Medifacts INTERNATIONAL

Cardiac Safety Research Consortium
Duke Clinical Research Institute (DCRI)

HESI

Cardiac Safety Research Consortium

Translational Medicine Meets Critical Path

Jeff Heilbraun, MS

Medifacts International, Inc.

New Horizons of Cardiac Safety Programs: Do we need “Thorough” Blood Pressure Studies?

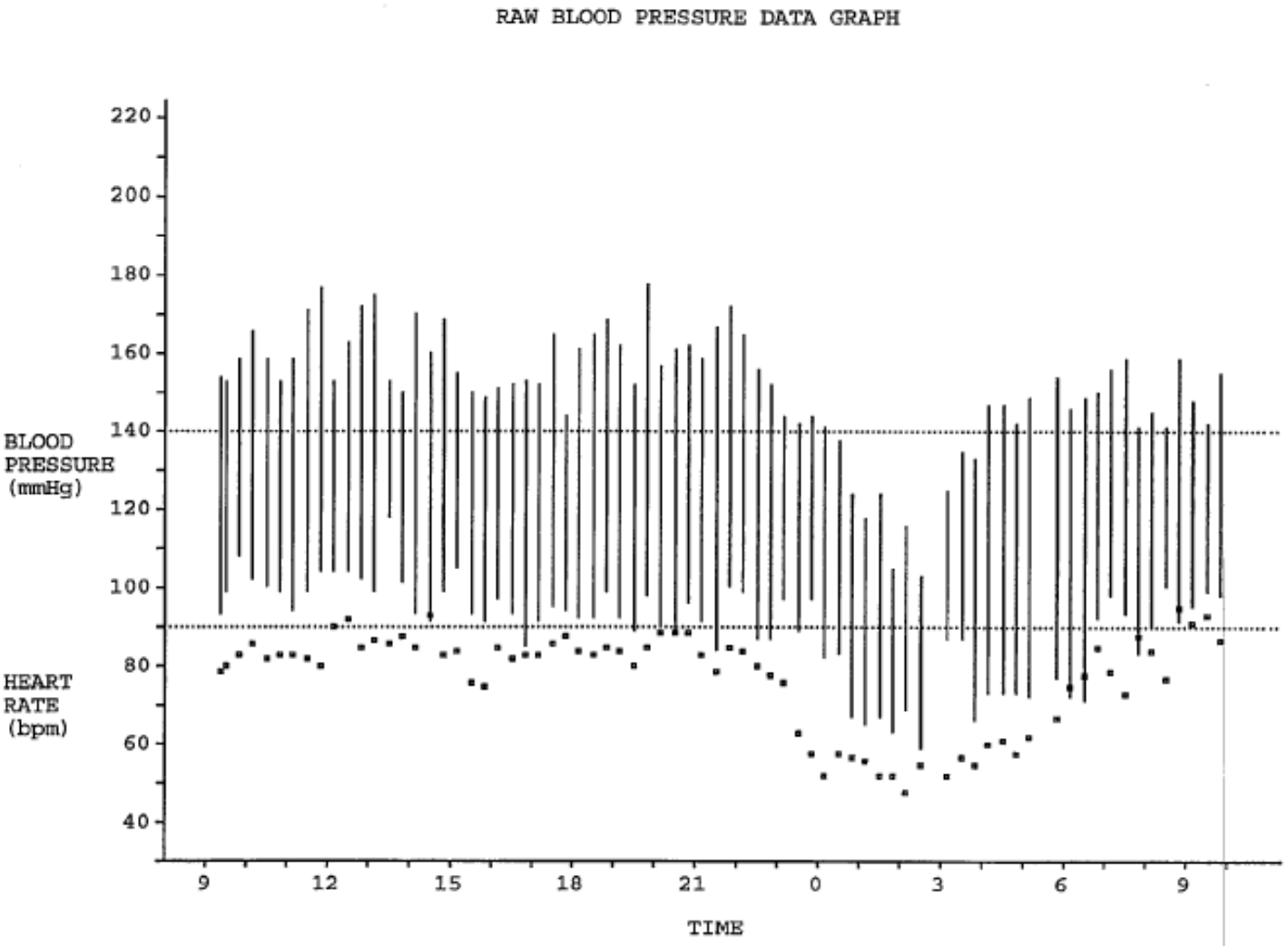
Overview of "Thorough" BP Question

- Is there a need to establish a study focused on defining BP response from a cardiac safety perspective?
- Studies are presently being completed from a BP safety perspective in oncology, CNS, Pain management and other indications
- Study compound may generate a hypotensive or hypertensive response

What Works Well Today

- Technology – Ambulatory Blood Pressure Monitoring (ABPM)
- Patient based/therapeutic focused trials
- Phase I cross over model
  - Dose response profile
  - PK
  - Circadian variability

ABPM Circadian Rhythm



What is Missing , Broken, or Does Not Work Well Today

- Defining specific BP response pathway (RAS vs neurological vs vascular)
- Defining BP response threshold (safety) for both a hypertensive and hypotensive response
- Safety classification of acute versus long term exposure
- BP Methodology Ascultatory versus Oscillometry & Manual versus Automated

Highest Priority – Short & Long Term

- Short term (1-3 years)
  - Define safety threshold for change in BP associated with cardiac safety risk
  - Generate case study based on existing/completed study
  - Is there a positive control compound with sufficient and clear BP response
  - Insight from population and therapeutic working groups

Highest Priority – Short & Long Term

- Long term (3-5 years)
  - Develop guidelines and paradigm for overall BP safety
    - Healthy volunteer
    - Patient-therapeutic population
  - Establish cross biomarker safety profile