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## DEVELOPMENTS

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### Oncology Thinking Cap: Scaffolded Use of a Simulation to Learn Clinical Trial Design

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**Background:** Physicians often are called on to participate in and interpret clinical trials, but their training in this area may not provide them with the inquiry skills that are needed. Simulations have the potential to be a promising tool for helping medical students learn the skills involved in clinical trial design. However, simulations may be complex and require additional scaffolding to support learning.

**Description:** The goal of this study was to teach aspects of cancer clinical trial design through the scaffolded use of a simulation, the Oncology Thinking Cap. The software-based scaffolding provided guidance in designing the trial. Subsequently, the simulation allowed students to run the designed trial, which produces detailed patient histories. This feedback then could be used to redesign the trial.

**Evaluation:** Twenty-four 4th-year medical students were asked to design a clinical trial in advance, on paper, to test a new anticancer drug. Student groups then designed and simulated running the clinical trial assisted by the software environment. Instructional effectiveness was measured using a pretest–posttest design that included having students (a) write a group research proposal and (b) individually critique a flawed proposal. At the group level ( $N = 6$  groups), students demonstrated a 34% increase in the number of elements of a clinical trial that they included in their research proposals. At the individual level ( $N = 24$ ), students improved by 48% in their critiques of flawed proposals.

**Conclusions:** Scaffolding embedded in the simulator is a promising approach to helping students learn about clinical trial design.

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“There Are No Bad Anticancer Agents, Only Bad Clinical Trial Designs” is the title of an article by noted cancer researcher Dan Von Hoff.<sup>1</sup> In this article, he claimed that many new cancer drugs never make it to the clinic because the appropriate clinical trials are not performed. He argued that this occurs because the researchers do not creatively exploit the attributes of drugs in designing clinical trials. Researchers often fail to consider the pharmacologic

mechanisms and the toxicity characteristics of drugs in planning the treatment regimes that are used for many trials. Flaws in research methodology also may play a role. A recent review of published clinical trials noted the methodological flaws in the design and reporting of clinical trials, whereas other work demonstrates limitations in many physicians’ knowledge of research methods.<sup>2,3</sup> This suggests that there is room for improvement in the training of medical stu-

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dents, in learning both the characteristics of anticancer drugs and clinical trials research methodology. Scientific inquiry skills such as these are increasingly important for physicians who may later conduct large-scale research such as clinical trials or be required to interpret and evaluate the results of such research with regard to their own practice. Understanding how to design effective trials is important in identifying drugs that may show promise in treating cancer and reducing the risks to patients from minimally effective and toxic drugs. One way that students can learn research design is through the use of simulations.

### Computer Simulations and Scaffolding

Simulations can offer the kinds of experiences that allow students to design studies under different assumptions and compare the results, with support to help shape their experience, model the inquiry process, and encourage reflection.<sup>4,5</sup> Allowing students to simulate their experiments and observe the results in real time provides the dynamic feedback needed to enhance their understanding of both the process of experimentation and their knowledge of the domain.<sup>6</sup> This interactive cycle of designing a trial, observing results, and redesigning may allow students to develop a deep understanding in a fairly short time span.

Simulations have a long history of use in medical education. In many simulations, students focus on treating or diagnosing a single patient.<sup>7</sup> In simulating a clinical trial, one needs to model effects of treatment of multiple patients who may exhibit a range of responses and side effects. The simulation approach has been used primarily to help learners focus on statistical issues in clinical trials rather than the broader nuances of treatment considerations and contingencies.<sup>8,9</sup>

There are also other aids that utilize expert knowledge to help design clinical trials. The expert knowledge approach has been used in developing “Design-a-Trial.”<sup>10</sup> In Design-a-Trial, the system interviews practicing physicians and prompts them for the key information needed to describe their clinical trial, perform the necessary statistical computations, critique the design, and print out the trial design protocol as a document. Although this approach is quite promising as a decision support tool, it is not designed for educational purposes and does not provide the experience of running the trial with a biologically based simulation.

Software advances have greatly expanded the sophistication of simulations, but using these simulations, often designed for experts, may impose excessive demand on those just learning to conduct trials and who may have misconceptions about this process.<sup>11</sup> Computer simulations can help students learn about designing trials by communicating the important con-

siderations that need to be taken into account as they design experiments. That is, software-based scaffolding can be designed to help the students focus on the relevant aspects of clinical trial design.

Scaffolding refers to certain kinds of support provided to learners while they solve a complex problem. Scaffolding is designed to help learners accomplish both learning and performance goals by providing a temporary framework that allows learners to succeed in tasks that are beyond their current capabilities.<sup>12–14</sup> By communicating and prompting the appropriate thinking processes, software-based scaffolding can be used to help students learn as they engage in complex tasks.<sup>13</sup> This concept played a key role as we designed software to help medical students learn about clinical trial design.

### Clinical Trial Design

The process of bringing a new cancer drug to market is complex. A drug must go through several stages of laboratory and clinical testing before it can be available for general use.<sup>15,16</sup> In the usual paradigm of drug development, Phase 1 of clinical testing involves a small number of patients. Its aim is to identify an acceptably safe dose, the “maximally tolerated dose” (MTD). A Phase 2 trial, usually with just one treatment arm, may subsequently be conducted to see if there is an indication of “activity” against the disease. Activity usually is measured by “clinical response,” generally measured as a change in tumor size. This may be followed by a randomized Phase 3 trial to compare some measure of genuine patient benefit, such as survival, against a standard treatment.

In the Phase 2 study design process, which is our focus, the researchers choose a single dosage and schedule for the drug. The researchers specify several requirements for the operational characteristics of the study, and a design is chosen to meet those criteria. Typically, the goal is to distinguish subtle effects with good accuracy.

Given the complexity of designing Phase 2 trials, support is needed to help students learn about the trial design process. Moreover, although students understand that the treatment dose and schedule need to be specified, they may fail to appreciate the interdependencies among the dose, schedule, and length of treatment and how those interact with conditional rules for modifying drug doses. Teaching students the skills of planning and interpreting clinical trials is difficult, and they need appropriate experiences that aid the construction of conceptual understanding, model the inquiry process, and encourage reflection. Simulations offer promise for providing these experiences. To help students understand these more subtle aspects of designing clinical trials, we implemented the Phase 2

Clinical Trial Wizard on the foundation of the simulation environment that the Oncology Thinking Cap (OncoTCAP) provides.

In this article, we describe scaffolded use of a simulation by medical students as they learned to design a clinical trial to test an anticancer drug. Based on theories of software-based scaffolding, we designed a “wizard” to communicate the process of designing a clinical trial.<sup>13</sup> In the wizard clinical trial design module, the major components of trial design are highlighted through screen-based forms, which walk the learners through the process of defining a trial design. Then, the actual detailed simulation of the trial is implemented, one patient at a time, using OncoTCAP.

OncoTCAP provides a comprehensive modeling workbench for experienced cancer researchers. This tool is versatile and can be used to model clinical trials, but its comprehensiveness may impose excessive cognitive difficulty for the novice. Clinical trial design involves knowledge of well-defined designs for testing new drugs. Experienced researchers develop this knowledge through extensive experience spanning numerous clinical trials. Baker and Dunbar<sup>11</sup> suggested that the expert scientist often has a mental “schema” with “slots” to be filled with the items needed to determine an experimental design. Communicating the slots in the design process is one way that learners can begin to construct these schemas.<sup>13</sup> A common approach to ensuring methodological quality control is through the use of checklists required when articles are submitted for publication.<sup>17</sup> This approach may not be sufficient to help novices learn key scientific inquiry skills. Such static support is not able to help students learn to exploit the drug-specific characteristics that Von Hoff<sup>1</sup> has identified as a key to designing effective trials.

### The OncoTCAP Software

The core concept underlying OncoTCAP is that tumors are composed of heterogeneous populations of cells, and this forms the basis for understanding cancer.<sup>18</sup> OncoTCAP can model the important concepts in cancer research and treatment such as cell cycle control; cell growth, death, and repair mechanisms; mutational processes, treatment characteristics, resistance, and schedules; and genetic characteristics.<sup>19</sup> OncoTCAP models these processes by specifying the different properties of cancer cells such as their genetic makeup, location, and presence of specific drug resistance mechanisms.<sup>20</sup>

To form the foundation for the trial construction aid (the “Trial Wizard”), OncoTCAP has to model a basic description of the target domain. In our application, the target domain was breast cancer. Using OncoTCAP, we constructed a simple model that included parameters for cell cycling time and turnover of the cell population, drug resistance phenotypes, and abnormal path-

ways due to genetic mutations. The model includes a tumor location description, with the breast being the primary location, and liver and lungs as potential sites for spread of the tumor. The model also includes a description of the hypothetical drug, Pittamycin, in terms of killing ability on the tumor subpopulations in the model, and a probabilistic toxicity model that includes hematologic toxicity (which affects the development of blood cells) and neurologic toxicity. The OncoTCAP simulation engine provides the means to represent a treatment regimen and simulate its effect on tumor growth and normal organ function. With this information, OncoTCAP performs a Monte Carlo simulation of breast cancer.<sup>19</sup> In this simulation, tumor cells grow based on their cell kinetics parameters and the nature of their heterogeneous properties. The schedule and applications of the drug reduce counts of different tumor cells based on dose and drug definition.

OncoTCAP provides two different ways of displaying the Monte Carlo simulation. In the Cancer Patient Simulator, the interactive simulation of tumor cell growth is shown by means of a graph of the number and characteristics of tumor cells in a single patient (Figure 1). The relative cell counts of the various different cell types determined by the heterogeneous properties are shown in different colors. The event window shows different clinical and simulation events, such as simulation start, diagnosis, tumor spread, treatment, and death.

The Multiple Patient Simulator (MPS) runs the same Monte Carlo simulation as the Cancer Patient Simulator over many patients. While the simulation is running, the MPS window shows a tally of the number of patients simulated and the number of responses, cures, and deaths. At the end of the simulation, the MPS window displays the clinical event history for any selected patient. The patient histories can be browsed, and a selected patient history can be recalculated and displayed in the Cancer Patient Simulator window, showing the ordinarily invisible details of cancer cell subpopulation sizes as a function of time. A variety of tabular and survival-plot summaries are available. A modified version of the MPS is used in the Trial Wizard, as shown in Figure 2.

### Phase 2 Clinical Trial Wizard

From earlier usability studies, it was clear that the OncoTCAP software was too complex for medical students.<sup>20</sup> In addition, we hypothesized that among the aspects of trial design that are important, some are not obvious to novices. The more obvious elements of a Phase 2 clinical trial design include

- Background information about the disease being treated.

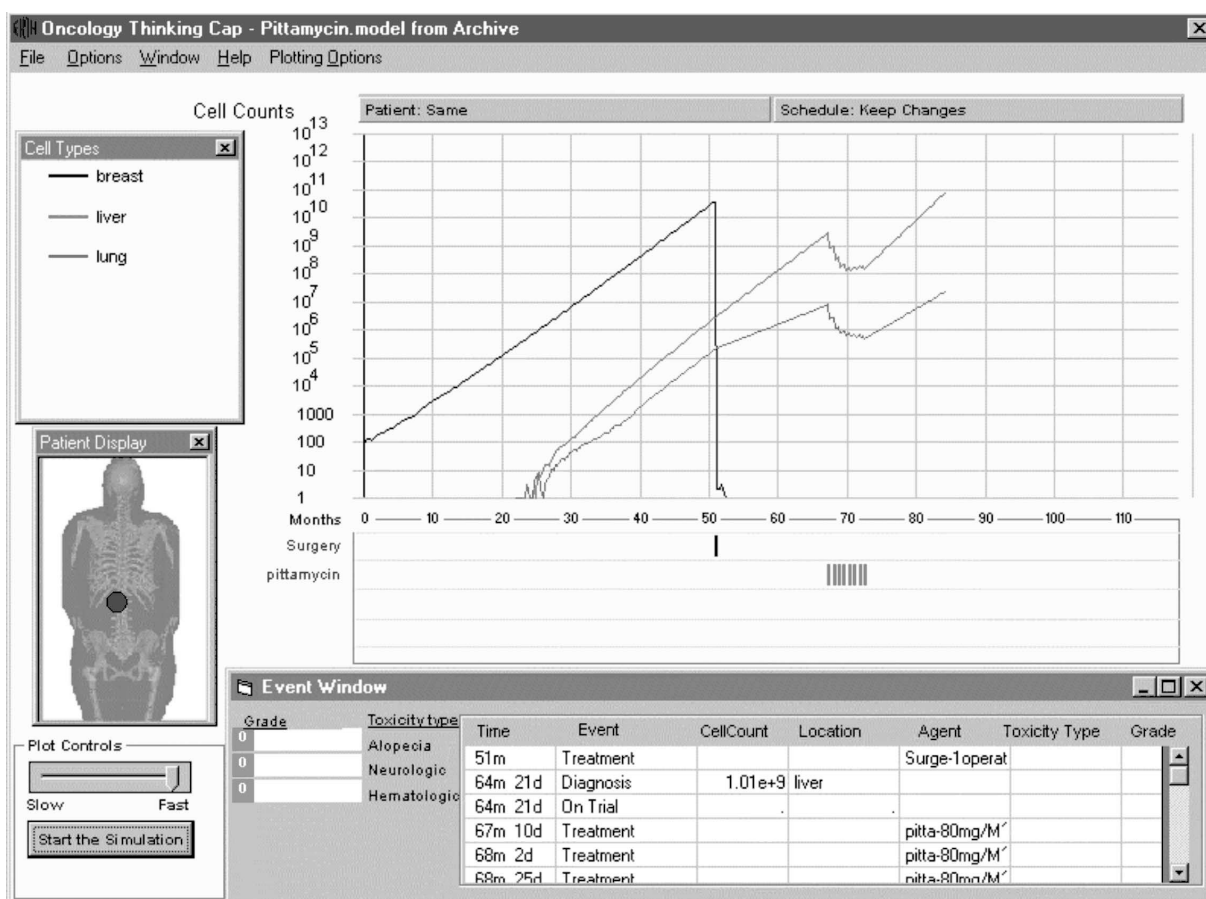


Figure 1. Cancer Patient Simulator.

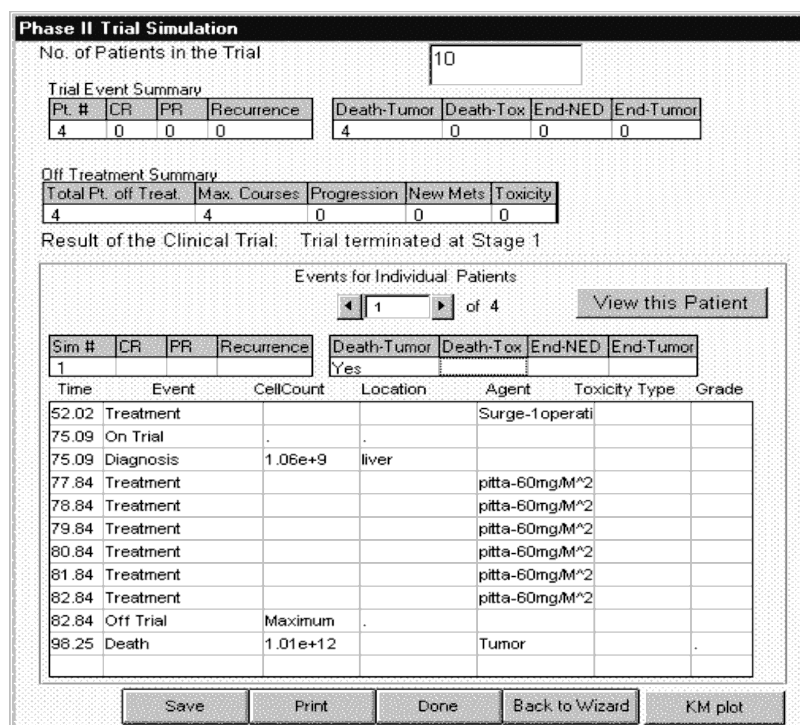
- Background information on the drug being tested, including the results of preclinical and Phase 1 testing.
- Criteria for including or excluding patients.
- Specifying the dosage, treatment schedule, and treatment duration.
- Choice of primary clinical measurement endpoint.

Students were aware that the elements in this first list were important but had less of an understanding of how they could be operationalized. Students rarely considered other elements that are part of an expert schema for trials, including

- Conditions under which the drug dosage is to be modified as a result of toxic side effects.
- Conditions under which the patient will stop receiving the experimental protocols.
- Operational characteristics needed for determining how many patients will be included in the study, and of that group, how many responses need to be observed to conclude that the drug is worthy of further study.

Thus, the Phase 2 Clinical Trial Wizard was developed to help scaffold student learning about trial design without dealing with the complexity of the underlying simulation environment. A *wizard* in a computer program is a set of simple screens that walk the user through a complex cognitive task. The screens were designed to help communicate the trial design process in terms of the Phase 2 clinical trial design schema. Moreover, by differentiating the task into multiple subtasks, the cognitive load required to complete the task is reduced. The wizard provides support for running the simulation in three ways. First, the user is made aware of the expected elements in the Phase 2 Clinical Trial by the contents of the various screens. Second, the user can accomplish the task by concentrating on one subtask at a time with less effort and confusion than if approaching the task as a whole.

The screens of the wizard allow the user to easily navigate from one subtask to another as needed. This helps reduce the cognitive demand associated with the clinical inquiry process. Third, much of the complexity of the simulation environment is reduced as the wizard uses a simplified interface to (a) transparently generate the input needed to run the simulation and (b) present only the relevant results to the learner.



**Figure 2.** Modified Multiple Patient Simulator summarizes the results of the simulation and allows students to examine individual patient event histories.

The computer-supported clinical trial design and interpretation process can be divided into four components. The first component is the introduction screen, which describes the objective of the wizard and the information the user will need to provide in the rest of the screens. The second component consists of a set of four well-defined steps, represented in screens, that lead the user through the subtasks. In these computer screens, the user specifies the schedule (Figure 3), dose modifications due to toxicity (Figure 4), off-treatment criteria (Figure 5), and statistical criteria (Figure 6). Built into the statistical criteria screen is a computational procedure that takes as input the user's statistical criteria and produces an optimal design following the methodology of Simon.<sup>15</sup> The third component is the summary, in which the user's trial design from Steps 1–4 is summarized in natural language, and from which the user can initiate the clinical trial just designed by clicking a button. The modified MPS, which actually runs and displays the results of the clinical trial, forms the fourth component of the process (Figure 2). There is easy navigation between the various screens in the wizard via "next" and "back" buttons. The MPS has a "Back to the Wizard" button, which enables the user to view the results of the current trial and return to the wizard screens to make further modifications to the design and run a new trial. The final summary screen also provides the user with the ability to print out the description of the trial design and results, as well as the results of any individual simulation run.

### Using the Simulation in the Classroom

We tested the Phase 2 wizard with 24 fourth-year medical students, who were divided into six groups of 4 students each. Prior to the computer session, they were asked to develop collaboratively a research proposal for a Phase 2 trial of the hypothetical drug, Pittamycin. Students were given laboratory and Phase 1 trial results. This information included the maximum dose that was tolerated by patients (MTD) and the types of toxicities that were observed (impaired neurological function and blood formation). Subsequently, each group of students worked collaboratively at a computer for a 2-hr session. The students first used the wizard to design and simulate the Phase 2 trial they had designed before coming to the lab. Cindy E. Hmelo facilitated the group's work by

1. Asking students to summarize their initial proposal.
2. Helping students with any interface problems they might have had and making sure that they understood relevant software features.
3. Asking students to justify their changes.
4. Encouraging students to reflect on what they learned from this experience.

The goal of this exercise was for students to create clinical trial concept sheets, which are short summary plans for testing a new drug. The concept sheet is a



**Phase II Clinical Trial Wizard - Step 4: Trial Design**

Trial Design. Assign the statistical parameters for the design of your clinical trial. On the basis of this information, the Wizard will determine (1) the optimal patient sample size and (2) the minimal number of patients that must respond to treatment in order to conclude that the drug is active. When you have completed these tasks, click Next.

Probability of accepting poor drug (alpha) :

Probability of rejecting good drug (beta) :

Response probability of poor drug :

Response probability of good drug :

First Stage Sample Size ( n1 ) : 4    Stop and reject drug if # responses < or = ( r1 ) : 0

Total Sample Size ( n ) : 11    Reject drug if total # responses < or = ( r ) : 2

**Figure 6.** Step 4 of the Clinical Trial Design Wizard: setting the statistical parameters.

brief summary of the research design and implementation. It generally contains sections such as objectives, eligibility criteria, study design, treatment plan, treatment modifications, definitions of study endpoints, and a definition of patient evaluability. The students received a one-page instruction sheet that briefly specified what should be included (i.e., introduction and background, significance, methods, risks, and benefits). Students worked on this task in their groups. The groups completed their first concept sheet before using the software and a second draft postsimulation.

For the investigators to assess individual learning, students critiqued a flawed concept sheet. This was a proposal to test another hypothetical drug that was active against lung cancer. The concept sheet was one-and-a-half pages long, including instructions. The students were asked to list any problems that they found and explain why each was important. The critiquing task was completed after students wrote the first draft of their concept sheet in groups and after the simulation.

Each run of the wizard generated a printout of the groups' design. In addition, students printed out the results of the simulation that represented their group's final design. We assessed individual and group learning using data from three sources: (a) group clinical concept sheets presoftware and postssoftware, (b) individual critiques of a flawed concept sheet, and (c) a questionnaire that asked about various aspects the software. The design summaries contained all of the characteristics the students specified: the dosage and schedule, any conditional rules for dose modification and removing patients from treatment, and the statistical considerations.

The six student groups ran an average of 8.67 simulations during their sessions. The students' first simulation run was an implementation of their initial proposal. For the majority of the groups, their initial dosage and drug schedule was consistent with the

MTD identified in the Phase I trial information they received. Five of the six groups' precomputer session concept sheets discussed monitoring patients for toxicity, but none of the six initial concept sheets specified dose modifications if toxicities were observed. In the first run through the trial wizard, when students reached the screen where they could set conditional rules for dose modification, students in all groups expressed surprise. In each session, the students initially skipped these rules in their first attempt and thus remained consistent with their original design. They were less surprised when they had encountered the screen that considers the off-treatment criteria. Although two of the concept sheets specified them vaguely, the students seemed to understand the importance of setting these criteria.

Finally, students specified the operational statistical characteristics of the clinical trial design. The program then computed the number of patients needed and the number of responses that would allow them to conclude that the drug had some clinical activity and was worthy of further study. The facilitator tried to elicit student understanding of these statistical considerations, but this remained a murky area for the students.

Following this, students simulated running the trial they had designed. The MPS summary displayed the results of the simulation and included information about patient responses, deaths due to tumor, and deaths due to drug toxicity. The students closely watched the cumulating results. They were able to view a survival plot that allowed them to see the increase in median survival time. This helped the students appreciate the therapeutic effect of the treatment. In addition, they observed that along with any responses, there were often many patients that died due to drug toxicity. Their perusal of individual patient records, particularly in the first few runs, led students to a

deeper understanding of (a) the types of toxicity that occurred, (b) how long they took to resolve, and (c) why responses tended to occur fairly early in the treatment process.

This concern with toxicity led all groups to add dose modification rules in their second design. The dose modification screen was an important focus for student discussion about the nature of different types of toxicity. For example, students noted that neurologic toxicity caused very severe consequences (i.e., death of brain tissue) and only resolved slowly, whereas toxicity that impaired the body's ability to make new blood cells resolved quickly and was treatable. Thus, students tended to be conservative about dose modification for brain toxicity and would severely reduce the dose. They were more liberal in tolerating hematologic toxicity, which reflects current oncology practice.

In several groups, students discussed the importance of only changing one variable at a time to understand the results of their experiments. However, this is rarely what actually happened. On the first few runs, the students changed two to three design characteristics per run. With subsequent redesigns, simultaneous modification of multiple design characteristics decreased over time. This may have occurred partly because the students were trying to balance multiple goals: maximizing responses while minimizing deaths due to toxicity.

A strategy that several groups converged on involved using a very large dose of the drug early in the treatment and allowing time for the body systems to recover from the toxicity before giving another dose of the drug. This was effective because it killed tumor cells before they developed resistance to the drug. This example shows how understanding the toxicity characteristics leads to designing a more effective trial for this new drug.

The students clearly were engaged in the iterative design and simulation process. When asked to reflect on what they had learned, students often mentioned statistics and an appreciation for the complexity of designing a clinical trial.

### Evaluation

The group preconcept and postconcept sheets were coded for the 24 elements of the Phase 2 clinical design schema described earlier; the concept sheet critiques were graded similarly for the 20 elements that were missing from the concept sheets. In the postcomputer session concept sheets, all groups modified their initial design to include specific dose modification rules and stop-treatment rules. They also specified their statistical parameters more completely. This suggests that students were constructing more elaborate trial design schemas. This elaboration was consistent with the

scaffolding provided by the wizard. The conditional rules (dose modification and off-treatment criteria) and statistical characteristics were either not fully specified or not considered in the initial trial designs, but were included after students were made aware of these factors in the wizard.

The preconcept and postconcept sheets were coded for the components needed for a complete trial design. The mean score for the initial trial design was 14.83 out of a possible 24 points ( $SD = 4.07$ ). The students improved on their postresearch proposals to a mean of 19.83 ( $SD = 1.55$ ),  $t(5) = 2.89$ ,  $p < .05$ ,  $d = 1.23$ .

Tested individually, students became better at critiquing the flawed clinical concept sheets. There were 20 components missing from the concept sheet used in the assessment. The mean number of missing components identified by students was 4.67 ( $SD = 3.25$ ) after the initial design and 6.92 ( $SD = 2.60$ ) after the computer session. There was a significant improvement as a result of the computer session,  $t(23) = 2.96$ ,  $p < .05$ ,  $d = 0.69$ . This effect was largely a result of improved knowledge of how to plan the treatment (including conditional rules for modifying dosages and taking patients off treatment). Because the students spent much of their time engaged in adjusting the treatment plan, this is where we expected to see the greatest effect.

The students rated the wizard positively, with a mean of 4.07 out of 5 on questions that asked students about different aspects of the learning environments' ease of use, helpfulness for learning, and understandability. They ranked this activity second only to their clinic time in value (students also received lectures and participated in a journal club). Their comments indicated that they liked receiving the rapid feedback on their experiments and having the opportunity to change variables and rerun their study.

### Conclusions

New approaches to teaching and learning in medicine stress the importance of teaching scientific inquiry in the context of authentic problems that integrate both the inquiry process and subject matter learning.<sup>21,22</sup> However, working on authentic problems can be extremely difficult for novices and requires additional support to help them manage the complexity. Scaffolding students' scientific inquiry using a complex modeling tool is a promising approach. Using the clinical trial wizard, students learned about the various components of the clinical trial design process. The dynamic feedback combined with ease of iteration proved crucial in allowing students to construct successively more effective trial designs. Students went from a rudimentary Phase 2 trial understanding to one that was much more elaborated after working with the OncoTCAP trial wizard. Our observations suggest that students used these



tools to not only focus on the inquiry process, but also discuss important issues in cancer treatment. A fine-grained analysis of the group discourse is being conducted to further our understanding of how student interaction with one another and the software contributed to the learning outcomes observed.

The students also learned to capitalize on the characteristics of the drug to design an appropriate trial. By being able to explore the nature of the toxicity, students were able to take a drug that appeared to be ineffective and consider different strategies that would allow them to get the most out of the drug that they were testing. Further work that incorporates pharmacokinetics and drug mechanisms into the software will allow students to understand more deeply how the drugs work to treat cancer, and how these mechanisms can be used to inform clinical research and prepare physicians to think like better scientists.

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