Cardiac Safety Research Consortium (CSRC) BP Thinktank

Need for new data: future approaches to the clinical significance of drug induced BP increases

Session V

18 July 2012

Jeff Heilbraun, MS
CoreLab Partners, Inc.

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Discussion Points

- **Blood pressure questions we should be evaluating in cardiac safety**
  - **"Building the best mouse trap"**
- **Paradigm shift**
  - **First in man to First in patient**
- **Case study**
- **Q&A – "Food for thought"**

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BP Study Design and Data Considerations : Future Approaches

- **Is the blood pressure response acute or gradual?**
- **Does the response plateau or with each exposure is there an additional change (incr. or decr.) in blood pressure (acute change)**
- ***Does the blood pressure response disappear – return to baseline upon discontinuation of study medication?***
- ***Positional blood pressure evaluation***
- **Integration of complimentary BP technology**
  - **ABPM**
  - **Remote telemonitoring**

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BP Study Design and Data Considerations : Future Approaches

- 1st in Man versus 1st in Patient
  - Majority of published studies to define BP response are conducted in phase II
- Additional BP measures and analysis
  - Central pressure and PWA
    - Static and 24 hour monitoring
  - Blood pressure variability- predictive value for cardiac safety assessment?
- Trial design
  - Parallel versus cross over (if intensive BP study)
  - Integration of BP sub-study
  - BP inclusion/exclusion criteria based on ABPM average (defining the population)
  - Blood pressure IRT-like resource
  - Complimentary biomarkers (i.e. C-reactive protein)
  - Should we apply similar statistical considerations to blood pressure safety as with efficacy – how do you power a study if there is no defined risk boundary or delta

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First in patient

Medical history	X																		
Pregnancy test for females	X	X								X						X	X			X
Adverse events					X	X	X	X	X	X			X	X	X	X	X	X	X	X
Serious adverse event	X	X			X	X	X	X	X	X			X	X	X	X	X	X	X	X
Concomitant meds	X	X				X	X	X	X	X				X	X	X	X	X	X	X
Full physical examination	X																			
Brief physical exam		X								X										
Drugs of abuse and alcohol tests	X																			
Vital signs (BP, HR, RR, body temp) – supine	X	X			X	X	X	X	X	X			X	X	X	X	X	X	X	X
End of 24hr BP monitoring[1]		X								X							X			

12-lead ECG	X	X		X	X					X		X	X							

Blood sample for PK		X		X	X	X		X		X		X	X	X	X	X	X	X		X

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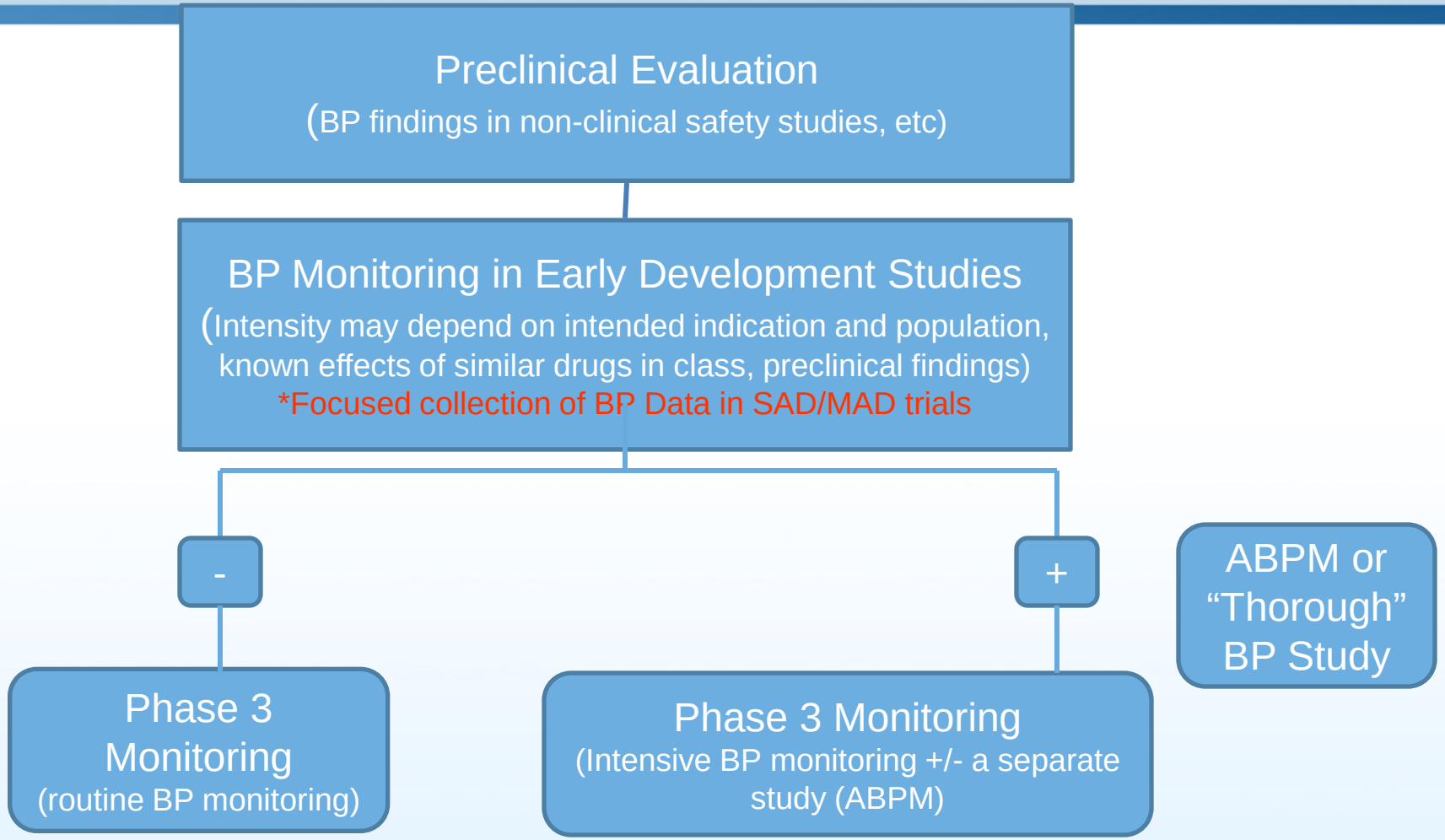
Decision Tree - Considerations



Dr. Mary Jane Gieger – Eli Lilly – BP Points to consider CSRC paper

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Case Study

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Case study – Sibutramine (1988)

- 6 healthy volunteers
- Single dose 30, 45, and 60mg of sibutramine
- Amitriptyline comparator
- Placebo controlled
- Supine and standing HR and BP were recorded with an automated device at baseline,1, 2, and 6 hours post
- Results: Supine systolic BP was significantly elevated by 60mg dose at all times and by 30 mg at 2 hrs compared to placebo

D.J. King and Noelean Devaney. British Journal of Clinical Pharmacology(1988) 26: 607-611

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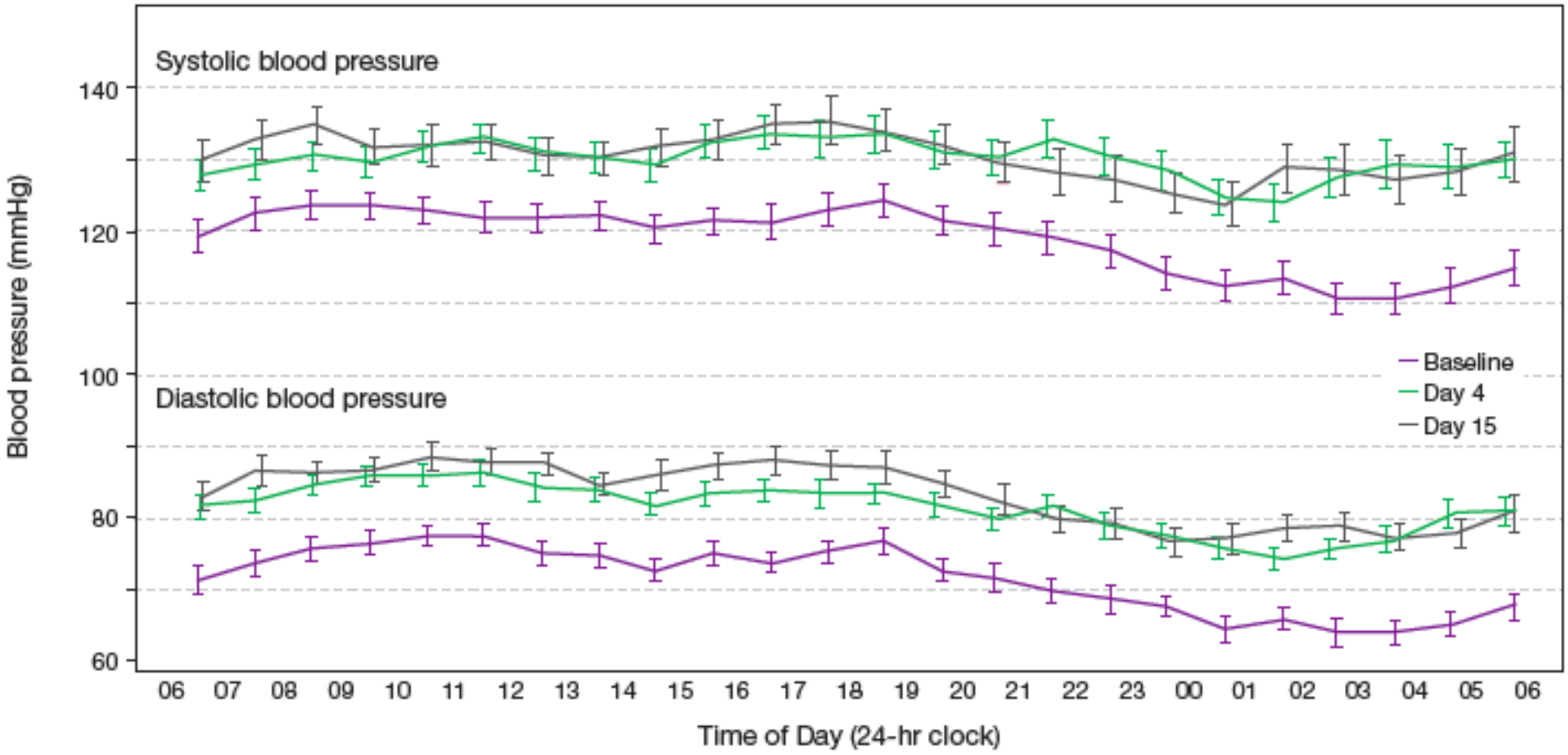
Axitinib Pharmacokinetics and Blood Pressure Changes in Front-line Metastatic Renal Cell Carcinoma Patients

Mayer N. Fishman,[1] Michael Carducci,[2] Angel H. Bair,[3] Ying Chen,[3] Brian I. Rini[4]
[1]H. Lee Moffitt Cancer Center, Tampa, FL, USA; [2]Kimmel Cancer Center at Johns Hopkins, Baltimore, MD, USA; [3]Pfizer Oncology, La Jolla, CA, USA; [4]Cleveland Clinic Taussig Cancer Institute, Cleveland, OH, USA



Slide courtesy of Angel Bair, PhD – Pfizer la Jolla

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Recent Compounds and Indications – BP Cardiac Safety

- **Axitinib Pharmacokinetics and Blood Pressure Changes in Front-line Metastatic Renal Cell Carcinoma Patients**
  - **Mayer N. Fishman, Michael Carducci, Angel H. Bair, Ying Chen, Brian I. Rini**
  - **ESMO Poster Milan 2010**
- **Conclusion**
  - **Axitinib-induced increases in dBP and sBP occurred early, by Day 4 of treatment, and remained consistent 2 weeks after initiation of axitinib therapy, supporting early monitoring and management of BP.**
  - **The observed BP responses appear to be independent of axitinib plasma exposure.**

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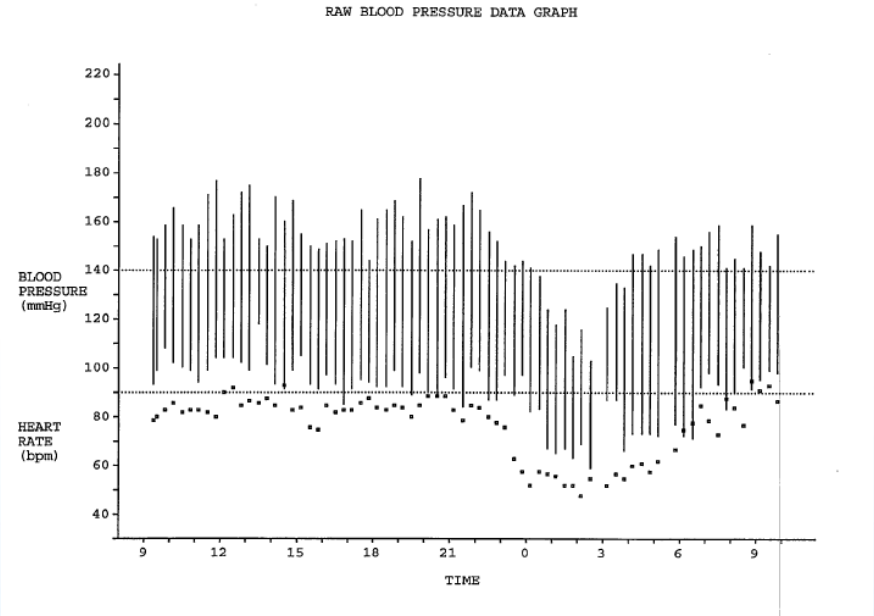
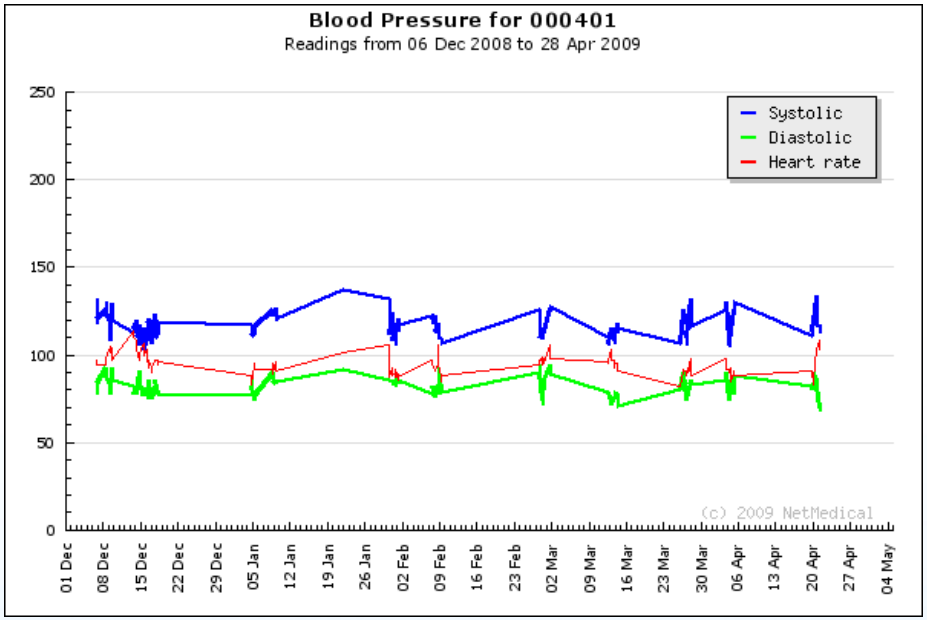
ABPM – T-SMBP Compliment





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The Effect of Sumatriptan 85mg Formulated with RT Technology/Naproxen Sodium 500mg (SumaRT/Nap), Sumatriptan, and Naproxen on Blood Pressure When Administered Intermittently for Six Months For the Acute Treatment of Migraine

Frederick J Derosier, April H Thompson, Bryan E Adams, David K Goodman
GlaxoSmithKline, Neurosciences Medicine Development Center, RTP, NC

Remote telemonitored home BP
Baseline period
6 month treatment period
407 study participants

Primary endpoint mean change in systolic and diastolic BP at 6 months from baseline

ORIGINAL PAPER

Evaluation of the Migraine Treatment Sumatriptan/Naproxen Sodium on Blood Pressure Following Long-Term Administration

William B. White, MD;[1] Frederick J. Derosier, DO;[2] April H. Thompson, MA;[2] Bryan E. Adams, PhD;[2] David K. Goodman, BS[2]

From the Calhoun Cardiology Center, University of Connecticut School of Medicine, Farmington, CT;[1] and Neurosciences MDC, GlaxoSmithKline, Research Triangle Park, NC[2]

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Q&A – “Food for Thought”

You are working on a breakthrough compound for a pain indication. In your SAD study an orthostatic BP change is identified in 3 volunteers, your next step is to:

a) In your MAD study include focused BP evaluation in the design
b) Extend your SAD study with additional cohort with more rigorous BP evaluation
c) Design an intensive BP study including ABPM (ambulatory blood pressure monitoring)
d) Other

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- Goldstein, D. et. al. Association between supine hypertension and orthostatic hypotension in autonomic failure. Hypertension 2003; 42: 136-142.
- Elliott, W, Drug Interactions and Drugs that affect blood pressure. J. Clinical Hypertension. 2006; 8:731-737

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Back-up slides

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Regulatory Considerations - BP

Current Approach

- Labels can be explicit about hemodynamic effects…***if they are known***

Hypertension and Other Cardiovascular Conditions

Stimulant medications cause a modest increase in average blood pressure (about 2-4 mmHg) and average heart rate (about 3-6 bpm), and individuals may have larger increases. While the mean changes alone would not be expected to have short-term consequences, all patients should be monitored for larger changes in heart rate and blood pressure. Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, e.g., those with pre-existing hypertension, heart failure, recent myocardial infarction, or ventricular arrhythmia.

5.9 Effect on Blood Pressure

In clinical trials across indications, relative to placebo, duloxetine treatment was associated with mean increases of up to 2.1 mm Hg in systolic blood pressure and up to 2.3 mm Hg in diastolic blood pressure. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure. In a clinical pharmacology study designed to evaluate the effects of duloxetine on various parameters, including blood pressure at supratherapeutic doses with an accelerated dose titration, there was evidence of increases in supine blood pressure at doses up to 200 mg twice daily. At the highest 200 mg twice daily dose, the increase in mean pulse rate was 5.0 to 6.8 beats and increases in mean blood pressure were 4.7 to 6.8 mm Hg (systolic) and 4.5 to 7 mm Hg (diastolic) up to 12 hours after dosing.

- **Robert Fiorentino,MD – CardioOncology – CSRC meeting 6-7 Sept 2011**

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Goals for BP Safety Evaluation Beyond Efficacy

- Defining specific BP response pathway (RAS vs. neurological vs. vascular)
- Defining BP response threshold (safety) for both a BP increase or decrease
- Safety classification of acute versus long term exposure (Lipid compounds, COX-2 compounds, Oncology compounds)

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Paradigm Shifts and drug development

Thomas Kuhn

- **The structure of scientific revolution (1962)**

- **“ Science does not progress via a linear accumulation of knowledge, but undergoes periodic revolutions, in which the nature of scientific inquiry within a particular field is abruptly transformed”**

- **“ A general improvement in success rates can result from better pre-clinical screening ….However, these savings would have to be balanced against additional costs associated with a better pre-clinical screening process.”**

Risks in new drug development: approval success rate for investigational drugs. Joseph DeMasi, Clinical Pharmacology Therapeutics 2001; 69: 291-307

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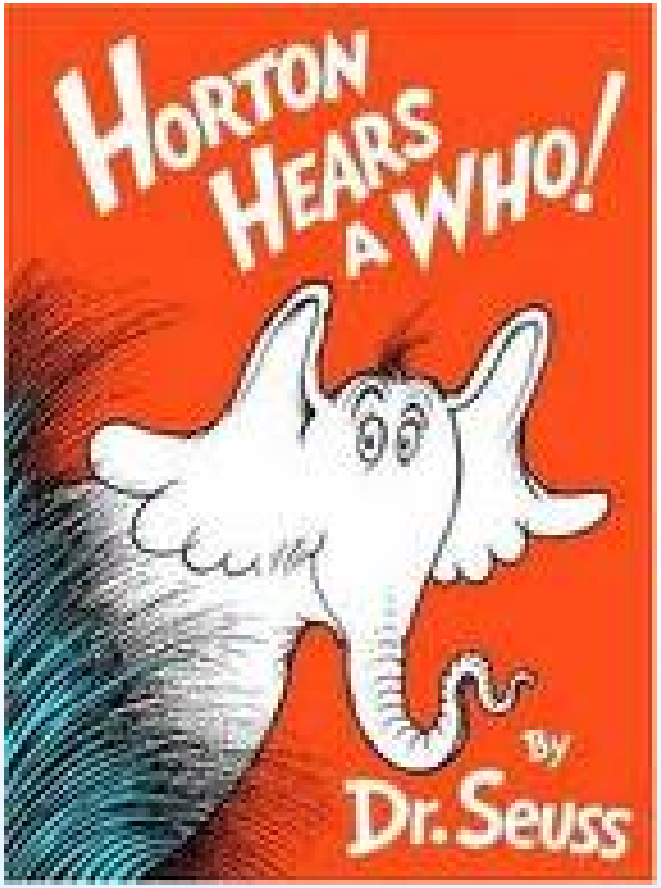
Research Philosophy – Dr. Seuss
“we are here, we are here”



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