldn't we be studying mice?

Preclinical: We need genetically modified mice for the study, and we are breeding a colony of them, but we are limited by their breeding speed. We wouldn't be able to breed enough mice to do the study in time to get results on the planned first dose in humans. We have done some smaller studies on these kinds of mice and found that in that model our drug does better than the competitor drug.

Biostats: Maybe we should think about doing a mouse study instead.

Preclinical: But the corporate goal for our team is to have the first human dosed by the end of next quarter. If we did the mouse study, we would miss that goal.

1. Observe the way differences in knowledge make people primed to take different actions.

To analyze why Biostats and Preclinical were so far apart, we used the Recognition-Primed Decision Model from the work of Gary Klein[1]. This groundbreaking research shows that the brain makes sense of situations by matching what's happening now to what's happened in the past. Past experience is archived in the form of stories – sequential, time-linked information associated with autobiographical events.

The brain takes in data from the current environment and starts searching for a match in the archive of stories - all without conscious awareness. As soon as it finds the first story that matches, it 'recognizes' the situation, and stops searching. Several elements appear to consciousness simultaneously — expectancies, clues, goals, and typical actions. This recognition primes people to apply their know-how right away.

Preclinical and Biostats, however, came up with conflicting expectancies, clues, goals, and actions. To plan the Biostats manager's next steps, we examined the different stocks of knowledge that led to such different ideas.

	Preclinical	Biostatistics
Expectancies: What you predict will happen.	Larger primate study will confirm efficacy. Leadership will believe $250,000 is worthwhile.	Larger primate study might not confirm efficacy. Leadership will balk at $250,000.

We realized that Preclinical and Biostats used different stocks of knowledge to address the issue of confirmation. Preclinical used what he'd seen in the literature on Factor A, and expected the study would confirm efficacy. Biostats used what she'd seen in studies at different companies, and expected it might not. Because of their different stocks of know-how, their expectations were far apart.

Their previous experience also led to different predictions of what leadership would do. Preclinical had known this leadership team for years and expected that they would go along. Biostats was newer to the company, and vividly recalled other leadership teams who'd battled budget requests.

	Preclinical	Biostatistics
Relevant Clues: The data that's important.	Trend toward significance, p=0.08, mouse studies show superiority.	Outlier in primate placebo group, factor A up 15% in both groups.

Their functional backgrounds led them to look at different things.

For the Preclinical lead, what seemed important in the primate study were the positive results in the treatment group. Being a biologist, the mechanism of action and the previous positive mouse study came to mind when he looked at the primate data.

In contrast, for the Biostats lead, what seemed important was the outlier in the primate placebo group. Being a statistician, algorithms for calculating significance came to mind when she looked at the data. She hadn't studied the mechanism of action, nor was she familiar with the previous mouse study.

In our discussion, the Biostats lead recalled that Preclinical's presentation was "sort of more descriptive," and realized that if they combined mechanistic and quantitative insights, they could provide a richer knowledge stock for the team to work with.

	Preclinical	Biostatistics
Plausible Goals: What you can achieve.	Meet Q1 deadline for first human dose.	Decide to discontinue if no significance.

We analyzed the different experiences that led to their different assumptions about plausible goals.

To Preclinical, the goal was to start the clinical trial on schedule. He had been at the company for many years and management had always set the milestones. It hadn't occurred to him to question the deadline.

To Biostats, the goal was to determine whether or not to start the clinical trial at all. It hadn't occurred to her to start a trial without conclusive data.

	Preclinical	Biostatistics

Typical Action: What you can do to achieve the goals.	Run larger primate study and start clinical trial in Q1.	Don't run larger primate study. Before deciding whether to start clinical trial, run mouse study to get more conclusive results on efficacy.

The two parties were thus primed to "recognize" different actions as logical next steps. Preclinical would run a new primate study and start the clinical trial on time. Biostats would run a mouse study and delay the decision whether to start a trial.

2. Reframe your own ideas as "options I see" instead of "solutions I know."

After this analysis, Biostats realized she never shared her statistical analysis in the meeting, so the team has no access to the knowledge she developed. She had been convinced she was right before entering the room. "At that meeting, I started shooting holes in Preclinical before explaining what I'd seen."

This reflection led her to reframe her role as a team member. Instead of trying to convince the team she was right, she pictured her role as building the team's knowledge. Instead of asking herself, "How can I stop this new study?" she composed a new question that would help the team: "How likely is the new study to give a conclusive result?"

> I came to it with an open mind. I didn't have a horse in the game as to whether we're doing a new monkey study or not. I could honestly have been persuaded to go either way, depending upon the discussion that ensued. It makes a difference, too, because I wasn't advocating either way. I was just saying, listen guys, I just want you to know what your 250 grand is buying you.

3. Pool team knowledge to structure decisions as choices between options.

The Recognition-Primed Decision Model helps in selecting a structured decision-making process that will work well for the organization. Roger Martin's work on strategic choices[2] is especially useful for biopharma R&D. He shows how cross-functional groups can array different action options and agree on the information that would enable the team to commit to a choice.

To start structuring options and information, Biostats compiled the analysis of the first study and prepared a statistical projection for the new design. After that, she set up an individual meeting with the Preclinical lead.

> I said to him, "Look I've gone to all this trouble to do the analysis on the first study results. It hasn't been presented at a team meeting. I think we should make an effort to integrate our results. Let's work together to come up with a joint story, because I think it's important."
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> He's open to that. We did the work beforehand to lay the groundwork.

For the next team meeting, Biostats and Preclinical agreed that she would lay out two options - running the new study or not. She'd share what she learned about how confident they could be in the results.

The next meeting found the team digressing into different details of the new study, but Biostats redirected the conversation.

> Again, they were trying to design the study before my presentation. I interrupted them and said, "I don't mean to be rude, but I would like to present the results of what happened in the last study because I think it would help our discussion of what we need to get out of the next study and whether we should do the next one.
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> "Let's look at what the new study will actually get us. We're actually at pretty low power on that. If you're going to say you want to see a statistically significant result from this study, you're right at that limit where you may get it, or you might not."

4. Specify the information that everyone would find compelling to eliminate options.

Once the options are arrayed, Martin suggests asking the proponents of each option, "What data would be compelling for you to change your mind?" This question acknowledges that the brain quickly delivers only one course of action to a person. It encourages people to slow down and reflect on aspects of the situation they hadn't considered before.

Biostats used this idea as she continued the conversation.

> My message to them was, do you want to stop the program or greenlight the program on something that's this low-power?
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> We discussed the existing evidence: the ambiguous findings of the first monkey study, a positive but small mouse study, and a second mouse study which will read out in the few months. I said since all of the studies we have are very small, it would be good if we could use all of the existing evidence together to create decision criteria for moving forward, since any single study was too small to be definitive.

Listening to this enabled team members to consider asking management to delay the first-patient-in milestone, which had not occurred to Preclinical. As it turned out, there was more management flexibility than they thought.

> We got lucky on the timeline. Our company ended up being short on funds for the next 6 months, so management was trying to spend less money, and push back non-essential trials. The human study for this new drug was considered to be non-essential, so we can wait to get the results from all of the preclinical studies and put the information into the predictive model so that we can make the best decision possible about whether to move forward into humans.

5. Efficiently produce robust data.

Martin encourages teams to collect the minimal information for making the choice, and to seek the most efficient way to compile it. He call this "the lazy man's approach to strategy," During the discussion, a new idea occurred to Biostats.

> I recalled that the Clinical Pharmacology group was working with a consultant on a PK/PD computer model which was using published information from the competitor's drug as well as our preclinical information as inputs to a predictive model. I asked if it would be possible to use that model to predict the efficacy of our drug. I thought maybe we can obtain predictions from it based on all of the preclinical information we will have available and develop decision criteria for whether we move ahead. The team liked that idea and agreed to connect me with the consultant.

Knowledge-Focused Decision-Making tools build long-term capabilities

Several years later, the Biostats manager reflected on how useful the tools have been as her career has progressed.

> I definitely find myself frequently referring to the concepts I learned with you. They are applicable in almost any situation. It's also been good for me just cultivating the habit of reflecting on key conversations and thinking about what I did well and how I could have done it better.

The habit of building knowledge lays a foundation for continuous performance improvement for the individual, the team, and the whole R&D organization.

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[1] Klein, Gary (1998) *Sources of Power: How People Make Decisions*, Cambridge, MA: MIT Press

[2] Martin, Roger (2000)."Generating Internal Commitment to Implementing Strategy," in Argyris, C. *Flawed Advice and the Management Trap*, Oxford University Press