7 January 2020

INDUSTRY EXPERIENCE IN APPLYING THE DISCOUNT POWER PRIOR

TED LYSTIG, PHD, FASA

TECHNICAL FELLOW
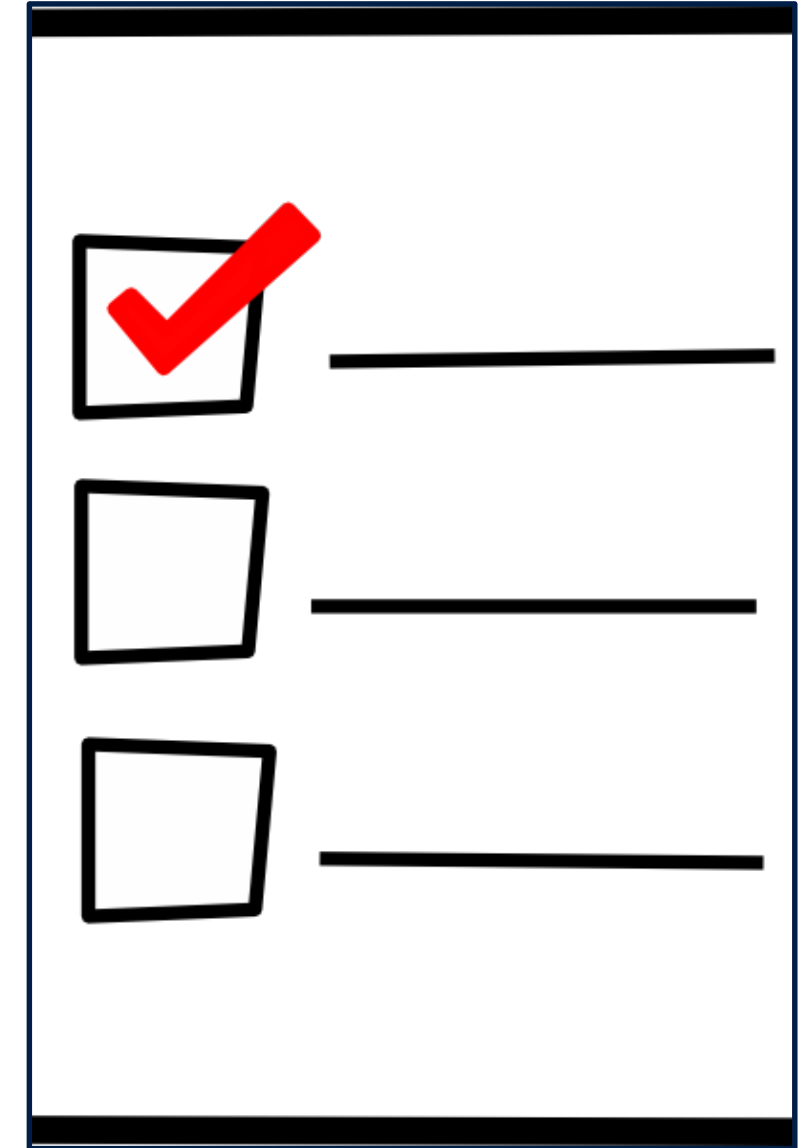
SENIOR DIRECTOR, CORPORATE BIOSTATISTICS

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OUTLINE OF PRESENTATION

- **External data**
  - What is it?
  - It's been used before
  - MDIC working group
- **Medtronic Spyral Renal Denvervation Program**
  - Therapy
  - Trials involved
- **Discount Power Prior Approach**
- **Closing**

With thanks to Graeme Hickey and Martin Fahy for slide material

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EXTERNAL DATA

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EXTERNAL DATA
DEFINITION

- External data is data that is generated outside of a contemporaneous clinical study.
  - Historical clinical trial data
  - Modeling & Simulation data
  - Registries/EHR
  - Administrative (e.g., claims, billing records)

- Registries/EHR/Administrative data are examples of Real World Data (RWD)

- With External data, we are usually considering the *combination* of some external information with some currently generated clinical study information
  - At least for the working group of MDIC
  - Will cover some external only examples in this talk

- Many cases of combining external data involve *borrowing* information

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Examples of borrowing

Them: "FDA will never go for that!"
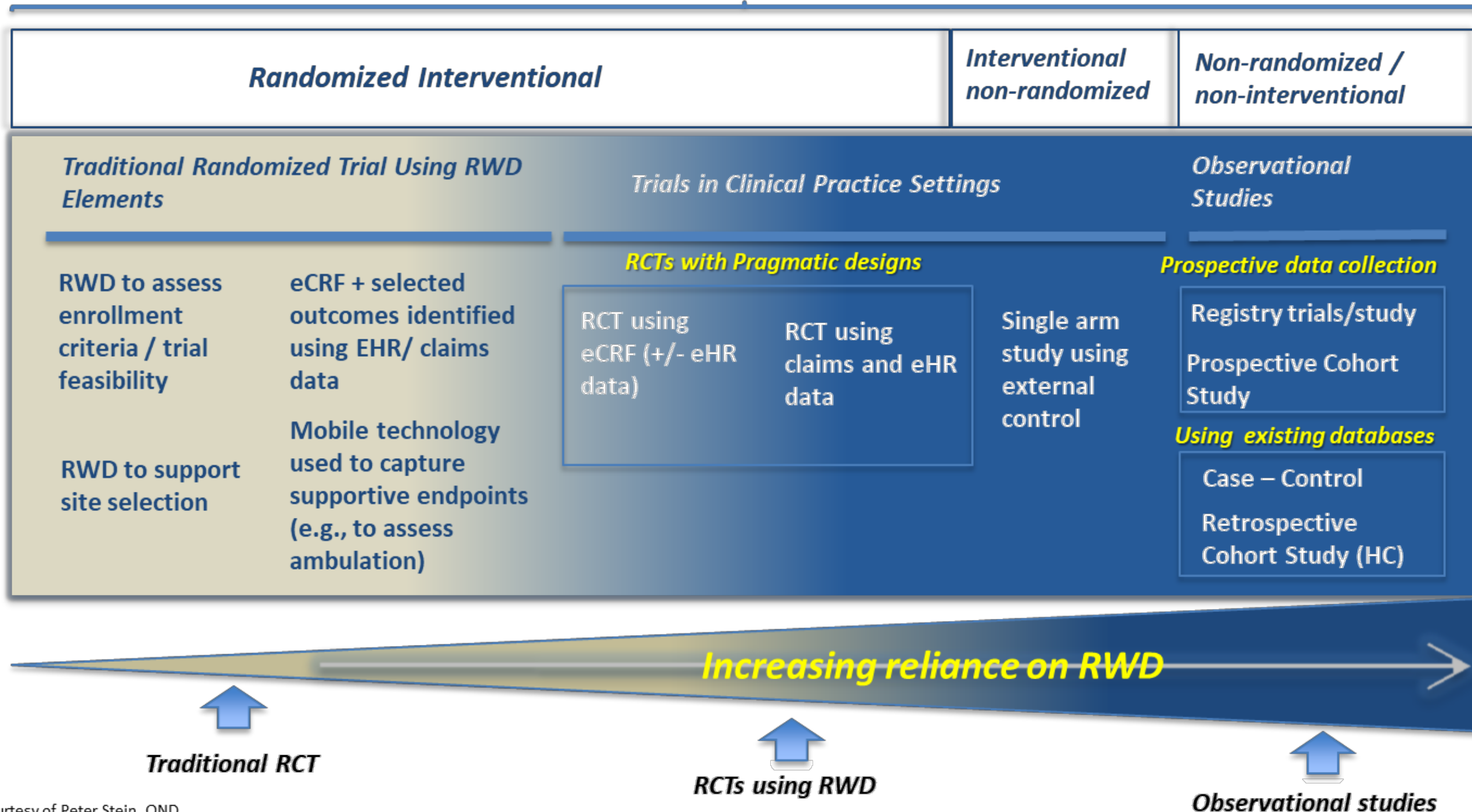**Me: "Well, they have."**

- Spectranetics
  - Arterial stenosis
  - Borrowing from 1-arm EU trial in 2-arm US RCT

- Livanova
  - Epilepsy
  - Borrowing from 4 prior trials, factoring adult/peds, in Japanese peds trial
  - Updated label to include 4-12 year-olds in whom epilepsy meds have failed

- Boston Scientific
  - Atrial fibrillation
  - WATCHMAN device borrowed 50% discounted data from previous trial

- Others ongoing / not yet publicly available

Dynamic Power Priors:
Acceptance by
Regulators, Sponsors, & Clinicians
and their role in reproducibility problem
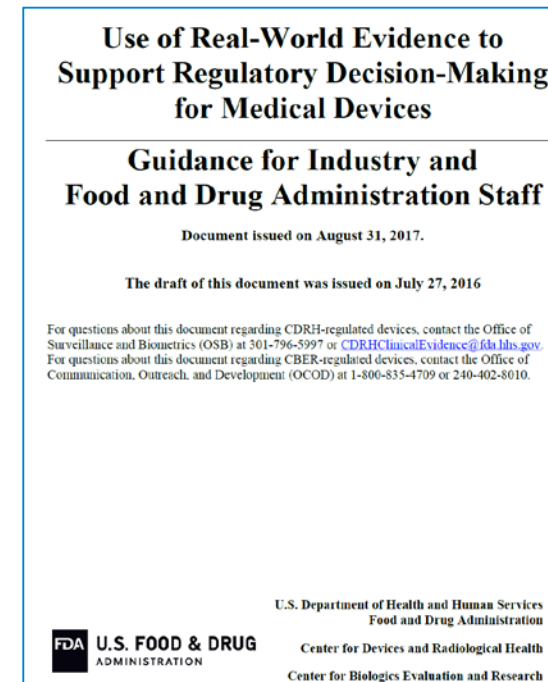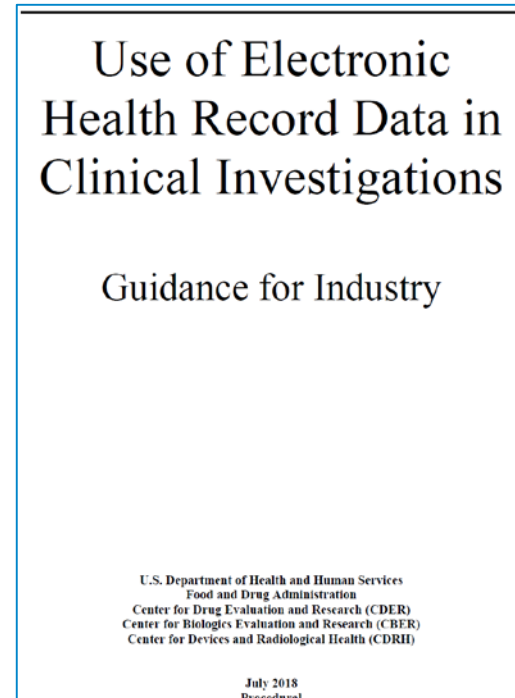
Jason Connor
May 22, 2018
SCT Portland

C**O**NFLUENCE STAT LLC

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Spectrum of Potential Uses of RWD

FDA

Randomized Interventional	Interventional non-randomized	Non-randomized / non-interventional

Traditional Randomized Trial Using RWD Elements

Trials in Clinical Practice Settings

Observational Studies

RWD to assess enrollment criteria / trial feasibility

RWD to support site selection

eCRF + selected outcomes identified using EHR/ claims data

Mobile technology used to capture supportive endpoints (e.g., to assess ambulation)

RCTs with Pragmatic designs

RCT using eCRF (+/- eHR data)

RCT using claims and eHR data

Single arm study using external control

Prospective data collection

Registry trials/study

Prospective Cohort Study

Using existing databases

Case – Control

Retrospective Cohort Study (HC)

Increasing reliance on RWD

Traditional RCT

RCTs using RWD

Observational studies
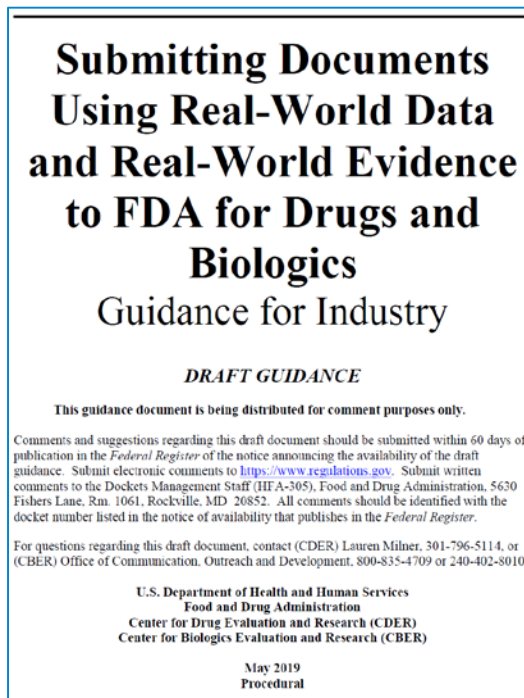
EXTERNAL EVIDENCE

- Scope issues
  - Focus here is on cases with a mixture of external and current data
  - Purely external data is out of scope
    - Meta-analysis of published literature
    - Claims data comparative effectiveness studies
    - Many registry based analyses using RWE/RWD
  - RWE/RWD issues well covered by existing guidances

Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics
Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the Federal Register of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the Federal Register.

For questions regarding this draft document, contact (CDER) Lauren Milner, 301-796-5114, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2019
Procedural

Use of Electronic Health Record Data in Clinical Investigations

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

July 2018
Procedural

Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

Guidance for Industry and Food and Drug Administration Staff

Document issued on August 31, 2017.

The draft of this document was issued on July 27, 2016.

For questions about this document regarding CDRH-regulated devices, contact the Office of Surveillance and Biometrics (OSB) at 301-796-5997 or CDRHClinicalEvidence@fda.hhs.gov. For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach, and Development (OCOD) at 1-800-835-4709 or 240-402-8010.

FDA U.S. FOOD & DRUG ADMINISTRATION

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

That's out of scope, bro.
TenTonTitmouse®

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FRAMEWORK

- General framework being developed through MDIC EEM WG
  - MDIC EEM WG: Medical Device Innovation Consortium External Evidence Methods Working Group
- Framework consists of multiple elements
  - **Classification** of external data sources
  - **Categorization** of how current and external data will be combined
  - **Compatibility** steps
  - **Cataloguing**/development of certain methods
  - **Charting** of regulatory interactions
- An expansion of earlier work done under a "virtual patient" initiative
  - That work laid out the discount power prior approach to be discussed

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EXTERNAL EVIDENCE

- Easy cases
  - Merging in mortality information for all subjects from Social Security Death Index for a US study
  - Merging in hospital costs for all subjects
    - Data generated during study, but captured without regular site staff
- Harder cases
  - Using only historical data for the control arm, and only current data for the experimental arm
    - Especially hard if data capture mechanism differ substantively between arms
  - Working with a novel virtual patient model derived from M&S
    - Unclear what level of validation is appropriate
- Focus today
  - Combined analysis of pilot and pivotal study data
  - Pilot data treated as external
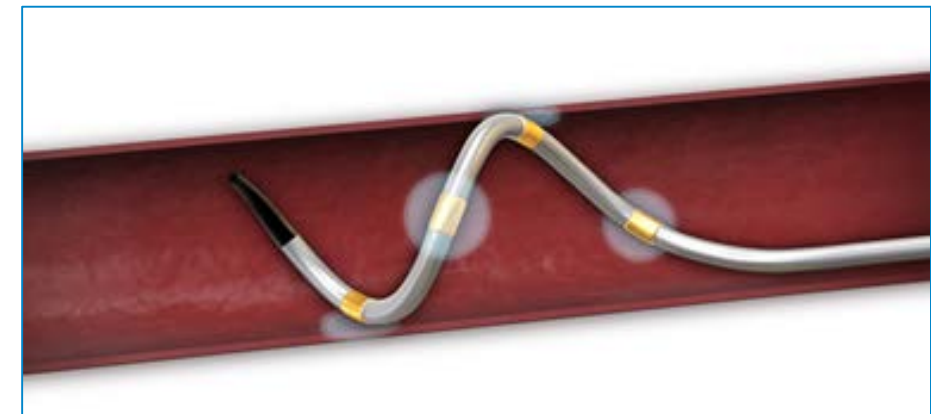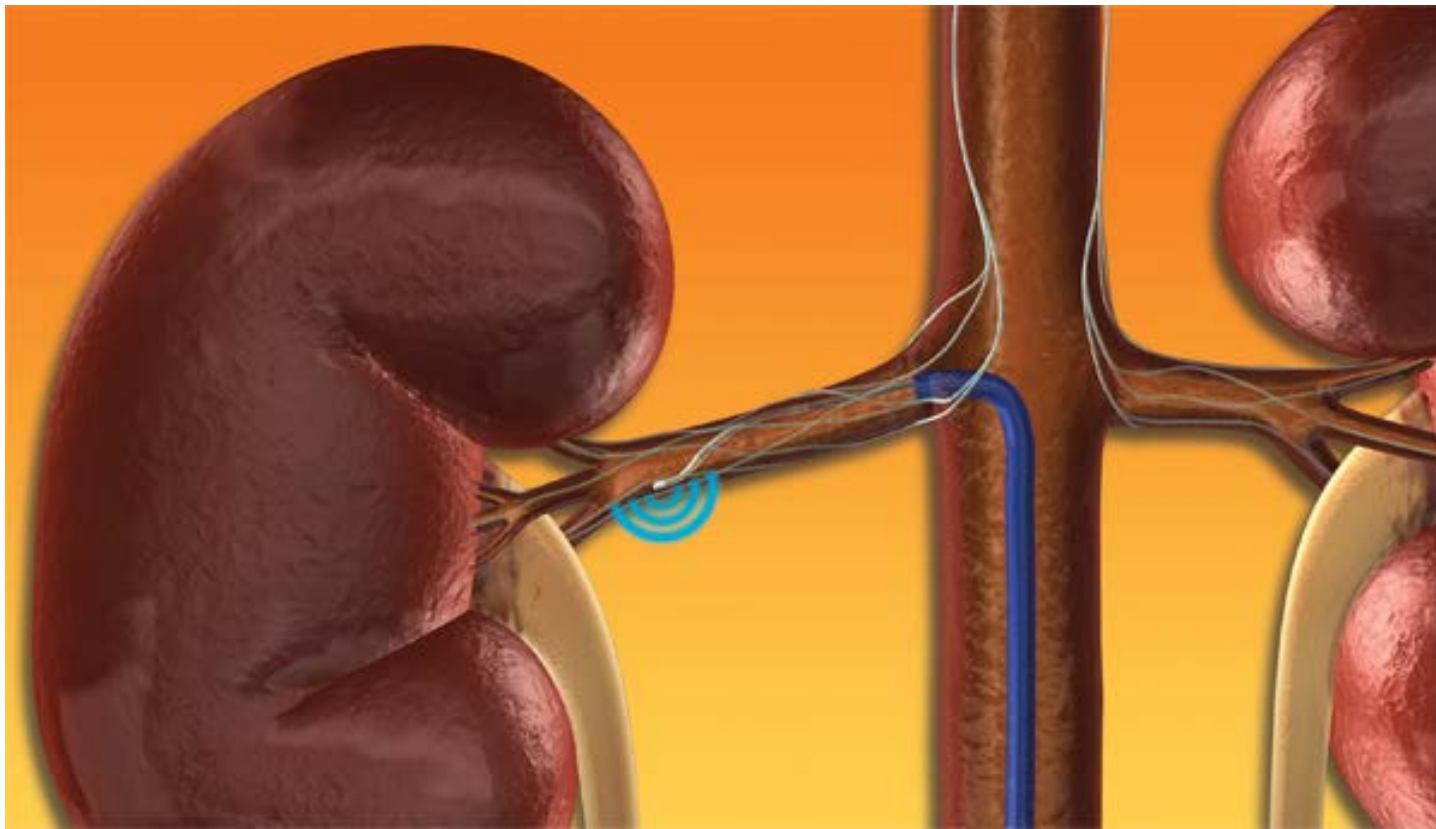
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RENAL DENERVATION PROGRAM

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Further, Together

RENAL DENERVATION

MEDTRONIC RENAL DENERVATION PROGRAM
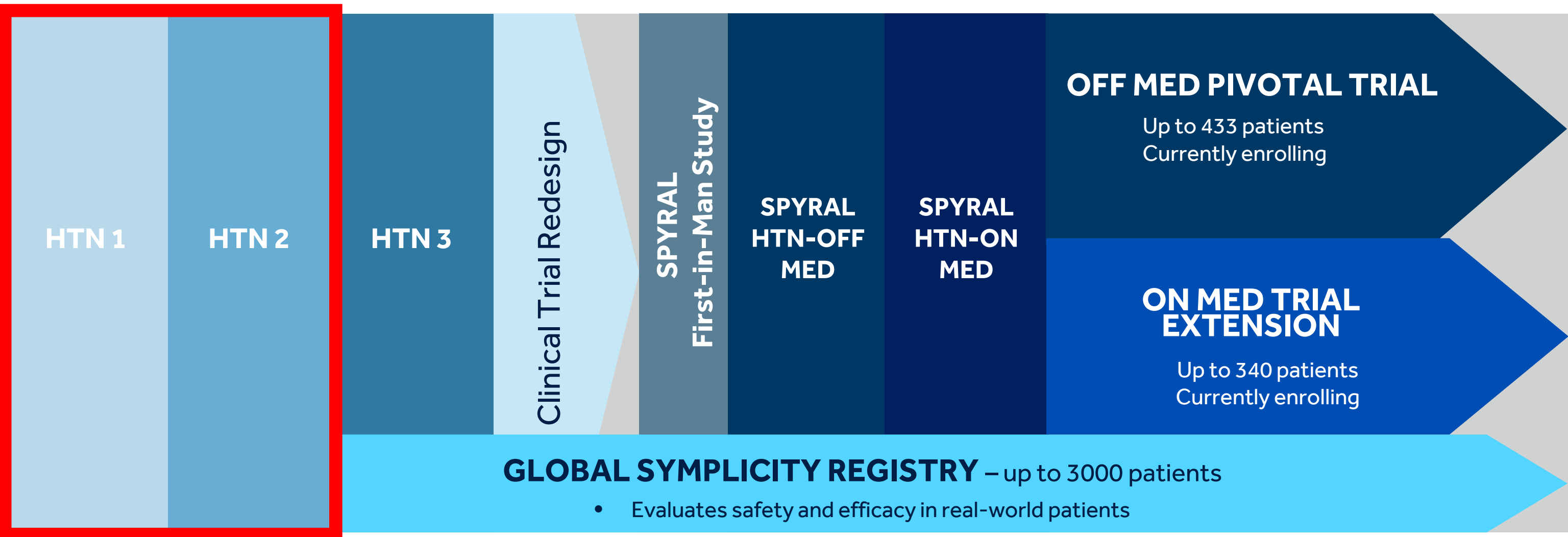
HTN 1

HTN 2

HTN 3

Clinical Trial Redesign

SPYRAL First-in-Man Study

SPYRAL HTN-OFF MED

SPYRAL HTN-ON MED

OFF MED PIVOTAL TRIAL

Up to 433 patients
Currently enrolling

ON MED TRIAL EXTENSION

Up to 340 patients
Currently enrolling

GLOBAL SYMPLICITY REGISTRY – up to 3000 patients
- Evaluates safety and efficacy in real-world patients
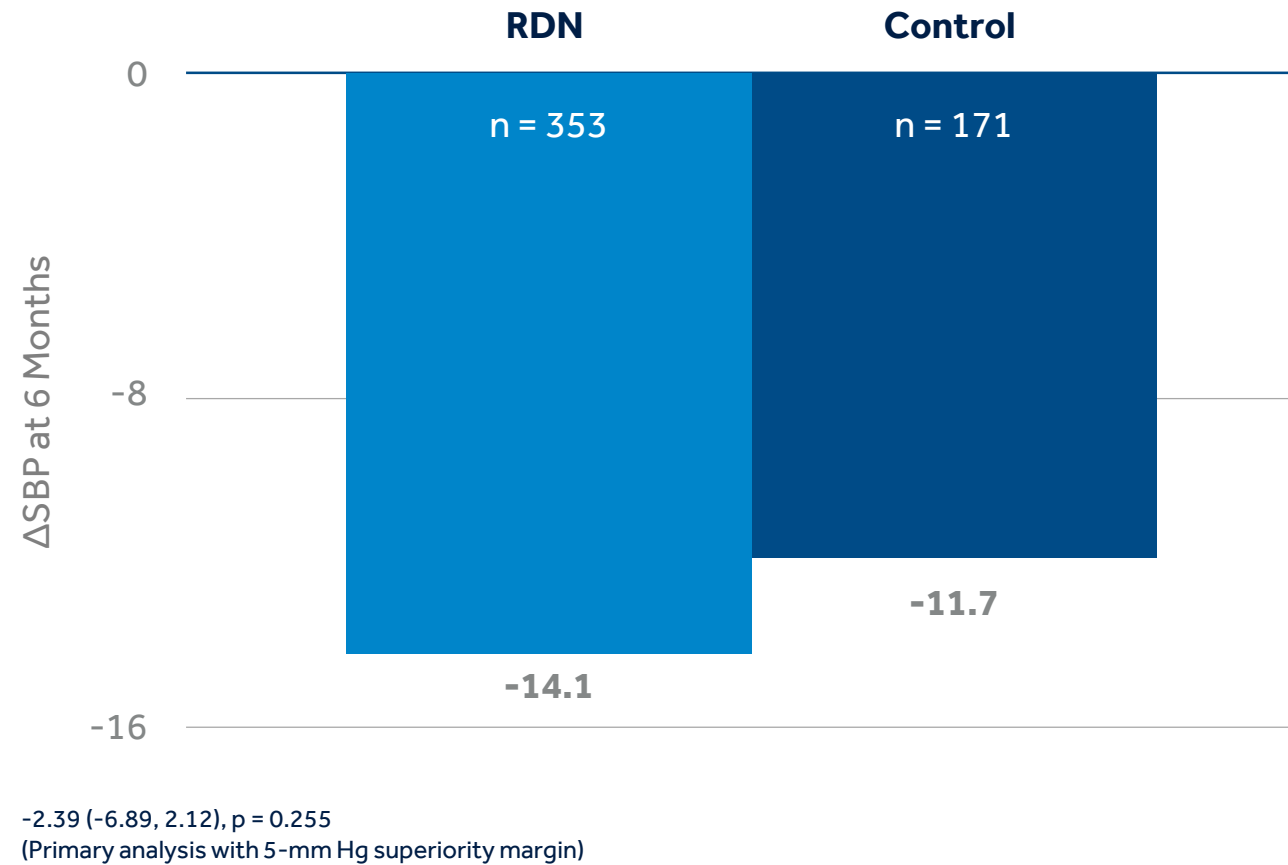
Symplicity HTN-1 Investigators. Hypertension. 2011;57:911-917. | Symplicity HTN-2 Investigators. *Lancet*. 2010;376:1903-1909.
Bhatt DL, et al. N Engl J Med. 2014;370:1393–1401. | Townsend RR, et al. Lancet. 2017;390:2160–2170. | Kandzari DE, et al. *Lancet*. 2018;391:2346–2355.

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SYMPLICITY HTN-1 AND SYMPLICITY HTN-2 CLINICAL TRIALS
SHOWED SIGNIFICANT AND SUSTAINED BLOOD PRESSURE REDUCTION

SYMPLICITY HTN-1 Long-Term F/U Change in office BP through 36 months[1]

Δ FROM BASELINE TO 6 MONTHS (mm Hg)

	1 mo (n = 80)	3 mo (n = 88)	6 mo (n = 88)	12 mo (n = 85)	24 mo (n = 82)	30 mo (n = 84)	36 mo (n = 88)
SBP mm Hg	-21	-22	-26	-27	-30	-33	-32
DBP mm Hg	-10	-9	-11	-12	-13	-15	-14

■ SBP mm Hg   ■ DBP mm Hg
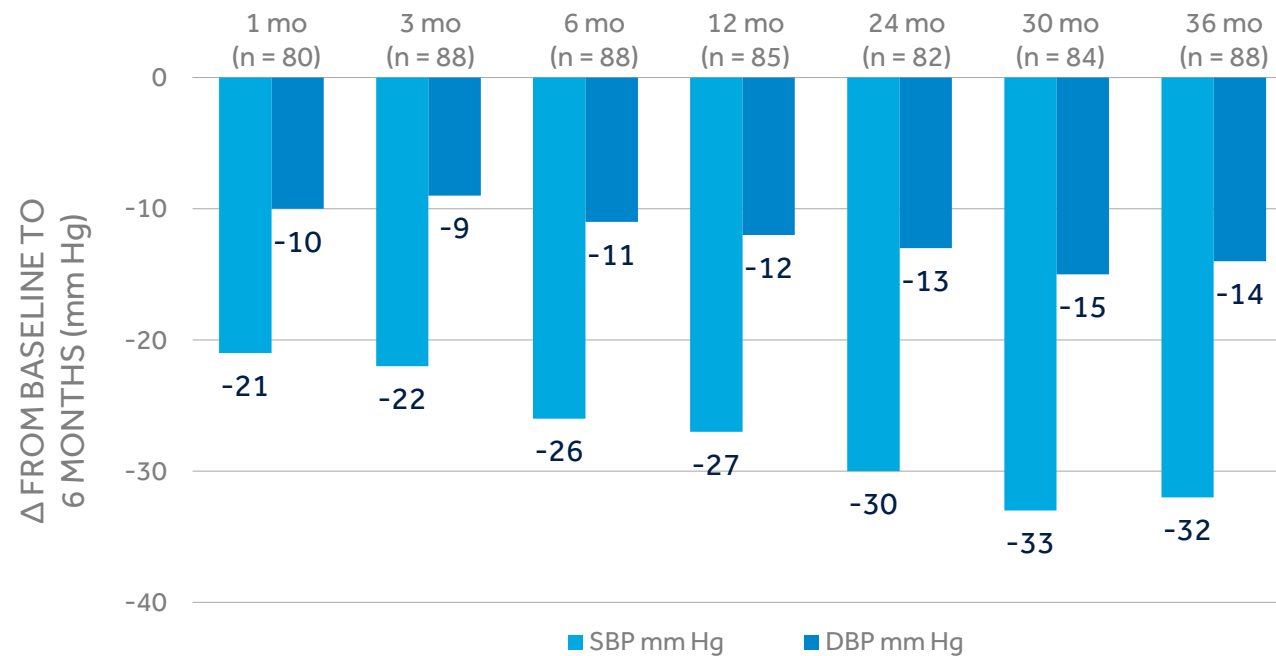
[1]Krum H et al. *The Lancet*. 2014;383:622–629.

SYMPLICITY HTN-2 RCT 6 month BP change

RDN (n = 49)   Control (n = 51)

Δ FROM BASELINE TO 6 MONTHS (mm Hg)

	Systolic	Diastolic
RDN	-32	-12
Control	1	0

Difference between RDN and Control highly significant (p<0.0001)
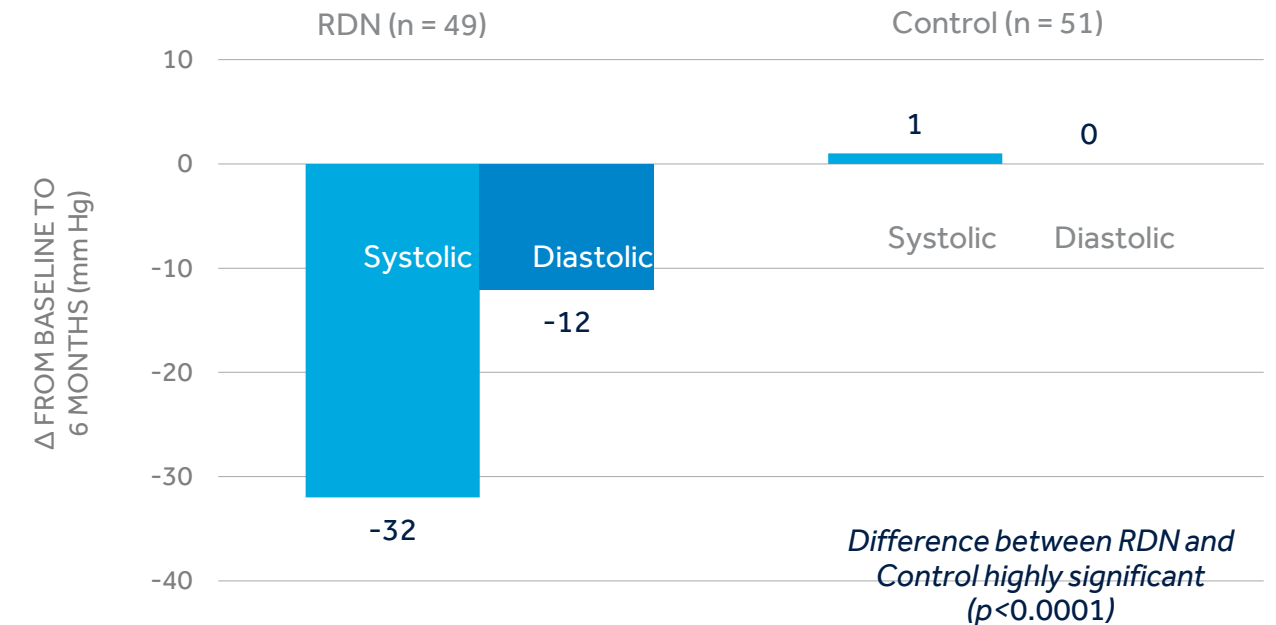
SYMPLICITY HTN-2 Investigators. The Lancet. 2010; 376: 1903-1909

Significant and **sustained blood pressure reduction out to three years**

Significant change in office **BP compared to a medication-only control group**

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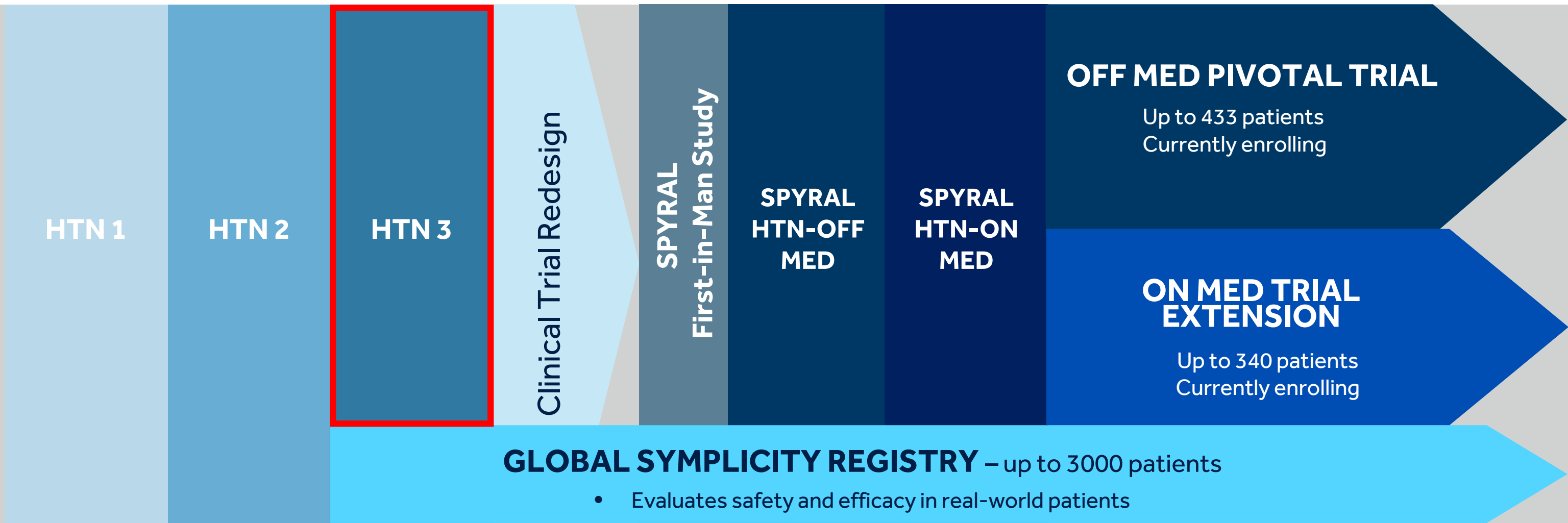
MEDTRONIC RENAL DENERVATION PROGRAM

HTN 1	HTN 2	HTN 3	Clinical Trial Redesign	SPYRAL First-in-Man Study	SPYRAL HTN-OFF MED	SPYRAL HTN-ON MED	

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ON MED TRIAL EXTENSION
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GLOBAL SYMPLICITY REGISTRY – up to 3000 patients
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SYMPLICITY HTN-3
LANDMARK TRIAL OF DEVICE THERAPY FOR HYPERTENSION

	RDN	Control

ΔSBP at 6 Months

0

n = 353

n = 171

-8

-11.7

-14.1

-16

-2.39 (-6.89, 2.12), p = 0.255
(Primary analysis with 5-mm Hg superiority margin)

There was **no significant difference in BP change** at 6 months
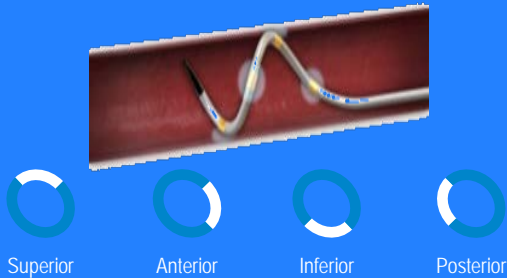
The large BP change in the control group suggested that there were **significant sources of variation** that were not controlled in the trial
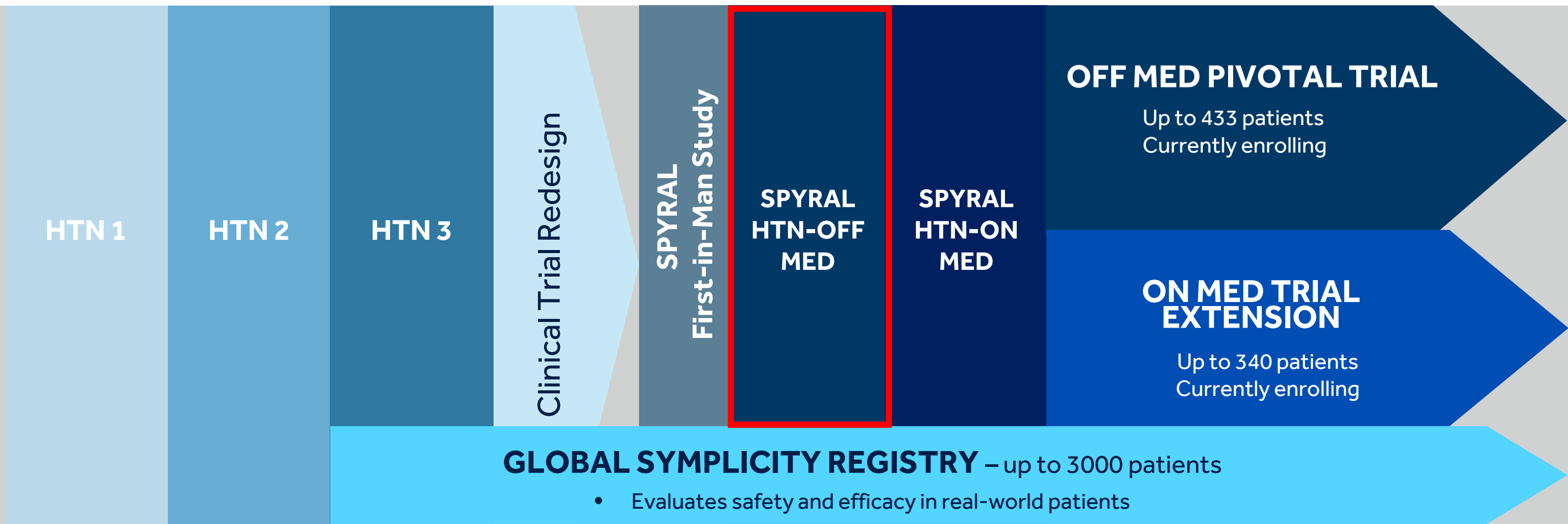
Bhatt DL et al. *N Engl J Med*. 2014;370:1393–1401.

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RESPONDING TO HTN3
ADDRESSING CONFOUNDING FACTORS* IDENTIFIED FROM SYMPLICITY HTN-3

	Medications	**Patients**	**Procedure**
SYMPLICITY HTN-3 (Utilized Flex Catheter)	Drug changes and variable patient adherence	Heterogenous study population	Procedural experience and variability
Recommendations	Observe pill-taking prior to ABPM measurement Measure drug adherence	Enroll more traditional pharmaceutical trial-like hypertension population, not "severe resistant"	Modified system: SPYRAL catheter Branch treatment
SPYRAL HTN	Off and On Med studies with drug testing	Excluding isolated systolic hypertension patients	Spyral catheter, branch treatment, case proctoring

Superior · Anterior · Inferior · Posterior

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MEDTRONIC RENAL DENERVATION PROGRAM

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SPYRAL HTN – OFF MED
STUDY DESIGN

- Randomized, sham-controlled, (patient and assessor) blinded, proof-of-concept trial
- 25 sites in Germany, UK, Austria, Greece, Japan, Australia and USA

SCREENING

TREATMENT

Inclusion criteria:
- Office SBP ≥150 to <180
- Patient is either drug naïve or permitting discontinuation of antihypertensive medications

VISIT 1
- Office SBP
  - SBP≥150 to <180
  - DBP ≥90
- Drug naïve or stop meds

3-4 weeks[1]

2-week safety check[2]

VISIT 2
- Drug testing
- Office BP
  - SBP≥150 to <180
  - DBP ≥90
- Witnessed drug intake
- 24-hr ABPM
  - SBP ≥140 to <170

1-2 weeks[1]

R

Sham Control + Medications

every 2 weeks

3M   6M   12-36M

Drug titration until OSBP<140

Unblinding

Renal Denervation + Medications

every 2 weeks

3M   6M   12-36M

- Office BP

- Drug testing[3]   ▪ Witnessed drug intake[4]
- Office BP   ▪ 24-hr ABPM

Screen failure if OSBP ≥180

- [1] According to scheduling [2] Only for patients discontinuing anti-hypertensive medications [3] Drug testing not done at 24 and 36 months [4] If prescribed to achieve OSBP <140
- Clinicaltrials.gov NCT02439749
- **Kandzari D, et al. *Am Heart J*. 2016;171:82-91.**

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SPYRAL HTN – OFF MED
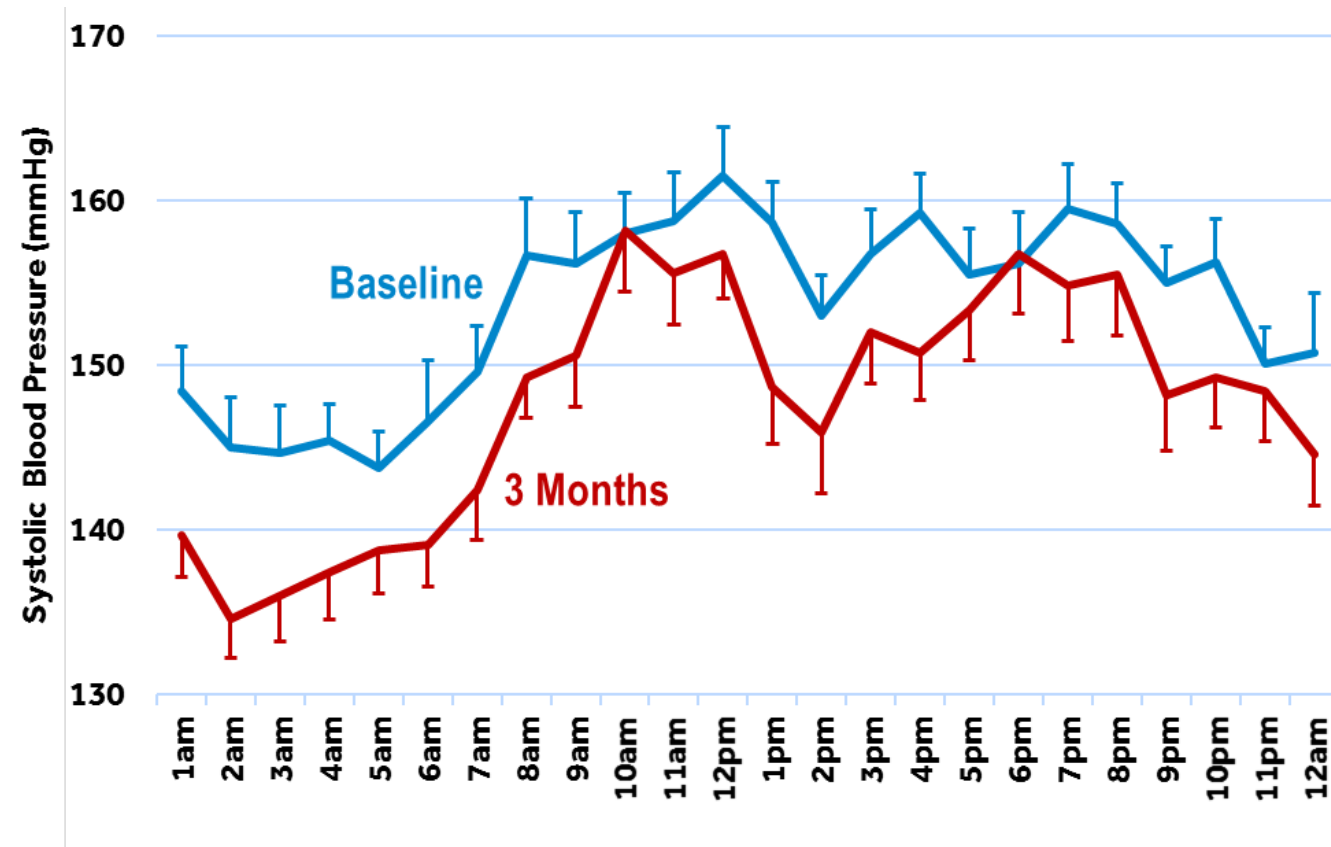## BLOOD PRESSURE CHANGE FROM BASELINE TO 3 MONTHS
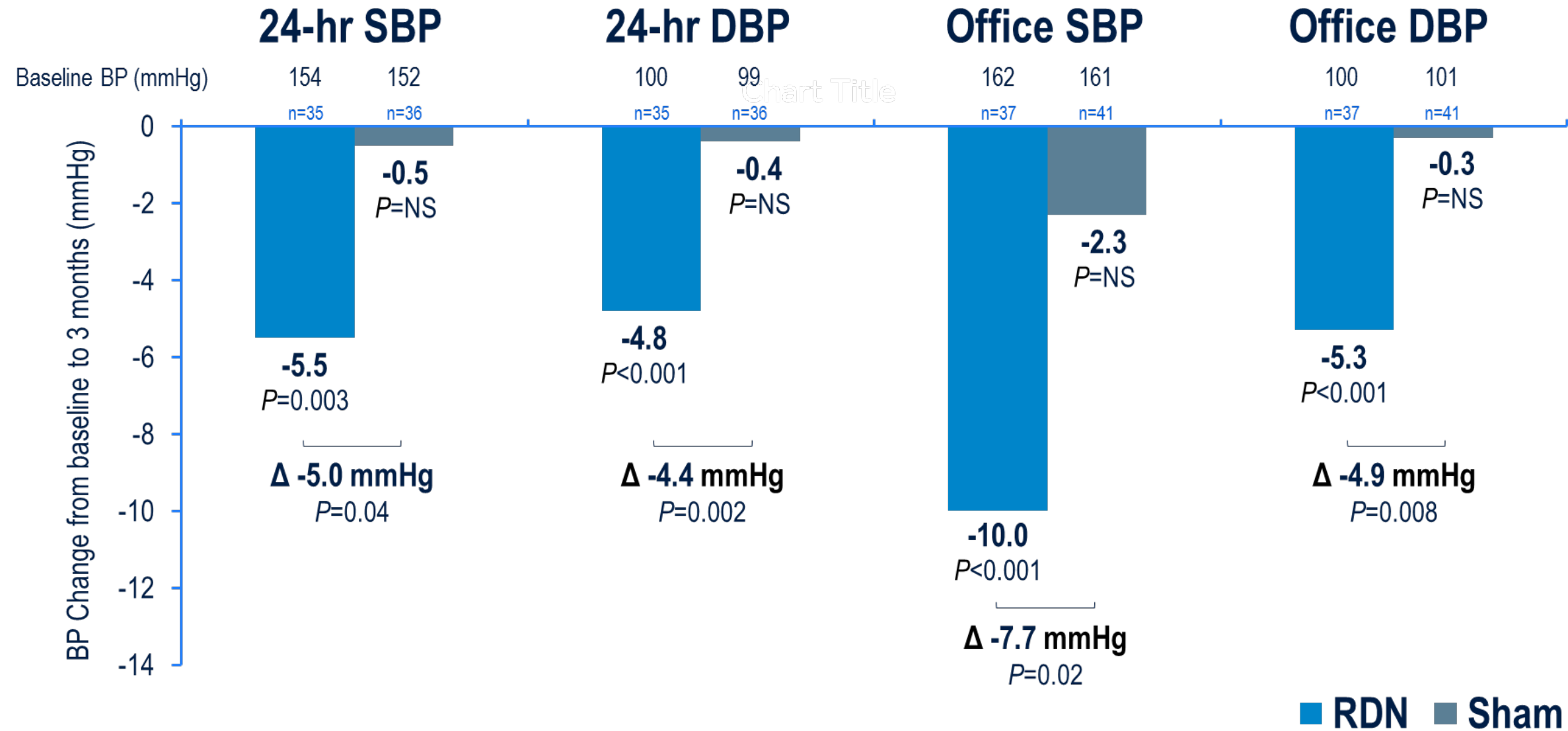
Townsend R, et al. *Lancet*. 2017;390:2160-2170.
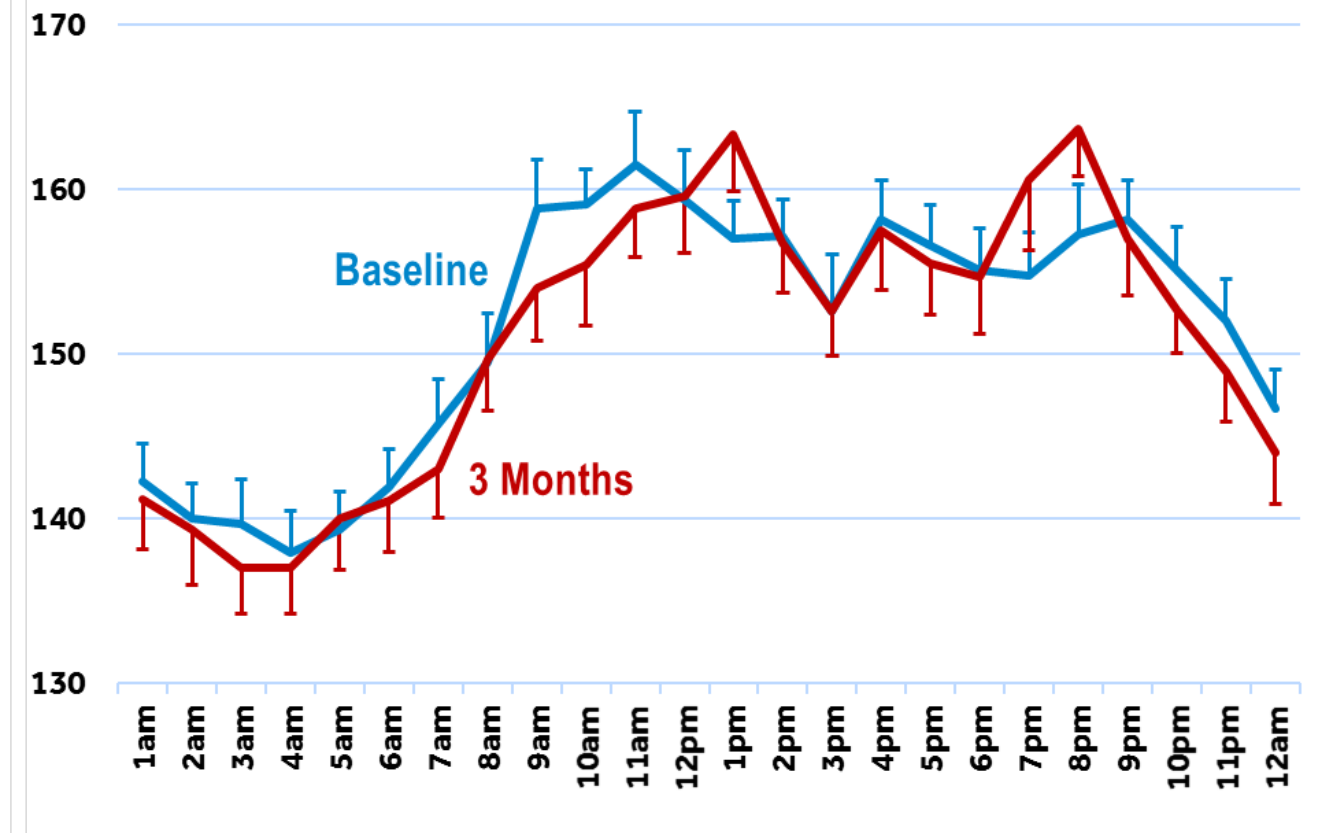
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SPYRAL HTN – OFF MED
24-HR SYSTOLIC BLOOD PRESSURE FROM BASELINE TO 3 MONTHS

- Graphs based on actual clock times. Similar results were observed when 24-hour BP patterns were normalized to patient reported time of waking.
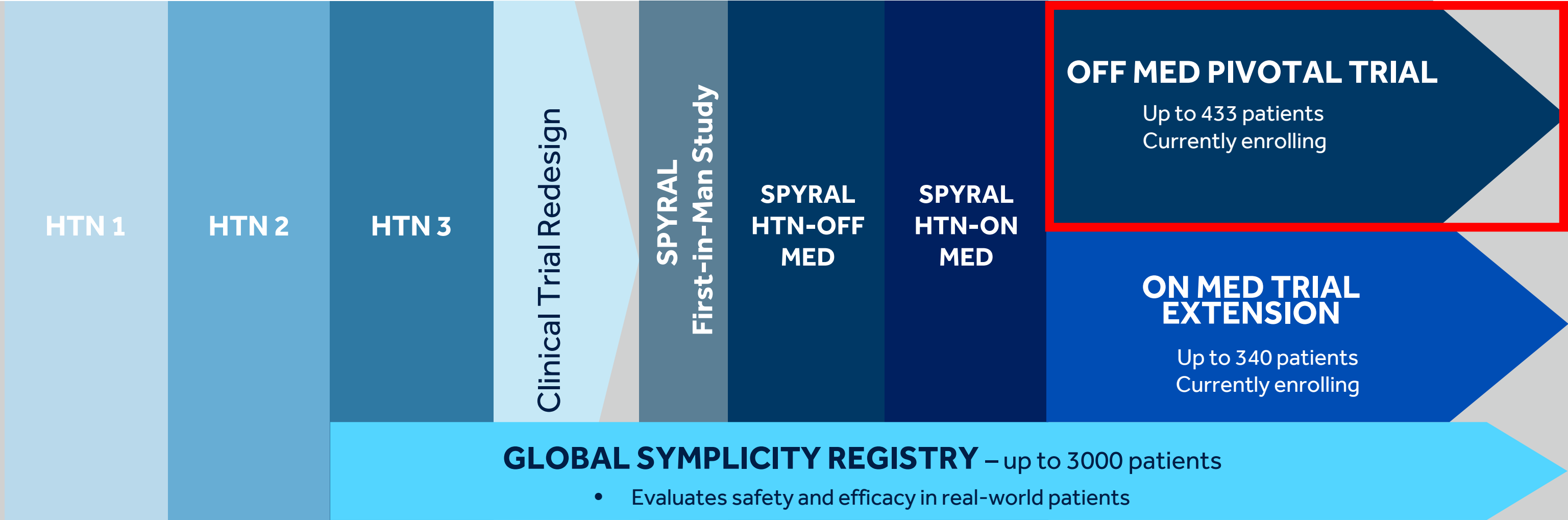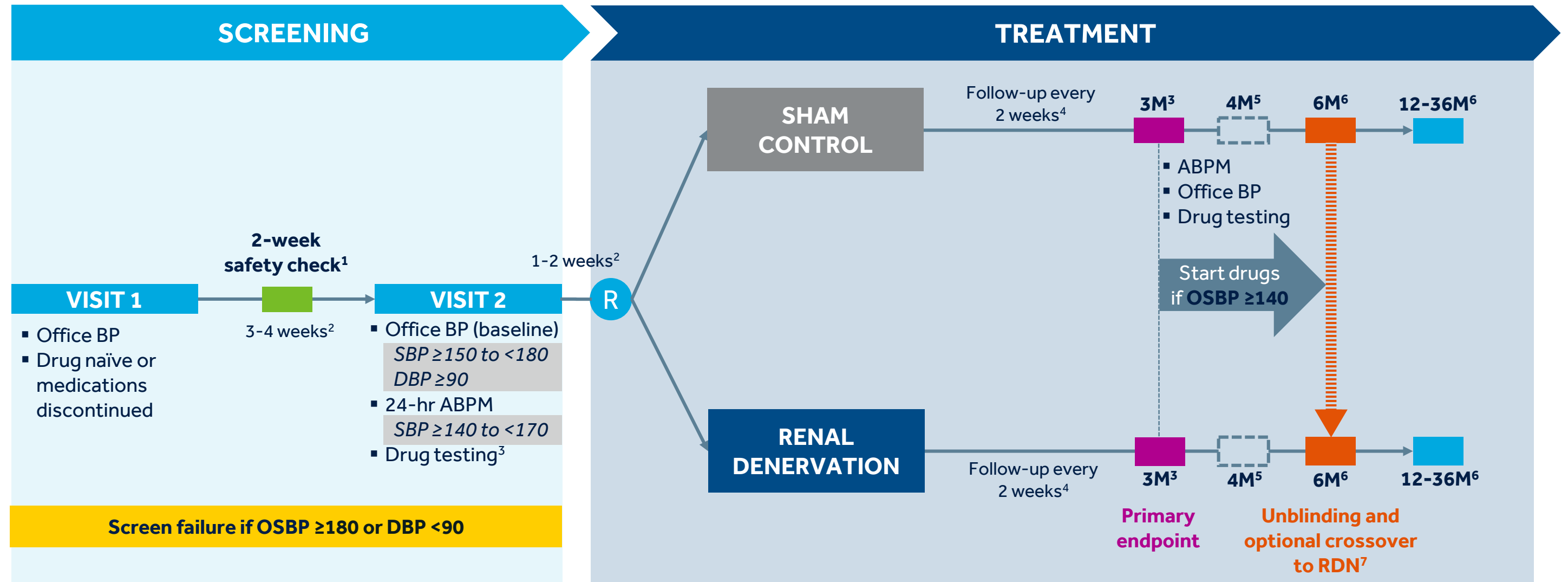

Kario K, et al. *Circulatiot*. In press

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MEDTRONIC RENAL DENERVATION PROGRAM

HTN 1

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SPYRAL PIVOTAL - SPYRAL HTN-OFF MED
RANDOMIZED, SHAM-CONTROLLED TRIAL

SCREENING

TREATMENT

VISIT 1
- Office BP
- Drug naïve or medications discontinued

2-week safety check[1]

3-4 weeks[2]

VISIT 2
- Office BP (baseline)
  - *SBP ≥150 to <180*
  - *DBP ≥90*
- 24-hr ABPM
  - *SBP ≥140 to <170*
- Drug testing[3]

Screen failure if OSBP ≥180 or DBP <90

R

1-2 weeks[2]

SHAM CONTROL

Follow-up every 2 weeks[4]

3M[3]   4M[5]   6M[6]   12-36M[6]

- ABPM
- Office BP
- Drug testing

Start drugs if **OSBP ≥140**

RENAL DENERVATION

Follow-up every 2 weeks[4]

3M[3]   4M[5]   6M[6]   12-36M[6]

Primary endpoint

Unblinding and optional crossover to RDN[7]

[1]Only for patients discontinuing anti-hypertensive medications. [2]According to scheduling. [3]Drug testing to ensure no medications are present. [4]Optional follow up at weeks 6 and/or 10 if the patient is not controlled. [5]Only for patients with BP ≥140 mmHg at 3M. [6]Drug testing to ensure prescribed medications are present (if on drug). [7]6 and 12 month renal imaging.

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DISCOUNT POWER PRIOR

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POSITION ON BAYESIAN DESIGN
FDA & NMPA

FDA Position

- Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials – 2010

- MDT has worked together with FDA for Bayesian design of Off-Med Pivotal Trial and On-Med Trial Extension

Bayesian Design Details

- Bayesian method for leveraging historical data

- Discounts the historical data if there is evidence of differences from the current data

  - *Built to avoid undue mixing of incompatible outcome data between historical and current sources*

- Prior to starting the trial define a discount function

- The method has four steps for estimating the parameter of interest

  1. Compare; 2. Discount; 3. Combine; 4. Estimate

- Method works in conjunction with an adaptive Bayesian trial

- Estimation is done at every interim look

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BAYESIAN DESIGN DETAILS
POWER PRIOR DISCOUNT FUNCTION METHOD

1. **Compare** historical and current data (poolability test)
   - Calculate p, the stochastic comparison between current and historical data
   - p=0.5 means perfect agreement, allowing maximum utilization of the prior dataset
   - p close to 0 or 1 means a high level of disagreement

current data
(Pivotal)

historical data
(OFF MED Prior)
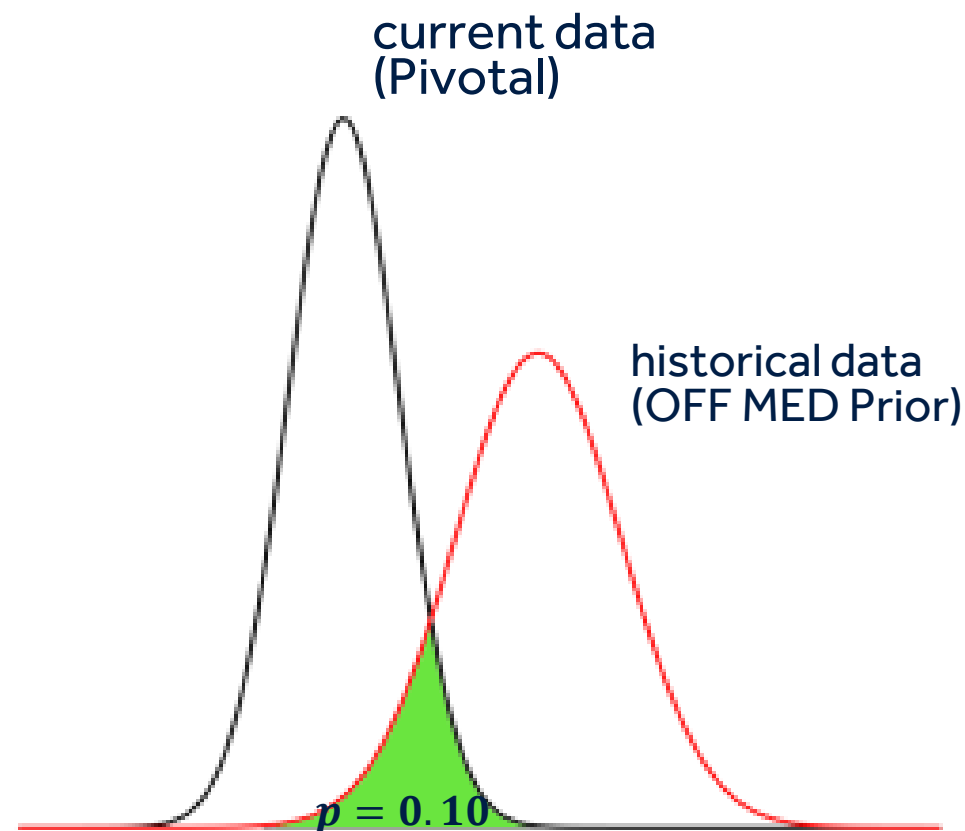
$p = 0.10$

In this example, the current data and the historical data are different from each other. The stochastic comparison gives a value of p=0.10, indicating that the two populations are different. This will lead to greater discounting of the prior data when calculating the Bayesian posterior estimate

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BAYESIAN DESIGN DETAILS
POWER PRIOR DISCOUNT FUNCTION METHOD

2. **Discount** strength of historical data using discount function

- Calculate α_0 using p from step 1

- When p=0.5, α_0 =1.00 (maximum prior dataset usage)

- When p=0.10, α_0 =0.33 (33% of the prior historical dataset usage)

- When p= 0 or 1, α_0 =0 (0% of the prior historical dataset usage)

α_0 = 0 means no prior data will be used

α_0 = 1 means all prior data will be used

α_0

Weibull Discount Function curve

1
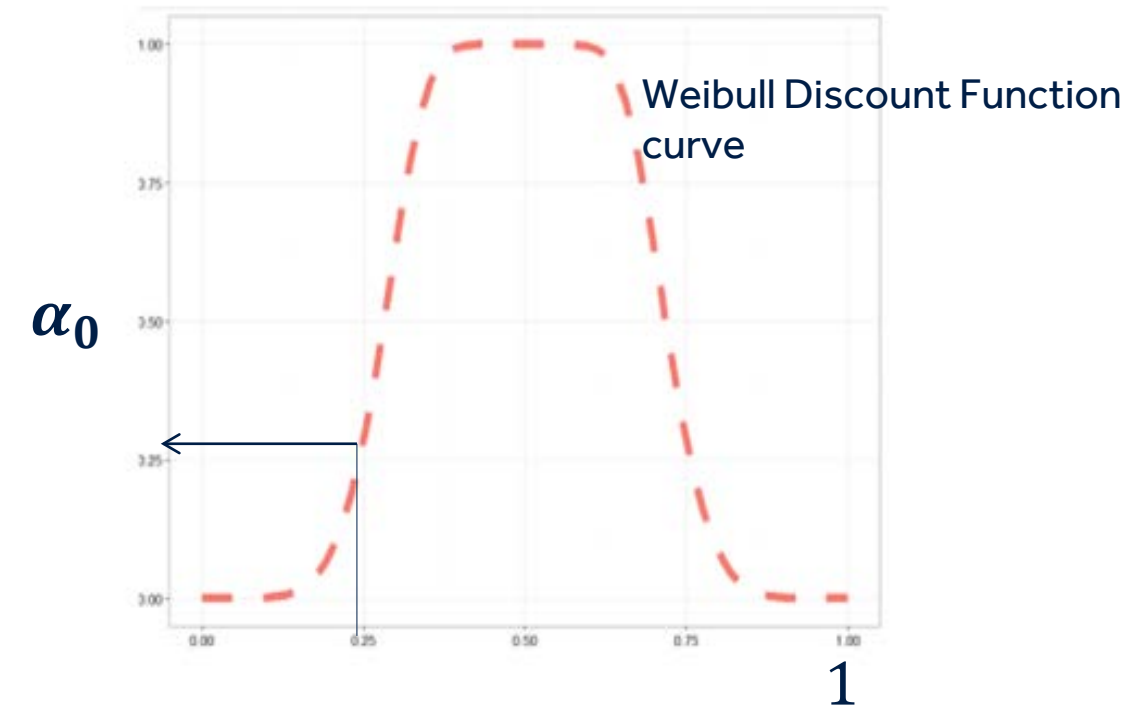
In our example, we use the value of p=0.1 from the previous slide, to calculate a value for the discounting parameter of α_0=0.33. This means that we will only use 33% of the prior/historical data when calculating the Bayesian posterior estimate. We are reducing the influence of the prior data on the final Bayesian estimate, because it is so different from the current/pivotal data

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3. **Combine** historical and current data

$$n_{total} = n_{pivotal} + \boldsymbol{\alpha_0} n_{historical}$$

Discount parameter

In our example, we calculated a value for the discounting parameter of $\boldsymbol{\alpha_0}$=0.33. This means that the final Bayesian posterior estimate will use ALL of the current/pivotal data, but only 33% of the prior/historical data

Overall sample size will include all pivotal patients along with the prior historical dataset after being discounted by a value of $\boldsymbol{\alpha_0}$

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BAYESIAN DESIGN DETAILS
POWER PRIOR DISCOUNT FUNCTION METHOD

4. **Estimate** Bayesian treatment effect from combined data

- The Bayesian posterior estimate uses ALL of the current/pivotal data, combined with the discounted historical /prior data.

Bayesian
Posterior
Estimate
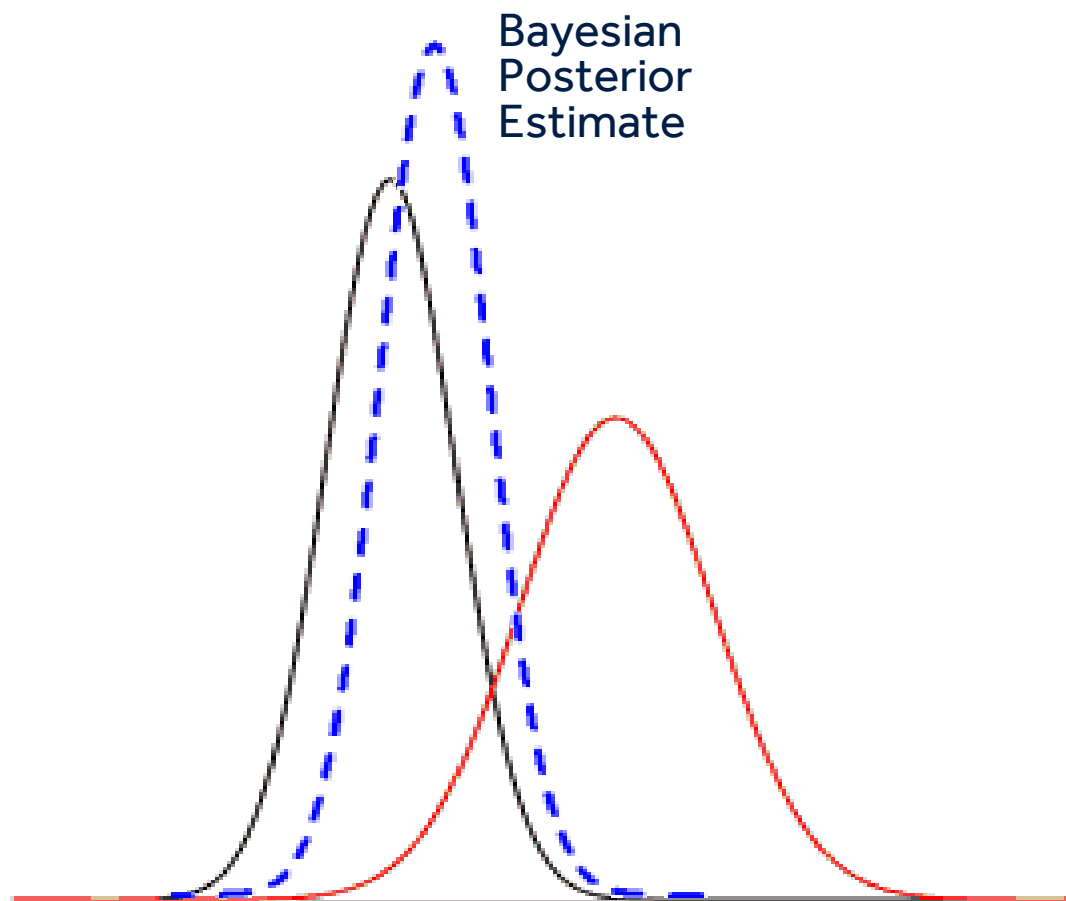
In our example, the current/pivotal data is different from the prior/historical data. The value of α_0=0.33 for the discount parameter reduces the influence of the prior data on the final Bayesian posterior estimate. The Bayesian posterior estimate is more similar to the current/pivotal data due to this discounting

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CLOSING

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FUTURE DIRECTIONS

- Real world data/evidence (RWD/RWE) is increasingly of interest
  - Vital to ability to *generalize* findings beyond specialized clinics, researchers
- Access to RWD remains a challenge
  - Access to historical study data is better; M&S is burgeoning
- Need to think more broadly about issues in incorporating historical data and M&S evidence (not just restrict attention to RWD)
- Want to combine external data with prospectively collected clinical trial data

- Questions for use of external data:
  - What data do you have? (Characterization)
  - How good is it? (Quality)
  - What do you want to do with the data? (Suitability)
  - How will you do it? (Methods)
- Alignment by industry and regulators on these issues will be key
- Public private partnerships such as MDIC and CTTI will be instrumental in advancing such activities
  - MDIC EEM WG will be a key contributor to these efforts

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