RE: [External] Re: Control limits for Stage 2

From: **Patrick Lyden** | plyden@usc.edu

Tuesday, Jun 22, 12:26 PM

To: **Diniz, Marcio A** | Marcio.Diniz@cshs.org, **'Andre Rogatko (Andre.Rogatko@cshs.org)'** | Andre.Rogatko@cshs.org, **Ryan Cabeen** | Ryan.Cabeen@loni.usc.edu

Cc: **Jessica Lamb** | lambj@usc.edu, **Karisma A Nagarkatti** | nagarkat@usc.edu

Marcio and Ryan,

As you may recall, we got into trouble in Stage 1 because we did not provide the sites timely feedback on their Day-2 lesion volumes, and two sites wandered out of control. I would like to being setting up the control limits for Stage 2. I believe we agreed to use the IV/IP control subjects from Stage 1. However, upon further reflection, I think it is more nuanced. First of all, we are waiting for the statistical comparison of IV vs IP controls vs RIC SHAM. Hopefully they will be concordant. Then there is the issue of JH. I think we should construct the Stage 2 control limits using all 3 control groups, excluding JH. I prefer one set of control limits for the entire network, even though we did briefly discuss site-specific control limits.

Finally, to compare rats and mice on the same graph, we would need to use stroke FRACTION, rather than actual lesion volume. There are several formulae to use. If possible, the best would be Day-2 lesion volume divided by contralateral hemisphere. Ryan, can you remind me what the variable names are in the output file you generate?

To make all this work, we need to be sure the sites upload their MRI weekly. That Ryan runs the pipeline often and sends the data in CSV to Marcio (and to Karisma for archiving). That Marcio directs Sungjin to produce the Control Limits graph on a timely basis. I hope we can produce a report every 2 weeks. We are drafting an SOP to codify this plan.

What do you all think?

Patrick D. Lyden, MD, FAAN, FAHA, FANA
Professor of Physiology and Neuroscience
Professor of Neurology
Zilkha Neurogenetic Institute
USC Keck School of Medicine of USC
O: (323) 442-3917
ZNI 245 MC 2821
1501 San Pablo Street
Los Angeles, CA 90089-2821
plyden@usc.edu

From: **Ryan Cabeen** | ryan.cabeen@loni.usc.edu Wednesday, Jun 23, 10:27 PM

To: **Diniz, Marcio A** | Marcio.Diniz@cshs.org, **'Andre Rogatko (Andre.Rogatko@cshs.org)'** | Andre.Rogatko@cshs.org, **Patrick Lyden** | plyden@usc.edu

Cc: **Jessica Lamb** | lambj@usc.edu, **Karisma A Nagarkatti** | nagarkat@usc.edu

Sounds good and doable — attached is a copy of the data dictionary. The lesion volume is “volume_lesion” and the left and right hemisphere volumes are “midline_tissue_volume_left” and “midline_tissue_volume_right” respectively.

Ryan P. Cabeen, PhD
Chan Zuckerberg Imaging Scientist
Assistant Professor of Research Neurology
Laboratory of Neuro Imaging
USC Stevens Neuroimaging and Informatics Institute
Keck School of Medicine of USC
University of Southern California
2025 Zonal Ave.
Los Angeles, CA 90033
Tel: (323) 44-BRAIN
Email: rcabeen@loni.usc.edu
Web: cabeen.io
www.ini.usc.edu

> From: **Patrick Lyden** | plyden@usc.edu Tuesday, Jun 22, 12:26 PM
>
> Marcio and Ryan,
>
> As you may recall, we got into trouble in Stage 1 because we did not provide the sites timely feedback on their Day-2 lesion volumes, and two sites wandered out of control. I would like to being setting up the control limits for Stage 2. I believe we agreed to use the IV/IP control subjects from Stage 1. However, upon further reflection, I think it is more nuanced. First of all, we are waiting for the statistical comparison of IV vs IP controls vs RIC SHAM. Hopefully they will be concordant. Then there is the issue of JH. I think we should construct the Stage 2 control limits using all 3 control groups, excluding JH. I prefer one set of control limits for the entire network, even though we did briefly discuss site-specific control limits.
>
> Finally, to compare rats and mice on the same graph, we would need to use stroke FRACTION, rather than actual lesion volume. There are several formulae to use. If possible, the best would be Day-2 lesion volume divided by contralateral hemisphere. Ryan, can you remind me what the variable names are in the output file you generate?
>
> To make all this work, we need to be sure the sites upload their MRI weekly. That Ryan runs the pipeline often and sends the data in CSV to Marcio (and to Karisma for archiving). That Marcio directs Sungjin to produce the Control Limits graph on a timely basis. I hope we can produce a report every 2 weeks. We are drafting an SOP

> to codify this plan.
>
> What do you all think?
>
> Patrick D. Lyden, MD, FAAN, FAHA, FANA
> Professor of Physiology and Neuroscience
> Professor of Neurology
> Zilkha Neurogenetic Institute
> USC Keck School of Medicine of USC
> O: (323) 442-3917
> ZNI 245 MC 2821
> 1501 San Pablo Street
> Los Angeles, CA 90089-2821
> plyden@usc.edu

From: **Diniz, Marcio A** | Marcio.Diniz@cshs.org — Monday, Jun 28, 3:48 PM

To: **Ryan Cabeen** | Ryan.Cabeen@loni.usc.edu, **Rogatko, Andre** | Andre.Rogatko@cshs.org, **Patrick Lyden** | plyden@usc.edu

Cc: **Jessica Lamb** | lambj@usc.edu, **Karisma A Nagarkatti** | nagarkat@usc.edu

Hi all,

Please see below a few questions, so I can start calibrating the control chart:

1. Is volume fraction defined as midline_tissue_volume_left/volume_lesion?
2. Will we plot all mice/rats or only the control ones? This issue was pointed by the Yale PI more than once. If we plot all animals, MRI volume data at day 2 may be contaminated by treatment effect, therefore, sites out of control could be generated because of treatment effect. If we plot only controls, then we have 20 animals per site which might limit our ability to identify a site out of control.

Also, in addition to the MRI dataset from Ryan, we need treatment labels for mice/rats already randomized produced by Jessica/Karisma. Otherwise, I am not able to filter only control mice/rats.

Kind regards,

Marcio

> From: **Ryan Cabeen** | Ryan.Cabeen@loni.usc.edu — To: **Diniz** — Wednesday, Jun 23, 10:27 PM

Sounds good and doable — attached is a copy of the data dictionary. The lesion volume is “volume_lesion” and the left and right hemisphere volumes are “midline_tissue_volume_left” and “midline_tissue_volume_right” respectively.

Ryan P. Cabeen, PhD
Chan Zuckerberg Imaging Scientist
Assistant Professor of Research Neurology
Laboratory of Neuro Imaging
USC Stevens Neuroimaging and Informatics Institute
Keck School of Medicine of USC
University of Southern California
2025 Zonal Ave.
Los Angeles, CA 90033
Tel: (323) 44-BRAIN
Email: rcabeen@loni.usc.edu
Web: cabeen.io
http://www.ini.usc.edu

From: **Patrick Lyden** | plyden@usc.edu Tuesday, Jun 22, 12:26 PM

Marcio and Ryan,

As you may recall, we got into trouble in Stage 1 because we did not provide the sites timely feedback on their Day-2 lesion volumes, and two sites wandered out of control. I would like to being setting up the control limits for Stage 2. I believe we agreed to use the IV/IP control subjects from Stage 1. However, upon further reflection, I think it is more nuanced. First of all, we are waiting for the statistical comparison of IV vs IP controls vs RIC SHAM. Hopefully they will be concordant. Then there is the issue of JH. I think we should construct the Stage 2 control limits using all 3 control groups, excluding JH. I prefer one set of control limits for the entire network, even though we did briefly discuss site-specific control limits.

Finally, to compare rats and mice on the same graph, we would need to use stroke FRACTION, rather than actual lesion volume. There are several formulae to use. If possible, the best would be Day-2 lesion volume divided by contralateral hemisphere. Ryan, can you remind me what the variable names are in the output file

you generate?

To make all this work, we need to be sure the sites upload their MRI weekly. That Ryan runs the pipeline often and sends the data in CSV to Marcio (and to Karisma for archiving). That Marcio directs Sungjin to produce the Control Limits graph on a timely basis. I hope we can produce a report every 2 weeks. We are drafting an SOP to codify this plan.

What do you all think?

Patrick D. Lyden, MD, FAAN, FAHA, FANA
Professor of Physiology and Neuroscience
Professor of Neurology
Zilkha Neurogenetic Institute
USC Keck School of Medicine of USC
O: (323) 442-3917
ZNI 245 MC 2821
1501 San Pablo Street
Los Angeles, CA 90089-2821
plyden@usc.edu
