Background:

The Ebola virus disease is a severe illness with an average fatality rate of approximately 50%. It is transmitted to people from wild animals, and spreads in the human population through human-to-human transmission via direct contact with blood, secretions or other bodily fluids of infected people. Burial ceremonies in which mourners have direct contact with the deceased body can also play a role in transmission.\(^1\) The largest outbreak to date is the ongoing epidemic in West Africa, which is centered in Guinea, Sierra Leone and Liberia. As of December 2014, there were 18,059 reported cases resulting in 6,809 deaths.

The first symptoms (2–21 days after infection) are fever, fatigue, muscle pain, headache and sore throat, followed by vomiting, diarrhoea, rash, impaired kidney and liver function, and bleeding.\(^2\) Ebola attacks nearly every organ in the body. After infection, the virus attacks the immune system, killing T-lymphocyte cells (the same ones affected by HIV). It then degrades collagen and the epithelial and endothelial cells which line blood vessels and organs. This results in blood clots, which thicken the blood, and internal and external bleeding, which reduces blood volume.\(^3\) Fluid loss and the resulting low blood pressure (hypotension) is commonly the proximate cause in deaths from Ebola.\(^4\)

There is, as yet, no proven treatment. However, several potential treatments are currently being evaluated, including blood products, immune therapies and drug therapies. While none are yet available, potential vaccines are also being tested.\(^5\) Clinical management is primarily supportive. Survival is improved by rehydration and symptomatic treatment (i.e. management of pain, nausea, fever and anxiety).\(^6\) Maintaining blood volume and electrolyte balance is essential as well as treating any bacterial infections that may develop.\(^7\)

Research Ethics and Biomedical Engineering Practice

It is well known that rigorous clinical testing of new treatments is a slow process. This process means a delay in treatment for the patients. A WHO panel considered this issue and decided:\(^8\)

In the particular circumstances of this outbreak, and provided certain conditions are met, the panel reached consensus that it is ethical to offer unproven interventions with as yet unknown efficacy and adverse effects, as potential treatment or prevention. Ethical criteria must guide the provision of such interventions. These include transparency about all aspects of care, informed consent, freedom of choice, confidentiality, respect for the person, preservation of dignity and involvement of the community.

On the other hand, a rigorous clinical test establishes the highest standard of evidence and understanding about a treatment. This information will be (at least partially) foregone if clinical testing is limited.

1. (15 marks) Consider the two options (full clinical testing) and (offering unproven interventions).
   a) How would you justify the claim that this choice is an ethical decision?
   b) Identify at least three groups with a stake in the decision, and construct a table of the impact of each option on each group.
   c) What is the best decision? Choose an ethical approach (e.g. utilitarian, Kantian) and, using the approach, discuss which option is best.

2. (15 marks) Consider a research study which gives an unproven anti-viral medication to Ebola patients in a clinic. Participants in the study (who receive medication) will be compared to non-participants at the same clinic. There are 500 patients at the clinic, but only enough medication for 100 to be studied.
   a) Describe a recruitment plan for this study.
   b) Discuss how your plan addresses (to the extent possible) the following research ethics issues:
      - Informed consent
      - Participants expectations and hopes (since the treatment is unproven)
      - Disappointment of those not selected for the new medication
   c) Discuss the extent to which your plan is able to avoid sampling biases.

3. (15 marks) Many organizations are working frantically toward the development of new treatments. Several promising antiviral treatments are being studied based on successful animal tests.
   a) The phase 0 of a clinical trial is designed to test for toxicity, but gives no information on safety or efficacy. Why can this phase not give safety/efficacy information?
   b) In order to speed up clinical trials, there is interest in trying to perform some of the phases simultaneously. What happens during phases I, II and III) of a clinical trial?
   c) Discuss whether, in order to speed up the testing, it would be best to try to run phases (I and II) or (II and III) simultaneously (discuss the objectives, the cost, and the possibility of failure at each phase).

\(^8\) WHO. Ethical considerations for use of unregistered interventions for Ebola virus disease 2014 Aug 12.
Sampling and statistical methods

Consider a case in which an accelerated trial of a new medication does not have a control group (or control arm). . . the control arm is the part of a trial that sets the benchmark a drug or vaccine must beat to prove that it is effective. One way to create a control arm is to pick some of the volunteers at random and give them not the new treatment, but the best existing one. For a disease as lethal and lacking in existing treatments as Ebola, though, that is regarded by many as unethical, since it denies some participants a possibly life-saving medicine.9

4. (15 marks) Consider a study performed without a control group: all patients in a given area are given the new treatment. Results (the measured mortality rate) are then compared to those from nearby region that has received no treatment.

   a) What type of study design is this? What are the variables? What type of variables are they?
   
   b) Discuss two types of bias could exist in this study design, and how they impact the interpretation of the results.
   
   c) What is the “placebo” effect? How could it affect such a study?

5. (15 marks) There is a considerable need for early screening for Ebola. Consider a new technology able to rapidly process saliva samples to detect biochemical markers.

   A study of 1100 subjects was performed, 100 of whom were later verified to be positive for Ebola, and 1000 of whom were later verified to be negative. As a function of test threshold ($\tau$), the following table shows the number of subjects tested positive.

<table>
<thead>
<tr>
<th>Threshold ($\tau$)</th>
<th>0.1</th>
<th>0.3</th>
<th>0.5</th>
<th>0.7</th>
<th>0.9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive (/100)</td>
<td>99</td>
<td>97</td>
<td>92</td>
<td>81</td>
<td>52</td>
</tr>
<tr>
<td>Negative (/1000)</td>
<td>205</td>
<td>105</td>
<td>52</td>
<td>23</td>
<td>4</td>
</tr>
</tbody>
</table>

   a) Sketch the DET curve in terms of sensitivity and specificity for this measurement device.
   
   b) In an area where the prevalence of Ebola is 1%, a subject receives a positive test result, when a threshold of $\tau = 0.5$ is used. How likely is the subject to have Ebola?
   
   c) A decision is made that subjects will only be told a positive result if they are more likely than 50% to have the disease based on their test result. What value of $\tau$ should be used?

Cells and electrophysiology

6. (15 marks) You read the following text on Ebola’s mechanisms

The Ebola virus structural glycoprotein is responsible for the virus’ ability to bind to and infect targeted cells. The viral RNA polymerase, encoded by the L gene, partially uncoats the nucleocapsid and transcribes the genes into positive-strand mRNAs, which are then translated into structural and nonstructural proteins. Newly synthesized structural proteins and genomes self-assemble and accumulate near the inside of the cell membrane. Virions bud off from the cell, gaining their envelopes from the cellular membrane from which they bud from. The mature progeny particles then infect other cells to repeat the cycle.¹⁰

A “virion” is an entire virus, and consists of the outer protein envelope called a capsid and an inner core of nucleic acid (RNA or DNA).

a) What is a gene?

b) Sketch a diagram and briefly explain the process of transcription and translation.

c) Sketch a diagram of a cell and cell wall, and indicate how the virions leave the cell.

7. (15 marks) As the body loses blood, the proteins and ions lost will upset the ionic balance of the body. This has severe consequences.

a) Sketch the axon of a nerve cell which is undergoing an action potential (AP). Show an area of the axon before and after the passage of the AP, and show the areas of absolute- and relative refractory periods. Explain why the AP propagates along the nerve fibre.

b) Explain the movement of K⁺ and Na⁺ in a nerve cell during the resting and AP phases.

c) Describe how i) the AP phase and ii) the resting phase will be affected if K⁺ and Na⁺ concentrations are dramatically reduced due to haemorrhage.

Ebola Virus Disease
**Oxygen transport and biomechanics**

8. (15 marks) In a healthy patient, the heart rate is 60 beats/min, the end-diastolic volume (EDV) is 120 mL, and LVEF is 75%. (LVEF = SV/EDV is the fraction of blood ejected by the left ventricle, where SV is stroke volume.) The systolic pressure is 120 mmHg while diastolic pressure is 80 mmHg.

The Ebola virus attacks the cells lining blood vessels and organs. These become more permeable and blood is lost through haemorrhage (either internally or externally).

a) For two beats of the heart, sketch the left ventricular pressure and blood volume in the left ventricle, as a function of time. Indicate when the aortic and mitral valves are open. **Label times and volumes.**

b) After massive loss of blood, the EDV is only 60 mL. Assume the volume remaining in the heart at end-systole, ESV, stays the same as in the previously healthy case. **Sketch how the curve in the previous question would change.**

c) In order to maintain the same cardiac output, what **new heart rate would be required?** Assume other physiological parameters stay constant. Comment on the work required to sustain this new heart rate, and whether it would be sustainable.

9. (15 marks) In the previous question, the loss of blood volume would cause several other physiological effects.

a) The right heart would begin to try to compensate for the difficulties of the left heart to maintain pressure. **What pressures are normally at the entry and exit to the right and left heart, and how would they change** with such haemorrhage?

b) The higher pressure from the right heart and increased vascular permeability would result in fluid accumulating in the lungs (oedema). **What is shunt, and how does oedema cause it?**

c) Before infection, a patient had CO = 6 L/min, \( \dot{V}O_2 = 0.25 \) L/min, \( S_aO_2 = 100\% \), and \( S_vO_2 = 70\% \). During infection, 50% of the lung tissue is filled with fluid and no gas exchange can occur in the fluid-filled region. Assume that the heart increases its activity to maintain \( S_vO_2 = 70\% \). The pattern of blood flow and oxygen consumption do not change. **Sketch a graph of the oxy-hemoglobin dissociation curve**, and label the values of \( S_aO_2 \) and \( S_vO_2 \), and (approximately) \( P_{aO_2} \) and \( P_{vO_2} \), before and after infection.

10. (15 marks) The Ebola virus attacks connective tissue and grows rapidly in collagen fibres, digesting them as it multiplies. Such connective tissue helps to keep the organs in place.

a) The mechanical properties of soft tissue are determined largely by elastin and collagen fibres. **Describe elastin and collagen**, and how they work together to create tissue with mechanical properties that stiffen with increasing strain.

b) **Sketch the stress-strain** relationship of soft tissue and label the various regions of behaviour. Indicate how the soft tissue stress-strain behaviour differs from that of bone.

c) In an experimental mouse model, we want to test how Ebola progressively attacks collagen and changes the mechanical properties of tissues. Animals are euthanized at different phases of the disease, and an artery extracted. The longitudinal stress-strain behaviour of the artery is tested as a measure of collagen destruction. **Briefly describe three of the factors which can introduce experimental variability into this testing scenario.**