Alternative Interventional/Surgical Methods for the
\textit{in-vivo} Thrombogenicity Test

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Traditional Method

• Canines are the preferred animal species (n=2).
• The animals are un-heparinized.
• A percutaneous stick or surgical cut down is performed to gain access to the treatment site.
• Equal lengths of both test and control devices (~10 cm) are inserted into alternating Right and Left Jugular Veins.
• The devices secured to the surrounding tissue to prevent movement.
• The devices are implanted for a total of 4-hours.
• Just prior to euthanasia, a bolus injection of heparin is administered to help prevent post mortem clotting.
• Devices are explanted and evaluated for the presence of thrombus in comparison to the control device.
Traditional Method (Key Concept)

- Reduction in blood flow = Increased probability of thrombus formation.
  
  - Variables that can affect blood flow
    - Treatment site access and securing the device to prevent movement during the 4-hour period.
    - Animal positioning.
    - Location of valves within the treatment sites.
    - Vessel Size and Device Placement.
Let's Take a Closer Look

- The use of fluoroscopic imaging can help to reduce a number of variables that the current model can overlook.
Animal Positioning

- The positioning of the animal throughout the study can have a dramatic impact on the blood flow around the device.
Blood Valves

- Variability in the locations of blood valves can vary from one animal to the next.
- A difference can be seen when comparing right and left jugular veins in the same animal.
- Placement of a device through a blood valve(s) can reduce the blood flow in that particular treatment site.
- This can cause variability amongst the treatment sites.
Vessel Size and Device Placement

- Size of the vessel in relation to the device can have an impact on thrombus formation.
- The size and shape of the device should be considered prior to deployment.
- Patency and proper deployment of the device must be evaluated immediately post implant with the use of fluoroscopy.
- If the Device is in contact with the vessel wall during the 4-hour indwelling period, there is a higher probability of thrombus formation.
Consider using both the Jugular and Iliac veins

- The Iliac veins provide another treatment site for both test and control device.
- The Iliac veins have adequate blood flow while the animal is on the table.
- This design allows for an evaluation of one additional test and control device in each animal on study.
- This helps to reduce the potential of receiving conflicting results.
Jugular and Iliac Method Considerations

- There are many procedural related variables that can affect blood flow.
- The use of fluoroscopic imaging can help to reduce these variables.
- Vessel size should be evaluated prior to implantation. *As a general rule, any device larger than 10 Fr should be evaluated in a sheep.*
- Proper evaluation of the device deployment and patency should be evaluated with the use of angiography.
- This method should be considered for the evaluation of devices such as dilators, sheaths, guidewires and standard catheters.
Swine Atrial Model (surgical approach)

- Two swine are subjected to bilateral atrial implants.
- A sternotomy is performed, a sheath is placed, and the test and control devices are deployed into the right and left atrium.
- The use of contrast and fluoroscopic imaging must be used to ensure the proper deployment of the devices prior to removing the sheaths.
- This design can be used without Heparin.
Considerations for the Swine Atrial Model

- This devices can be implanted without the use of Heparin.

- Device Recommendation: Balloon Catheters, Mapping Catheters and Larger devices.
Interventional Thrombogenicity Test

- Canine, Sheep or Swine can be used.
- Clinical relevance (intended implant location, venous verses arterial blood flow), vessel size, blood flow, size and shape of the device should be considered with the design.
- A surgical cut down or percutaneous stick may be used to gain access to the vascular system (example: femoral vein access)
- Heparin is administered to maintain an Activated Clotting Time (ACT) level > 250 seconds during the device placement procedure.
Interventional Thrombogenicity Test

- Devices are deployed under fluoroscopic guidance.
- Fluoroscopic images are obtained with the use of contrast to ensure proper placement and blood flow around the device.
- ACT’s are taken until the animal approaches baseline and then the four hour indwelling period begins.
- I will give a few examples of recommended deployment sites, but this design is very robust, minimally invasive, and the model is completely customizable to the device.
Interventional Thrombogenicity Test

- By far the best design.
- Minimally invasive.
- Devices are deployed under fluoroscopic guidance.
- Fluoroscopic images are obtained with the use of contrast to ensure proper placement and blood flow around the device.
- The design is customized to the device.
Thrombus Evaluation

- Take Pictures!!!
### Thrombus Evaluation Scores

<table>
<thead>
<tr>
<th>Device Thrombus Formation Score</th>
<th>Descriptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Minimal to nonexistent formation (1% or less)</td>
</tr>
<tr>
<td>1</td>
<td>Minimal – Observed to be covering 2 to 10% of material length</td>
</tr>
<tr>
<td>2</td>
<td>Mild – Observed to be covering 11 to 25% of material length</td>
</tr>
<tr>
<td>3</td>
<td>Moderate – Observed to be covering 26-50% of material length</td>
</tr>
<tr>
<td>4</td>
<td>Extensive – Observed to be covering 51-75% of material length</td>
</tr>
<tr>
<td>5</td>
<td>Severe – Observed to be covering &gt;75% of material length</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vessel Thrombus Formation Score</th>
<th>Descriptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Minimal to non-existent occlusion (1% or less)</td>
</tr>
<tr>
<td>1</td>
<td>Minimal – Vessel observed to be 2 to 10% occluded by thrombus</td>
</tr>
<tr>
<td>2</td>
<td>Mild – Vessel observed to be 11 to 25% occluded by thrombus</td>
</tr>
<tr>
<td>3</td>
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</table>
Interpretation of the Results

<table>
<thead>
<tr>
<th>Test Score of the Device</th>
<th>Comparison to the control</th>
<th>Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>NA</td>
<td>Non-Thrombogenic</td>
</tr>
<tr>
<td>2</td>
<td>Equivalent</td>
<td>Non-Thrombogenic</td>
</tr>
<tr>
<td>2</td>
<td>Not Equivalent</td>
<td>Further evaluation required</td>
</tr>
<tr>
<td>3 or higher</td>
<td>Equivalent</td>
<td>*Suspected Thrombogenic further</td>
</tr>
<tr>
<td></td>
<td></td>
<td>evaluation required</td>
</tr>
<tr>
<td>3 or higher</td>
<td>Not Equivalent (Control</td>
<td>Thrombogenic</td>
</tr>
<tr>
<td></td>
<td>Score is 2 or less)</td>
<td></td>
</tr>
</tbody>
</table>
Thank You!!!