Percutaneous Closure of Patent Foramen Ovale in Migraine with Aura

PRIMA

David Hildick-Smith, Heinrich P. Mattle, Stefan Evers, Werner J. Becker, Helmut Baumgartner, Jeremy Chataway, Marek Gawel, Hartmut Göbel, Axel Heinze, Eric Horlick, Iqbal Malik, Adam Zermansky, Simon Ray, Oliver Findling, Stephan Windecker, Bernhard Meier.

On Behalf of the PRIMA Investigators

tct2014 In Partnership with the ACC

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	Company
▪ Grant/Research Support ▪ Consulting Fees/Honoraria	▪ St. Jude Medical

Migraine and PFO - Background

- Migraine is common
  - estimated prevalence of 8% to 13%
  - ~55 million people across USA and Europe
- PFO closure associated with high rate of resolution of incidental migraine
- Hypothesis of right-to-left shunting of chemical or physical triggers for migraine

MIST
(Migraine Intervention with Starflex)

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

Migraine Intervention With STARFlex Technology (MIST) Trial : A Prospective, Multicenter, Double-Blind, Sham-Controlled Trial to Evaluate the Effectiveness of Patent Foramen Ovale Closure With STARFlex Septal Repair Implant to Resolve Refractory Migraine Headache

Andrew Dowson, Michael J. Mullen, Richard Peatfield, Keith Muir, Arif Anis Khan, Christopher Wells, Susan L. Lipscombe, Trevor Rees, Joseph V. De Giovanni, W. Lindsay Morrison, David Hildick-Smith, Giles Elrington, W. Stewart Hillis, Iqbal S. Malik and Anthony Rickards

MIST

- Failed to meet primary endpoint
- Secondary endpoints: promising trends
  - Migraine frequency
  - Migraine severity

PRIMA

- Purpose
  - To evaluate whether percutaneous PFO closure is effective in reducing migraine headache in patients who have migraine with aura refractory to medical treatment

PRIMA

- Design
  - Multicenter: 20 sites
    - Canada, Germany, Switzerland, United Kingdom
  - Prospective, Randomized, “Open label”
  - Closure Group
    - Amplatzer PFO Occluder implantation
    - 3 months clopidogrel; 6 months aspirin
  - Medical Group
    - Continuation of current medication
    - 3 months clopidogrel; 6 months aspirin

PRIMA

- Sample Size
  - Reduction in migraine days
    - 50% closure group
    - 25% medical group
  - Planned 144 subjects
- Sponsor
  - St. Jude Medical, St. Paul, MN
  - Study initiated under AGA Medical, Plymouth, MN

Study Governance and Organization

Steering Committee

- Werner Becker, MD, University of Calgary-Foothills Hospital
- Stefan Evers, MD, University Hospital, Muenster
- David Hildick-Smith, MD, Brighton and Sussex University Hospitals
- Heinrich Mattle, MD, Bern University Hospital
- Bernhard Meier, MD, Bern University Hospital

Clinical Endpoint Committee

- James R. Couch, MD, PhD, University of Oklahoma Health Sciences Center
- Lawrence D. Robbins, MD, Robbinsville Headache Clinic

Data Safety Monitoring Board

- Felix Berger, MD, German Heart Center, Berlin
- Marek Jauss, MD, OEHK Hospital, Muehlhausen / Thueringen
- Volker Limmroth, MD, Merheim Hospital, Cologne
- Frederick Taylor, MD, Park Nicollet Headache Clinic and Research Center
- Marc Schwartz, Biostatistician

Echo Core Lab

- Victor Davila-Roman, MD, CVR Consulting, PC

Sites involved in PRIMA

St. Mary's Hospital
London, United Kingdom
J. Chataway, I. Malik

University Hospital of Muenster
Muenster, Germany
E. Baumgartner, S. Evers

University Hospitals of South Manchester
Manchester, United Kingdom
C. McCollum, S. Ray, A. Zermansky

Davisville Medical Center
Toronto, Canada
M. Gawel, E. Horlick

Kiel Migraine and Headache Centre
Kiel, Germany
H. Göbel, A. Heinze

Montreal Heart Institute
Montreal, Canada
R. Ibrahim, L. Marchand

Brighton and Sussex University Hospitals
Brighton, United Kingdom
D. Hildick-Smith, A Romi Saha

Headache Center Hirslanden
Zurich, Switzerland
R. Agosti, P. Wagdi

University of Calgary - Foothills Hospital
Calgary, Canada
W. Becker, F. Spence

Bern University Hospital
Bern, Switzerland
H. Mattle, B. Meier

Unfallkrankenhaus Berlin
Berlin, Germany
L. Bruch, I. Schmehl

Quebec Heart and Lung Institute/Laval University
Quebec City, Canada
J. Rodés-Cabau, D. Rivest

Martin Luther University Halle-Wittenberg
Halle, Germany
S. Gielan, S. Zierz

Inclusion criteria

- Migraine headache with aura
- Migraine onset before age 50
- > 3 migraine attacks or 5 migraine days per month
- < 14 headache days per month
- Failed >=2 commonly accepted migraine medications
- Preventative migraine medications stable for 4 weeks prior to and during screening
- Right-to-left shunt documented by TTE or TCD
- PFO documented by TEE

Exclusion criteria

- Patient age <18 years or >65 years
- Medication overuse (defined by IHS criteria)
- Contraindication to aspirin and/or clopidogrel
- Clinical indication for aspirin/clopidogrel/warfarin
- Severe nickel allergy

Study endpoints

- Primary Endpoint
  - Reduction in migraine days 1 year after randomization
    - Mean number of migraine days in months 10-12, subtracted from…
    - Mean number of migraine days in months “-3” to 0 (3 months roll-in)

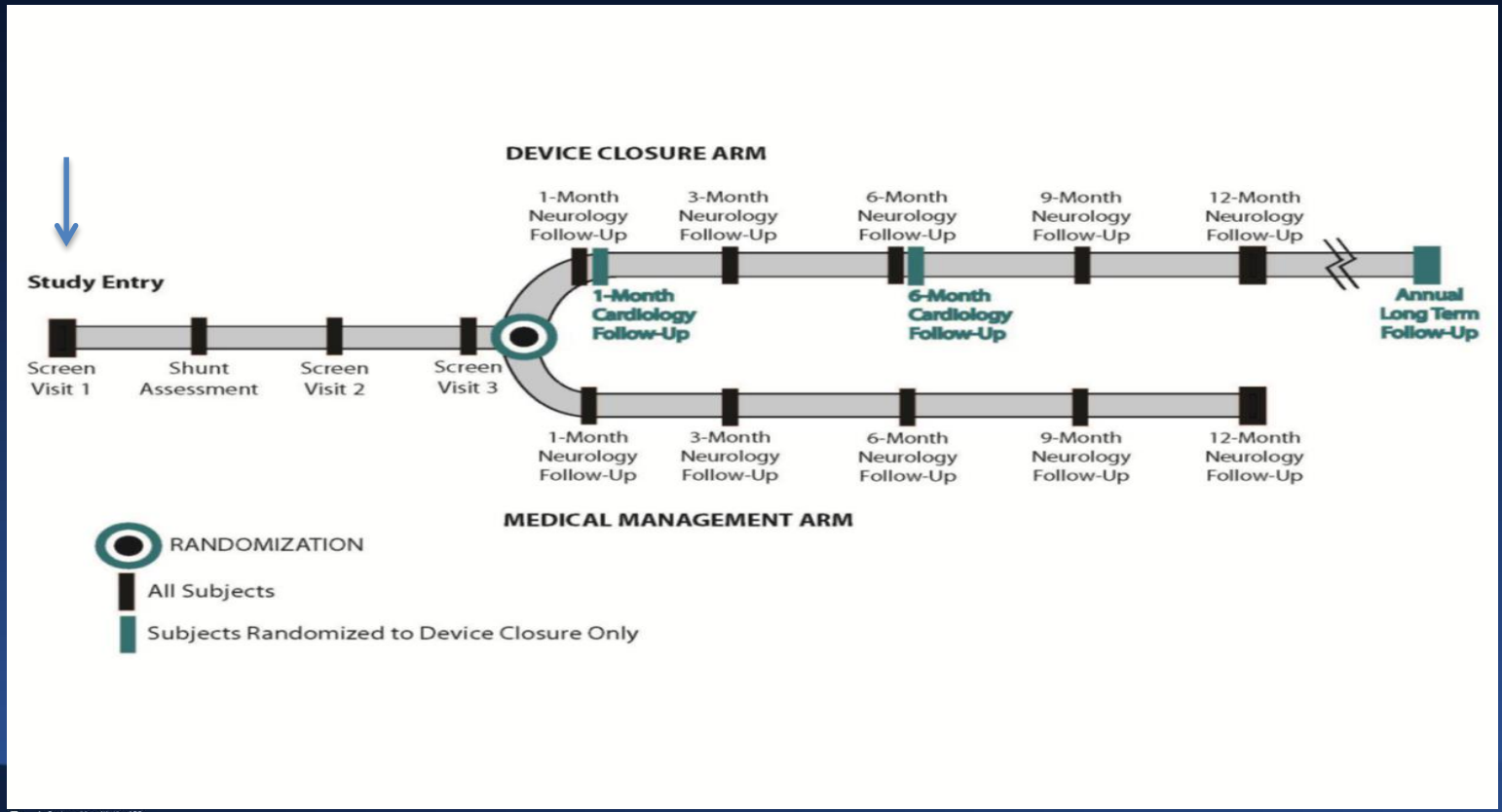
Study endpoints

- Secondary Endpoints
  - Change in responder rate
    - (≥50% reduction in number of migraine days)
  - Change in the number of monthly migraine attacks
  - Change in use of acute migraine medications
  - Change in MIDAS score
  - Quality of life measures
  - Beck Depression Inventory Score
  - Effects of antiplatelet medication during study
  - Completeness of PFO closure at 12 months

Screening Visit 1

Neurologist

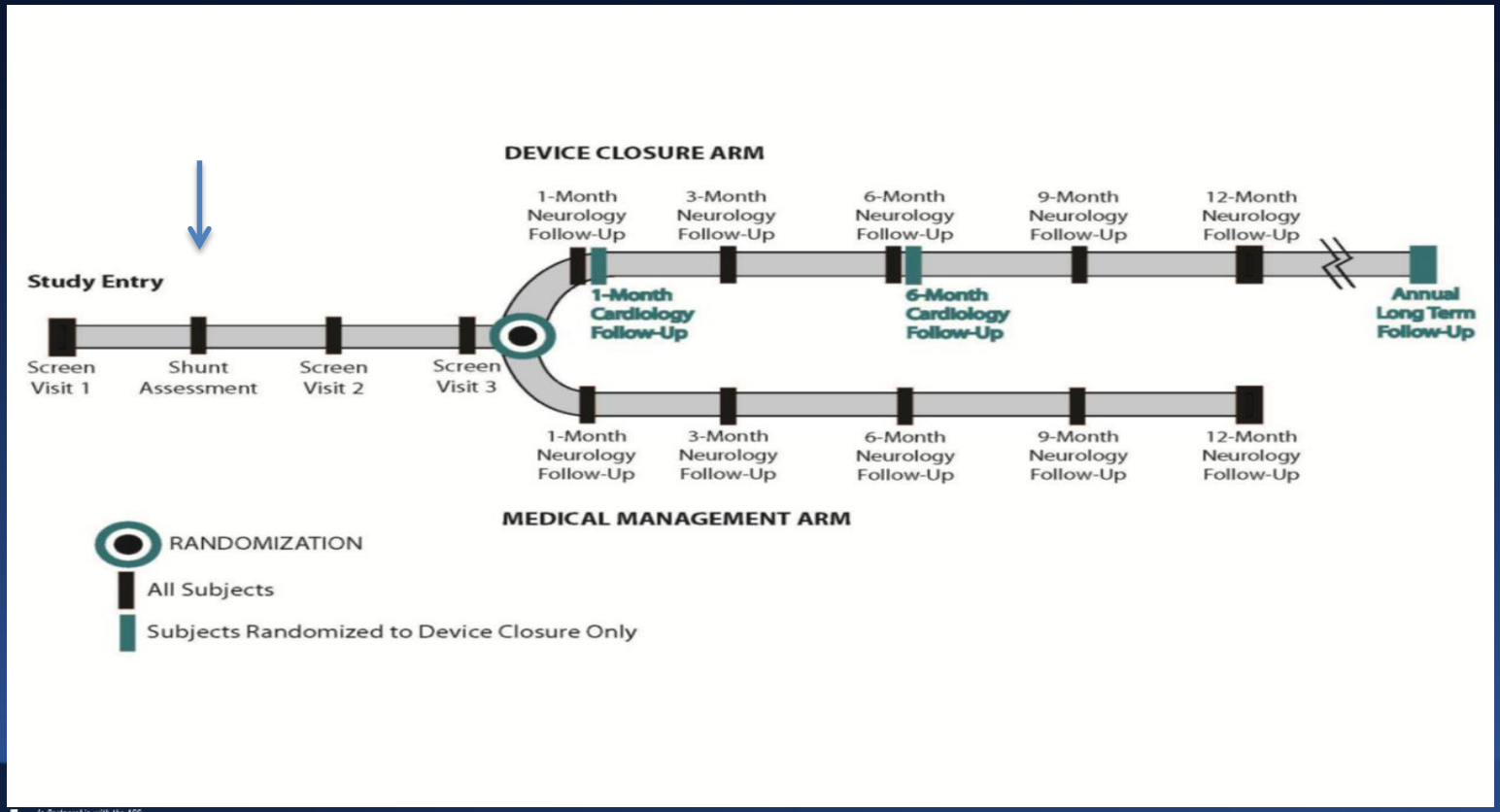
- Consent
- Inclusion/exclusion criteria
- Compliance with possible PFO closure
- Compliance with headache diaries



Shunt Assessment

Cardiologist

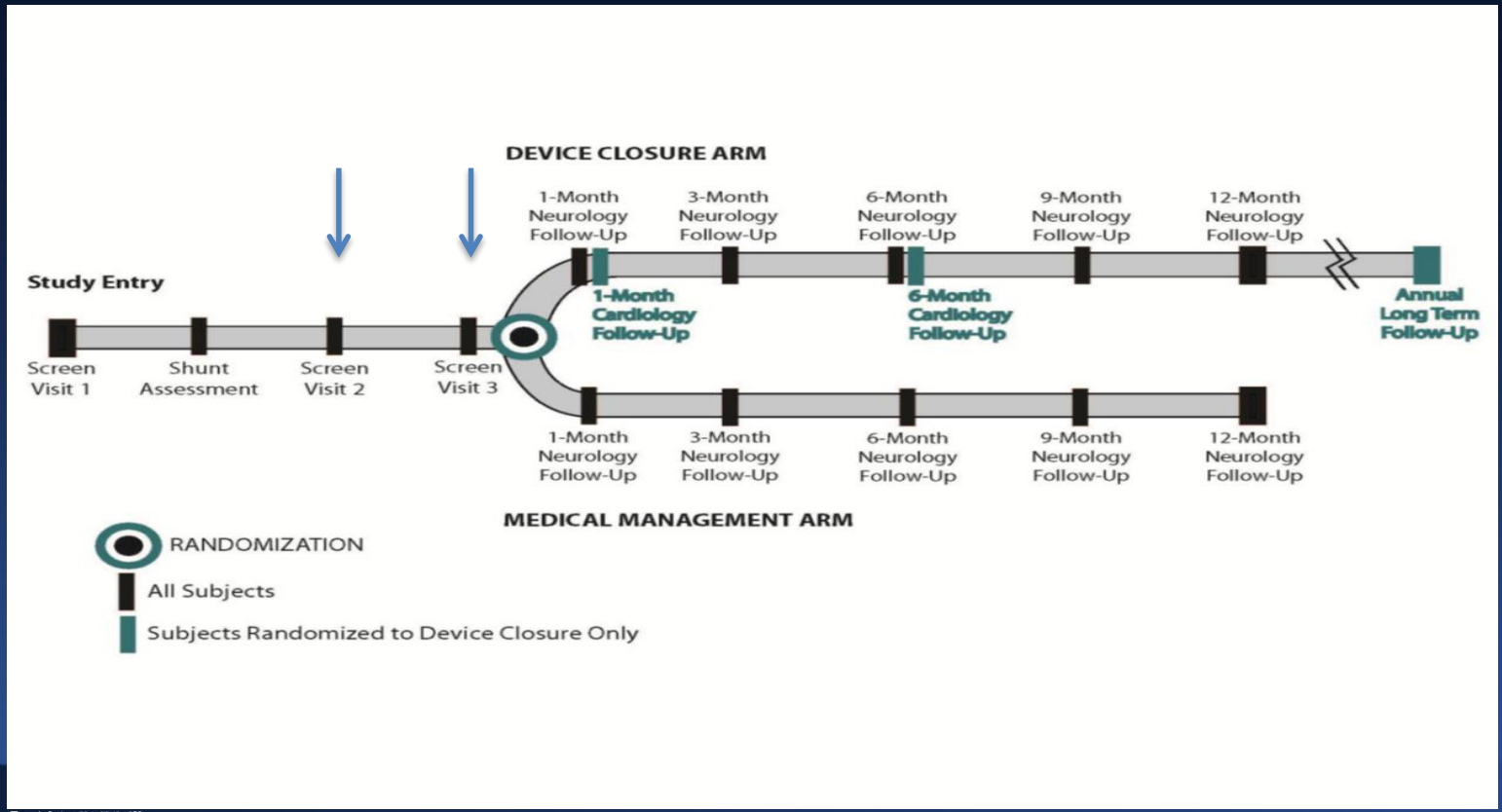
- TTE or TCD to demonstrate presence/absence of R to L shunt
- TEE to confirm presence/absence of PFO



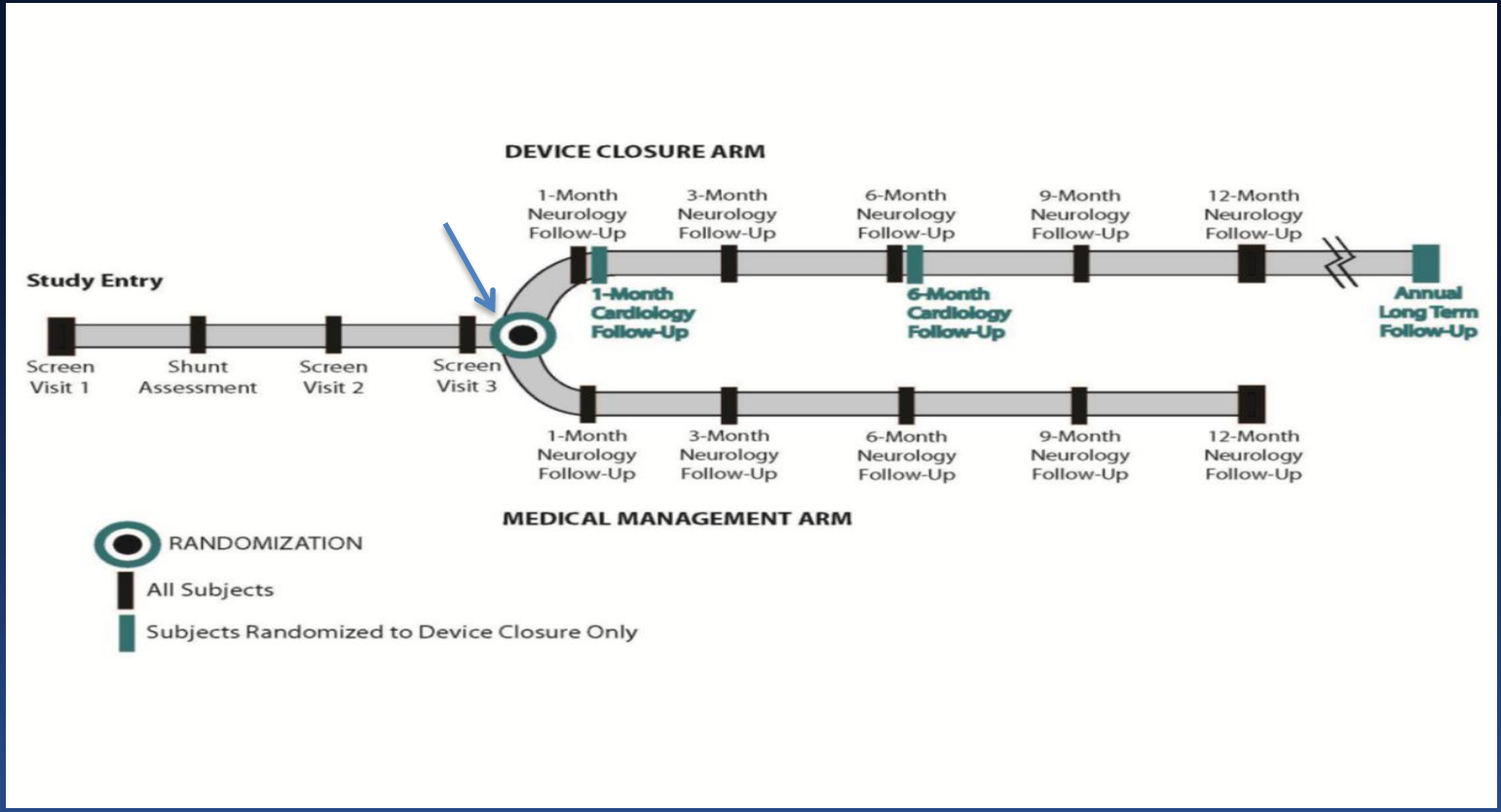
Screening Visit 2 and 3

Neurologist

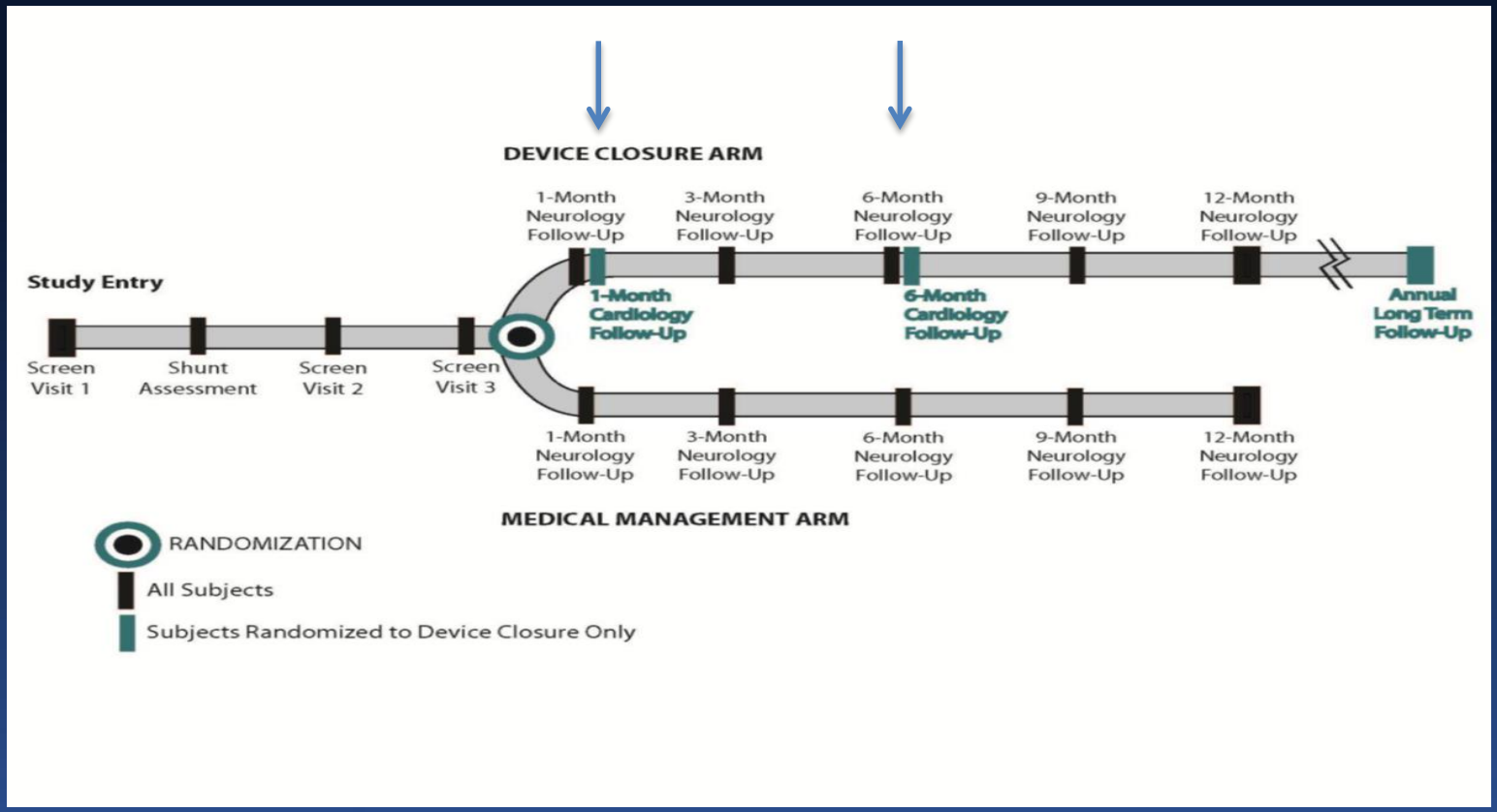
- Headache diary review
- Medication review
- MIDAS
- Depression inventory
- QOL



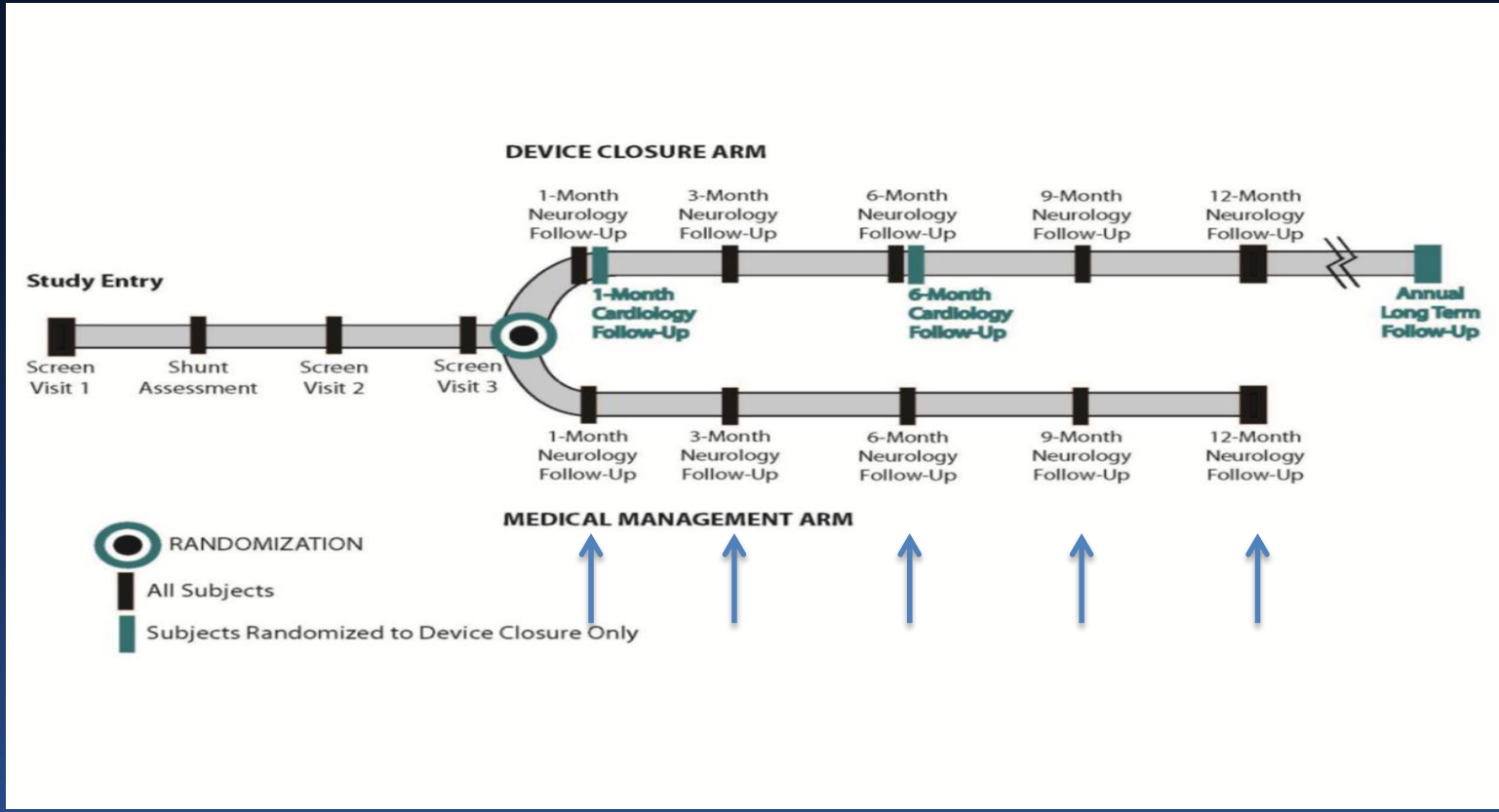
Randomization



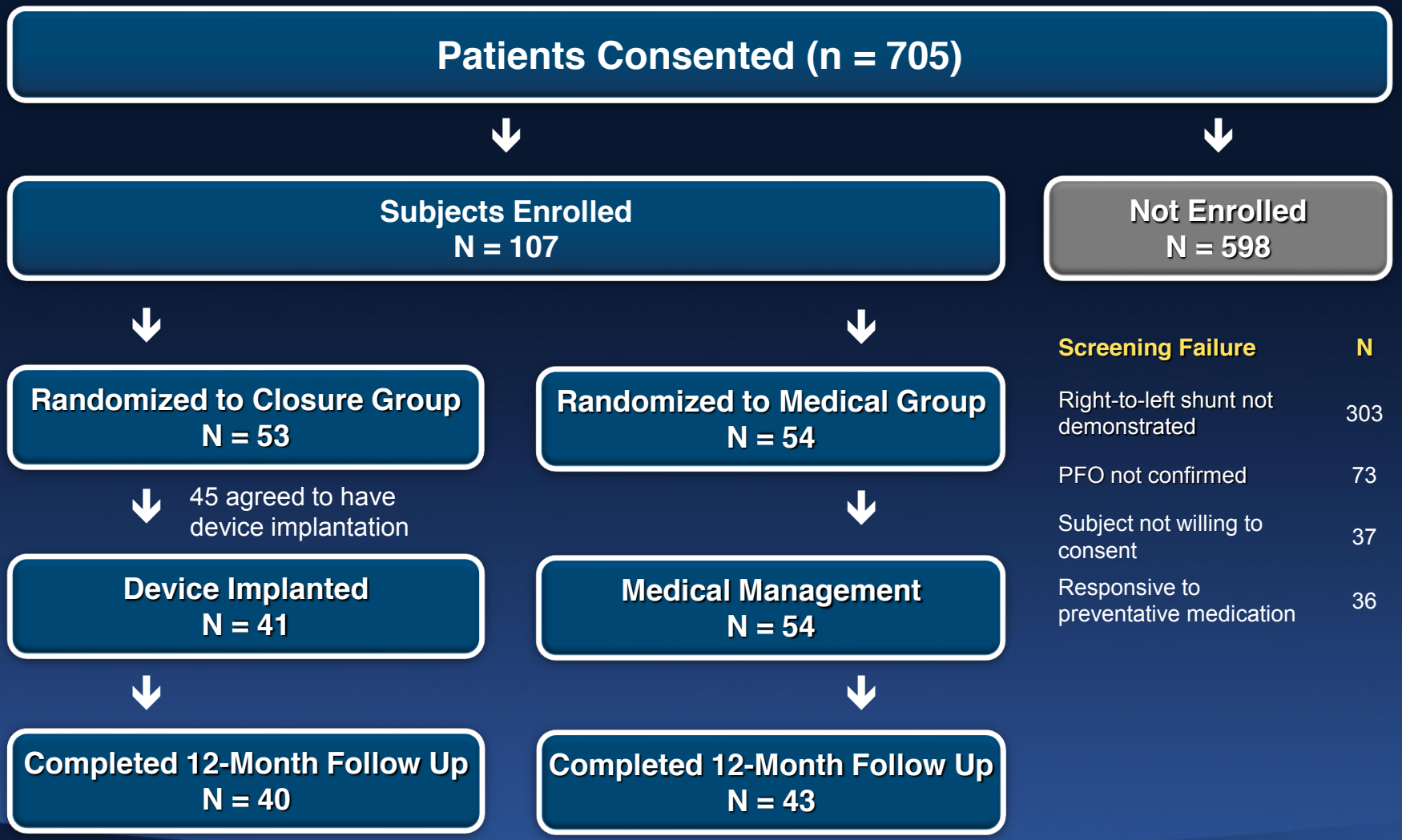
Device Arm (Closure)



Both Groups


DEVICE CLOSURE ARM
1-Month Neurology Follow-Up
3-Month Neurology Follow-Up
6-Month Neurology Follow-Up
9-Month Neurology Follow-Up
12-Month Neurology Follow-Up
Study Entry
1-Month Cardiology Follow-Up
6-Month Cardiology Follow-Up
Annual Long Term Follow-Up
Screen Visit 1
Shunt Assessment
Screen Visit 2
Screen Visit 3
1-Month Neurology Follow-Up
3-Month Neurology Follow-Up
6-Month Neurology Follow-Up
9-Month Neurology Follow-Up
12-Month Neurology Follow-Up
MEDICAL MANAGEMENT ARM
RANDOMIZATION
All Subjects
Subjects Randomized to Device Closure Only

Patient Flow



Screening Failure	N
Right-to-left shunt not demonstrated	303
PFO not confirmed	73
Subject not willing to consent	37
Responsive to preventative medication	36

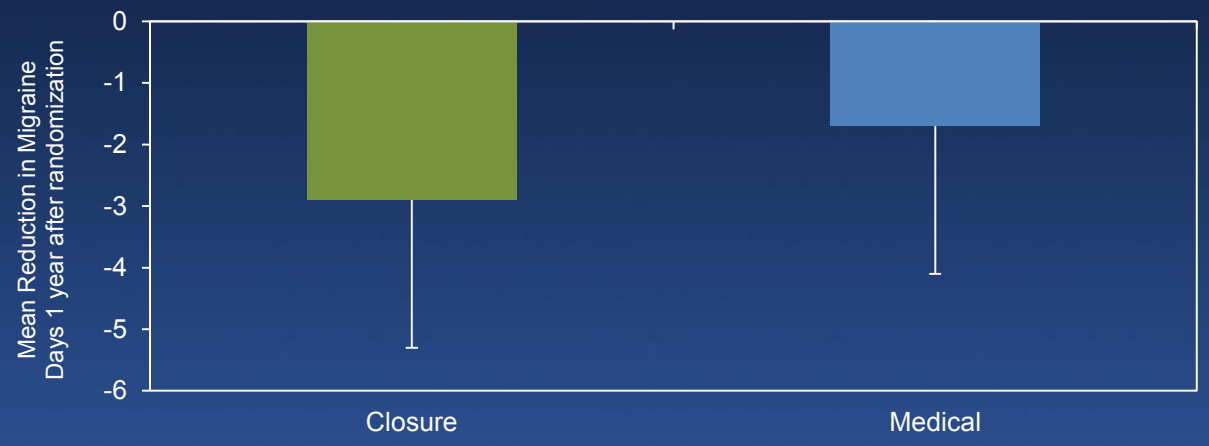
Baseline Characteristics

	Closure N=53, n (%)	Medical N=54, n (%)
Age (years)	44 ± 11	43 ± 11
Female	45 (85%)	45 (83%)
Mood disorder	1 (2%)	5 (10%)
Hypertension	4 (8%)	3 (6%)
Arrhythmia	1 (2%)	1 (2%)
Diabetes	0 (0%)	1 (2%)
Transient ischemic attack (TIA)	1 (2%)	0 (0%)
Unresponsive to two medications	52 (98%)	53 (98%)
IHS classification - migraine with aura	53 (100%)	53 (98%)
Majority of migraines with aura	28 (55%)	30 (58%)

RESULTS

Primary Endpoint
Reduction in Migraine Days

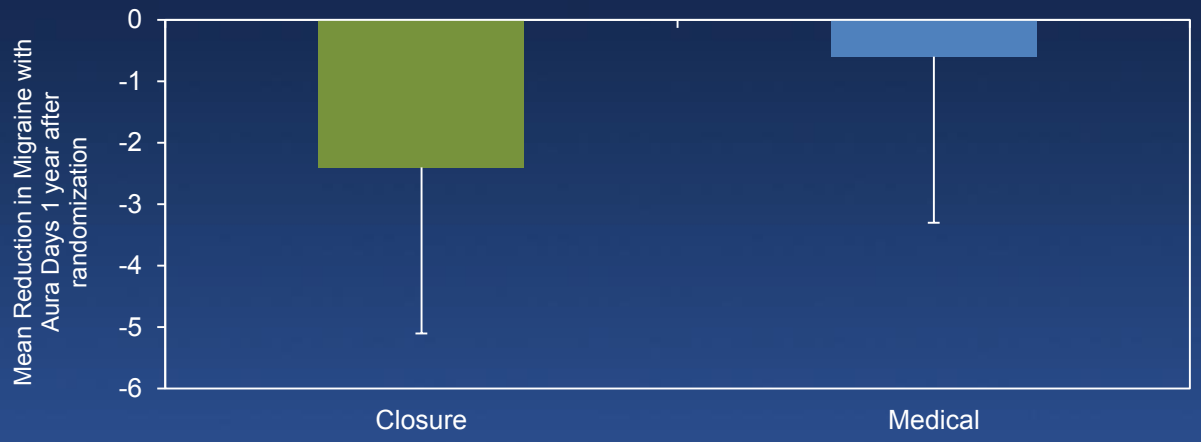
	N	Mean Days at Baseline	Mean Days at Months 10-12	Mean Reduction	Std Deviation (Min, Max)	P-Value
Closure	40	8.0	5.1	-2.9	4.7 (-11.7, 9.0)	0.17
Medical	41	8.3	6.5	-1.7	2.4 (-6.3, 3.5)	



Secondary Endpoint

Reduction in Migraine with Aura Days

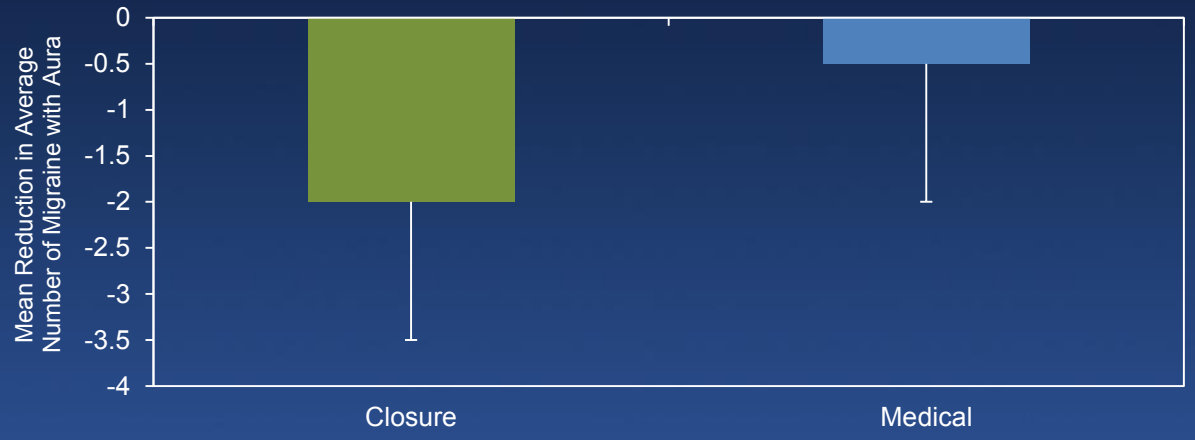
	N	Mean at Baseline	Mean at Months 10-12	Mean Reduction	Std Deviation (Min, Max)	P-Value
Closure	40	4.1	1.7	-2.4	3.6 (-9.7, 7.3)	0.01
Medical	40	4.0	3.4	-0.6	2.7 (-9.1, 5.5)	



Secondary Endpoint

Reduction in Migraine with Aura Attacks

	N	Mean at Baseline	Mean at Months 10-12	Mean Reduction	Std Deviation (Min, Max)	P-Value
Closure	40	3.0	1.0	-2.0	2.0 (-7.16, 1.00)	< 0.01
Medical	40	2.8	2.3	-0.5	1.5 (-3.3, 3.4)	



Secondary Endpoint

Effect of aspirin and clopidogrel on headache days

	Mean at Baseline	Mean at Months 1-3	Mean at Months 4-6	Mean at Months 10-12
Antiplatelet treatment	None	Aspirin Clopidogrel	Aspirin	None
Closure	9.2	6.7	5.8	6.3
Medical	9.4	7.7	8.2	7.5

Secondary Endpoint
Responder Rate

	Responder	P-Value
Closure	15 (37.5%)	0.02
Medical	6 (14.6%)	

Secondary Endpoint
Freedom from Migraine

	Freedom from Migraine	Freedom from Migraine with Aura	P-Value
Closure	4 (10%)	16 (40%)	<0.05
Medical	0 (0%)	4 (10%)	

Adverse Events

- Closure group:
  - Major vascular complication with bleeding (n=1)
  - Atrial fibrillation requiring DC cardioversion (n=1)
- Medical group:
  - none

Limitations

- High screen-to-recruitment ratio
- Long recruitment phase
- Patients not blinded to allocation
- High dropout post-randomization
- Failure to undergo randomized treatment
- Early termination

CONCLUSIONS

- Interventional studies in migraine/aura patients are difficult to do
- 40% of patients in PRIMA had a R to L shunt
- PFO closure is safe in these patients
- PFO closure did not reduce total migraine days significantly compared to medical therapy

CONCLUSIONS

- Migraine with aura days significantly reduced
- 40% of device closure patients had headache burden reduced by ≥50%
- 10% of closure patients became migraine free
- 40% of closure patients became free of migraine with aura

CONCLUSIONS

- There remains an intriguing relationship between PFO, PFO closure, migraine and migraine with aura
- This relationship is unequivocal
- Real and tangible benefit accrues to some migraine patients after PFO closure
- Results of PREMIUM are awaited with interest