The LAWA technique implemented in a course in nanomedicine

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Advanced engineering topics are essential to a complete undergraduate engineering education. In biomedical engineering, advanced topics often require integration of many fields of study, understanding of the technical aspects of wet-lab experimentation methods, and relating mathematical concepts to biological systems - making such topics particularly challenging to teach. To help meet this challenge, we have developed and evaluated the lecture – assessment – worksheet – article (LAWA) technique in an upper-level elective course titled “Nanomedicine” in the Department of Biomedical Engineering at the University of Virginia (UVA). We hypothesized that this method would increase understanding and improve student performance as measured by comparison of graded assessments from the redesigned course with those of previous years when the course was taught in a traditional lecture format. Topics in nanomedicine included the design of nanoparticle drug delivery systems, molecular imaging, and materials biocompatibility. To understand these topics, students had to learn more than simply the facts about existing nanoparticles and nanotechnologies; they also needed to learn how to apply relevant knowledge from previous courses in the basic sciences (biology, chemistry, physics, biotransport) and basic mathematics (algebra, calculus, differential equations) to address disease-specific problems. Students were additionally required to make engineering design choices compatible with current laboratory experimental techniques and consider constraints like cost, manufacturability, and FDA regulations as other influential factors. Students were challenged to expand their knowledge base through in class note taking but importantly, they also had to critically read relevant journal articles (some provided by the instructor and others self-identified).

In this paper, we first describe the course organization and the LAWAB technique, which presents context-specific knowledge in the form of a lecture, encourages students to study that material and recall it in a quiz, has students work on group activities to apply and build on that knowledge, then has them read a related research article. We also discuss participation-based assessment that focuses on completion rather than accuracy, which we implemented for all of the worksheets. In addition to comparing performance on graded assessments of the redesigned and traditionally formatted course, we gain insight into the efficacy of these teaching tools via multiple forms of anonymous student feedback and a mid-semester Teaching Analysis Poll, where the instructors exited the classroom and trained staff from UVA’s Teaching Resource Center elicited feedback from students about their learning in the course in a confidential and interactive way. We found that LAWAB increased understanding and development of independent learning skills, and generated more interest and excitement about nanomedicine among the students.

#### Course Organization

While many university classes aim to teach a large amount of information each semester, we decided to scale-down the amount of information we covered in order to allow for more time to cover each topic. Overlearning has been shown to be less dominant (yet helpful) in long-term retention, but essential to achieving a certain level of mastery. Therefore, we systematically reiterated the most important concepts by relating them back to the specific content we were teaching each week. Additionally, we took advantage of the testing effect to have students
retrieve information multiple times and in different formats (frequent quizzes, tests, worksheets, presentation question and answer sessions, debates) to promote long-term retention.\textsuperscript{2,3} The midterm and final exams tested material that had already been assessed by quizzes, but were intended to enhance learning by spacing retrieval over time (a.k.a. distributed practice) and included non-multiple choice questions to require effortful recall, which has more benefit to the students’ retention.\textsuperscript{4} We strongly encouraged participation since, as the name suggests, active learning elements (worksheets, presentations, discussions, debates) are most effective when students actively take part in them. As instructors, we consistently encouraged our students both verbally and through emails to participate in class and allotted 10 percent of the final course grade to participation. We encouraged students who are introverted to find another way to show us that they were interacting with the material and making an effort. We designed one project to provide some breadth, but the main focus of the course was to have students truly understand the most important concepts. In other words, rather than being able to remember certain formulas in the future, we wanted students to be able to look up formulas and still understand what they mean. The course was organized based on three learning objectives. Students should be able to:

1. identify and apply the important considerations for drug design, including the ability to design mathematical models of drug transport
2. recognize areas where nanomedicine could be used
3. talk intelligently about nanotechnologies

Our style became LAWA, where at times the worksheet was replaced by a project or debate. Table 1 shows the concepts that we covered with their related quiz topics, active learning elements, and associated journal article.

**Objective one:** Identify and apply the important considerations for drug design, including the ability to design mathematical models of drug transport. We used lectures and worksheets to accomplish this objective. To guide students in the important elements of drug design, we devised lectures around each concept breaking the concepts up into smaller parts. Students were quizzed on the main concepts from each lecture the next class period, which encouraged them to spend time learning and understanding the material. Students would then complete an in-class worksheet that required them to build off of their base, explore new concepts, and apply the drug design elements previously covered. Worksheets were graded on completion and effort so that students could be creative and focus on the process of drug design instead of the “right answers.” Alternatively, we sometimes had students do a project or participate in an in-class debate in lieu of a worksheet to accomplish a similar goal of deepening their understanding of the material and getting a chance to apply their knowledge.

**Objective two:** recognize areas where nanomedicine could be used. Journal articles were assigned as homework to accomplish this objective. The articles reinforced the concepts from class by explaining them in a different way. Each article was selected because it directly showed application of the concept in nanomedicine research (Table 1). The articles had the added benefit of also requiring the students to analyze data and concepts critically.

**Objective three:** talk intelligently about nanotechnologies. For this objective, we assigned two projects and held two in-class debates. The first project divided students into teams and assigned
<table>
<thead>
<tr>
<th>Lecture Concepts</th>
<th>Quiz Topics</th>
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<th>Journal Article</th>
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<td>pharmacokinetics, pharmacodynamics, compartment models</td>
<td>meaning of equations, assumptions, biological relevance of variables</td>
<td>worksheet: designing a compartment model for a specific disease</td>
<td>Pharmacokinetics of pegylated liposomal Doxorubicin.⁵</td>
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<td><em>In vivo</em> nanoparticle characteristics, targeted drug delivery, PBPK models</td>
<td>biodistribution, digestion &amp; absorbance of drugs, interaction of nanoparticles and immune system, toxicity, clearance pathways from body</td>
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<td>worksheet: designing a liposome that incorporates Eribulin</td>
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<tr>
<td>types of nanoparticles &amp; nanotechnologies</td>
<td>basic descriptions, special properties</td>
<td>presentation: general information, how it works, applications, advantages and disadvantages</td>
<td>Selected by students to prepare for presentations</td>
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<tr>
<td>CT and MRI imaging</td>
<td>imaging planes, spin, types of relaxation images, contrast agents, image reconstruction, collimation</td>
<td>worksheet: starting with the first generation of CT and re-evolving to the reach current CT technology debate: should low-dose computed tomography lung cancer screening be implemented as part of the Medicare program</td>
<td>Principles of CT and CT technology.⁸</td>
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<td>PET and SPECT imaging</td>
<td>tracer decay and detection, functional vs. anatomical imaging, half-life, sensitivity</td>
<td>worksheet: creating a textbook-style application box that describes how PET/SPECT use radioactivity</td>
<td>PET/SPECT: functional imaging beyond flow.⁹</td>
</tr>
<tr>
<td>clinical trails</td>
<td>phases, randomization, FDA approval, ethical considerations</td>
<td>worksheet: designing a clinical trial based on a drug with promising preclinical data</td>
<td>An overview of the drug development process.¹⁰</td>
</tr>
<tr>
<td>drug study design social and ethical issues</td>
<td>sample size, measured outcomes, potential sources of bias, study length</td>
<td>debate: based on a given study, should emergency contraception be available over the counter</td>
<td>The effects of self-administering emergency contraception.¹¹</td>
</tr>
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**Table 1: The LAW A approach.** First, basic understanding of each group of concepts is achieved by a quiz. Next, the understanding of these concepts is deepened through completion of an in-class worksheet. Finally, a related journal article shows how those concepts have real-world application.

them a type of nanoparticle or nanotechnology. This survey familiarized students with many disparate types of nanomedicine research and also made them very knowledgeable about one type. These presentations generated more excitement about nanomedicine because students were able to see the cool and creative cutting-edge research. The journal articles assigned prepared them for this project. For the second project, we divided students into teams, assigned them each a disease, and told them to design a nanoparticle or nanotechnology to ameliorate that disease. We lectured on presentation skills as they applied to talking about nanomedicine research, then paired two groups and had them take turns practicing presenting and offering feedback. Students were informed that how they presented would be a portion of their grade. Additionally, we held two in-class debates that encouraged students to learn about some of the social and ethical issues that influence nanomedicine research.
An example of the LAWA format

Here we illustrate an example of our approach: we taught students in a lecture format about a standard one-compartment model for pharmacokinetic analysis. Their quiz focused on the concepts important to the connectivity of the models, important assumptions, and the equations they would be using (Box 1). The in-class worksheet then had them apply this knowledge. First, they predicted input and output function characteristics and did simple calculations using the equations based on a one-compartment model. Next, they read a short paragraph about what compartments biologically represent, chose a disease and drew what they thought a three-compartment model might look like. This really assesses how well students grasp the connection between the model components and the biology. As the instructors walked around the room, we would ask probing questions about their choices. For example, “It looks like you chose to make compartments that each represent an organ of the body, could you explain what each arrow you drew represents biologically?” They were also prompted in the next section to make a few changes to their design based on the fact that most of the time a three-compartment model allows you to predict what is happening at the tissue and cell level from measurements taken from the blood; here, students realized that they must start with a plasma compartment and work their way physically from capillary to interstitial space to intercellular space. Finally, students wrote out equations for their three-compartment models using an example two-compartment model and the associated equations. Students would have to reverse engineer the way to develop equations using the two-compartment model example and then apply it to their own model, helping them to associate variables with model components. To demonstrate to students where compartment models are used in nanomedicine, they read the journal article Pharmacokinetics of Pegylated Liposomal Doxorubicin.\textsuperscript{5} In figure six of this paper, a diagram of a three-compartment model shows how doxorubicin goes from the blood into the interstitial space while still in a liposome. Once it is in the interstitial space, the doxorubicin is released from the liposome and continues on into the tumor cells. Students could easily see the relevance of the class material to actual research.

Box 1: Sample concept-oriented multiple-choice questions. These questions test students’ understanding of when a certain simplified equation can be applied and how the half-life of a drug is related to other pharmacokinetic variables.

1. \( C = C_0e^{-kt} \) should not be used to calculate concentration when (answer all that apply)
   - A. the system has heterogeneity
   - B. the drug takes effect immediately
   - C. the system is open
   - D. the drug accumulates over time in the area of interest
   - E. the system is homogenous

2. Which of the following might occur if you underestimate the half-life of a drug?
   - A. effective dose won’t be reached
   - B. toxic dose
   - C. overestimate the area under the curve
   - D. underestimate the area under the curve
**Comparison of the redesigned course with the former traditional style course**

In previous years, this class had been taught by one of the same co-instructors, covering many similar concepts. This traditional style included lecturing each class period, three exams, and a final project. Due to limited availability of previous examinations, we selected three true-or-false questions and two short-answer questions to repeat on quizzes in our redesigned course. Because these repeated questions differed in style from our quizzes, the questions were given as extra credit on a quiz. We defined a specific rubric for the short answer questions that was used to re-grade short answer questions from the traditionally taught course and the redesigned course. The rubric for the first short answer question contained five metrics and that of the second contained two metrics. Students from the traditional course performed slightly better on one of three true-false questions (p=0.03), while the other two true-false questions were not significantly different between the two groups (p>0.05). The short answers were divided; students from the traditional
course did better on the first short answer question \( (p<0.03) \), while students from the redesigned course scored higher on the second short answer question \( (p<0.02, \text{ Figure 1}) \). Interestingly, in accordance with the student feedback from the redesigned course about seeing the “big picture”, we noticed that given the same short answer question prompt, “big picture” ideas were more likely to be described by students taught in the redesigned course; whereas, smaller details were more likely to be presented by students taught in the traditional course.

**Participation-based assessment from student feedback**

Engineers must solve problems by know the facts and equations and being able to apply them to the appropriate situation. Since facts and equations can be easily looked up, but understanding is a longer process that requires pondering, practicing, and often correction, we tried participation-based assessment. We hypothesized that grading the worksheets for completion would create an environment where students could toil with complex ideas and think of creative approaches to solving problems without being worried that it would negatively impact their grades. Thus, worksheets and debates were graded solely on completion and effort rather than accuracy.

We provided several channels for feedback from the students so we could make the necessary adjustments to make this tactic successful in helping students to learn. Students could send in anonymous feedback at any point during the course. We used this feature to request that students answer the following questions about midway through the semester and again at the end of the course:

1. In your opinion, what teaching tools are most and least beneficial to your learning (for example, the lectures, lecture recaps, frequent quizzes, the worksheets, small group discussions, large class discussions, in-class debates)? Please comment on how one or more teaching tools helps or impedes your learning.
2. Do the worksheets increase or decrease your confidence in approaching nanomedicine-related questions?
3. Does it help you that the worksheets are graded for completion rather than accuracy?

Additionally, the Teaching Resource Center (TRC) polled the students in absence of the instructors about which parts of the class they felt were helping their learning and which parts were hindering it. We consistently made changes based on what the students answered and this feedback helped us to gain perspective on what the students’ response. 33 percent of students responded to the mid-semester feedback request, 63 percent of students responded to feedback questions on the end-of-course evaluation, and all of the students present on the day of the TRC poll participated in that. Figure 2 summarizes the feedback from the students. The most frequently answered beneficial teaching tools were frequent quizzes (68% average), lectures (55% average), quiz preparation documents (44% average), and worksheets (36% average). Students felt the least beneficial teaching tools were small group discussions (23% average) and large class discussions (23%). The students overwhelmingly responded that the worksheets increased their confidence in approaching nanomedicine-related questions (85% average), with the remaining students responding that it did not alter their confidence one way or the other.
Similarly, the vast majority of students (92% average) felt that having their worksheets graded for completion rather than accuracy increased their learning.

Figure 2: Student Feedback. (A) Students were moderately consistent between their mid-semester and end-of-course feedback. Students felt that their learned profited most from the frequent quizzes, lectures, quiz preparation documents, and worksheets. They felt that their learning was most hindered by large and small discussions, with some students (<20%) also feeling that the debates and worksheets were not helpful. (B) 85% of students said the worksheets increased their confidence in approaching nanomedicine-related questions. (C) 92% of students credited participation-based grading with aiding their learning.

Student comments helped us to determine if the participation-based worksheets did indeed create a more inventive environment where students could critically analyze new and complex problems. Students needed some time to get accustomed to participation-based grading. A student summarized, “Initially, we all felt so lost because we were used to having an exact correct answer, and we didn’t know what the right answers were. Later we became used to the completion rather than accuracy system and I think it aided our learning a lot. It encouraged thinking and free class discussion without grade-related concern.” Many of the students noted that it was less stressful to be graded by completion. The students found that they could focus on understanding the material instead of on getting a good grade. One student explained, “With the emphasis away from correct answers, I started to just explore the knowledge I obtained from the class and think about how I would apply it.” Students also reported feeling more comfortable.
taking risks, seeing the “bigger picture”, and not being afraid of being wrong on the first try. However, there were also some common criticisms. Multiple students said that the worksheets felt like “busy work” at times. A few students also recognized that the same system that allowed them the freedom to contemplate the material and focus on understanding it also made it possible to put in a sub-par level of effort. One student stated, “some students might try harder if they were graded for accuracy and would get more from them.” Students also pointed out that the frequent quizzes fulfilled the role of grading for accuracy while the worksheets were completed when the information was still very new and that it would have felt unfair to be expected to get all of the answers correct. Several students agreed that increasing instructor-led discussion of the worksheets would make them more effective and wished that there had been a smaller instructor-to-student ratio (we had two instructors, one teaching assistant (TA), and 70 students).

**Participation in class weakly correlated with student performance on graded assessments**

The TA kept track of participation points for each class and provided students with summaries of their level of participation during the semester as a checkpoint. We hypothesized that a higher level of participation would lead to better grades and a better understanding of the material. To test our hypothesis, we compared the average participation level as determined by participation points to average exam scores, average quiz scores, and final project grades. We found that high participation had a weak positive correlation with average exam scores (p=0.06) and final project grades (p=0.05, Figure 3). Therefore we concluded that participation can lead to better grades in classes that employ active learning techniques.

**Conclusions and lessons learned**

* Worksheets and participation-based assessment can be effective. Worksheets can be a useful teaching tool, but are difficult to create. We found that some of our worksheets were well received and others did not accomplish our goals. The greatest difficulty was in writing questions that were challenging and would push the students, but also not so hard that students...
felt incapable and frustrated. We identified a few common themes among the less successful worksheets: (1) they assumed more background knowledge than students remembered, (2) the questions were so open-ended that students were unsure where to begin, and (3) the questions were too obvious so students felt like they were childish. We recommend carefully gauging students’ level of knowledge and exposure to the material in writing worksheets. In the case of the more successful worksheets, students appreciated the learning opportunity provided by participation-based assessment. We were especially able to see great depth of knowledge during the final projects. In addition to presenting sophisticated ideas, students were able to intellectually defend the ideas and their design decisions during the question and answer portion.

Review relevant material from other courses. Nanomedicine builds on the foundation laid by several other courses. Our listed prerequisites include cell and molecular biology and biomechanics. Additionally, we expect students to be familiar with ordinary differential equations, mathematical modeling, and basic physics. About half of the students have also taken a course in biotransport. Certainly it is not possible to reteach the building blocks from these courses, but we found that students had forgotten much of the material and needed more review than we had anticipated. For example, students had difficulty grasping drug clearance concepts because they no longer remembered the difference between monoexponential and biexponential decay. It has been suggested that advanced courses should begin by reviewing the information from other courses that students will need and that instructors should design the course to “retroactively reinforce the consolidation of knowledge accumulated in previous courses.” As part of the poll conducted mid-semester by the TRC, students explained that the instructors assumed they had more background knowledge than they did for certain graphs and equations.

Student evaluations did not reflect quality of presentations. In an effort to help students pay closer attention to their peers’ presentations and provide peer feedback to students, we had each student fill out a short evaluation after each presentation. Students circled on a scale of one to five the slide quality, verbal content, and presentation skills, and listing one thing that was well done and one thing that needed improvement. We then compiled the results of the evaluations for each group. In a side-by-side comparison of the peer evaluations and the instructor evaluations, there was little correspondence. In fact, there was very little variation at all between the student evaluations, indicating that the students may not have wanted to be overly harsh with each other or perhaps did not put forth the effort to give a good evaluation. In comparing and contrasting the various comments, we found that many students said the same criticism over and over for each group. Additionally, the comments were very contradictory, making it less constructive as peer feedback for the students. Although different circumstances or different types of peer evaluations may enhance learning, we concluded that these student evaluations were not helpful and discontinued their use.

Resistance to new learning techniques. This course was taught to upper-level students who have specific expectations for course format, namely lectures and tests. Therefore, they were very uncomfortable with the format at the beginning of the semester. This was clearly reflected in the student feedback that we received. A typical student comment was “at first, worksheets were strenuous but it helped in applying learned material from class.” We found that explaining the
reasoning behind doing a certain activity made the students more open and willing to give it a serious effort. We recommend having a high level of transparency when trying out new teaching methods in upper-level courses.

Class discussions. We used two types of discussions: (1) large class discussion in which all of the students could raise their hands and ask questions or comment, and (2) small group discussions during lectures where students were asked to think about a question and then discuss it with a partner or in a group of three or four students (usually 3-5 minutes). Both of these discussions were unpopular with the students. The most common reason given was that it was too difficult to figure out the most important and correct information from large group discussions and that the small group discussions often got tangential. As part of the poll conducted mid-semester by the TRC, students explained that the discussions were too long and that they wanted really clear answers that they could use to study for quizzes and tests. As a result of the mid-semester feedback, we discontinued the large group discussions. We believe that this is why fewer students listed large group discussions as least beneficial teaching tools at the end of the semester compared to midway through (Figure 2A). In contrast, we tried to improve the small group discussions by shortening them and giving more hints. This resulted in only slightly less students (20% compared to 26%) naming small group discussions as a less helpful teaching method at the end of the semester compared to midway through (Figure 2A). End-of-the-course evaluations revealed that students had a hard time staying on track, and we recommend displaying a slide with the questions that are to be discussed as well as some thoughts to get students started if small group discussions are used.

The lecture – quiz – activity – journal article (LAWA) method. Overall, this style of teaching seemed to help students to gain a good understanding of the most important concepts. Students performed well on these concepts on quizzes and tests, and were able to apply them on worksheets and in projects. This style of teaching did not seem to improve student answers on specific questions compared to a previous traditionally taught semester. However, students clearly went beyond rote memorization in interacting with the material and demonstrated impressive critical thinking of drug design in their final projects. We also found an unexpected outcome: increased interest and excitement about nanomedicine. We had students staying after class to discuss different things they learned in class. Students would email us about news articles they saw that involved nanomedicine or tell us about times in other classes that they used knowledge from this class. Five of our students started volunteering in labs to do nanomedicine research. Though not formally a part of our course objectives, this signified to us that these teaching tools were successful.

References

Appendix 1: Example worksheet

We have talked extensively about the reasons for using nanoparticles for drug delivery, especially in the context of cancer. There are two dominating reasons for using this type of delivery system. The first we saw when we studied doxorubicin/Doxil. Describe critical toxicity in your own words and how it relates to doxorubicin/Doxil.

Eribulin is currently in a clinical trial for liposomal incorporation for treatment of metastatic breast cancer, yet the toxicity profile of Eribulin has been shown to be manageable. Postulate why it would be beneficial to incorporate this drug into a liposome.

For the purposes of this worksheet, you are the lead designer of a liposome that will incorporate Eribulin. Based on class discussions of size, charge, and hydrophobicity, what characteristics would you want your liposome to have? Justify your selections.

Did you remember to consider RES in your design? If not, what changes would you make?

Draw a schematic of your liposome. Be sure to include: (1) the basic bilayer of the liposome, (2) aqueous soluble drug trapped in the liposome interior, (3) lipid soluble drug trapped in the lipid membrane, (4) PEGylation, (5) attachment of a targeting ligand.

What advantages are there to having both (2) and (3)?

What is the purpose of (4)?

Imagine a targeting strategy for your liposome, remembering that you are trying to reach metastatic breast cancer cells. What disease characteristics would influence this strategy? How are you going to target these cells?

Congratulations! Your liposome synthesis was successful and now you want to validate whether or not your liposomes are working. Write out hypotheses that you would need to test in order to be confident that your liposomes are going to do exactly what you want them to!

I hate to be the bearer of bad news, but your experiments show that the spleen is getting a toxic dose of Eribulin. What can you do about this? First think about changes you might make in the liposomes themselves. Now think about changes in dosing and include a graph of concentration versus time for your toxic liposome dosing and altered non-toxic liposome dosing.

Your liposome is looking really great thanks to the alterations that you made, but you want to know that the pharmacokinetics look like so you decide to fit a model to data that you get in a study with rats. Draw a diagram of the PBPK model that you would like to use to represent your liposomes in rats. For one organ, illustrate what the 3-compart ment model would look like and write out equations.
Appendix 2: Example project guidelines

Create a presentation in which you detail the design of a nanoparticle for your assigned disease (lung cancer, liver cancer, diabetes, bone infection, or myocardial infarction). You will have 10 minutes for your presentation plus 5 minutes for questions. You must include the following:

**Introduction (20 pts)**
What are the disease and its significance?

**Materials & Methods (35 points)**
What is your specific target (ex. receptor on type of cell) and why is it a good choice of target?
What type of nanoparticle did you select and why?
What are the specifications of your nanoparticles (size, charge, etc.) and your rationale for each choice?
What is your route of administration and how is it ideal for your situation?

**Results & Discussion (35 points)**
Create mock data that shows the concentration versus time. Calculate the clearance, AUC, and half-life.
Diagram the compartment model that you would use and write out the equations. Explain why you chose that type of compartment model.
What is the specificity?
What is the biodistribution?
Appendix 3: Example debate moderator material

You have been selected to be a moderator for the upcoming debate: Imaging Costs. In this debate, 2 assigned teams of students will debate whether or not low-dose computed tomography scans should be implemented as part of the Medicare program to screen for lung cancer. The debate will go as follows: Each team will have 20 minutes to prepare their opening statement, principle argument, and closing statement. You will flip a coin to determine which team (pro-imaging or anti-imaging) says their opening statement first—this will be team 1. During the preparatory portion, you will listen in for 10 minutes to team 1 and then 10 minutes to team 2 and prepare any questions that you might want to interject.

During the debate portion, you will adhere to the following schedule (cut off students who continue past the time limit):

- Team 1 Opening Statement (3 minutes)
- Team 2 Opening Statement (3 minutes)
- Team 1 Principle Argument (5 minutes)
- Team 2 Rebuttal (2 minutes)
- Team 2 Principle Argument (5 minutes)
- Team 1 Rebuttal (2 minutes)
- Team 1 Closing Statement (3 minutes)
- Team 2 Closing Statement (3 minutes)

You reserve the right to interject in between sections to ask clarifying (or probing) questions. You are also responsible for ensuring that teams do not directly contradict their “facts.” Each team will only be privy to their own facts, whereas you have access to both sides.

At the conclusion of the debate, you will decide whether or not to implement the imaging technology.