AngelMed Guardian System

P150009

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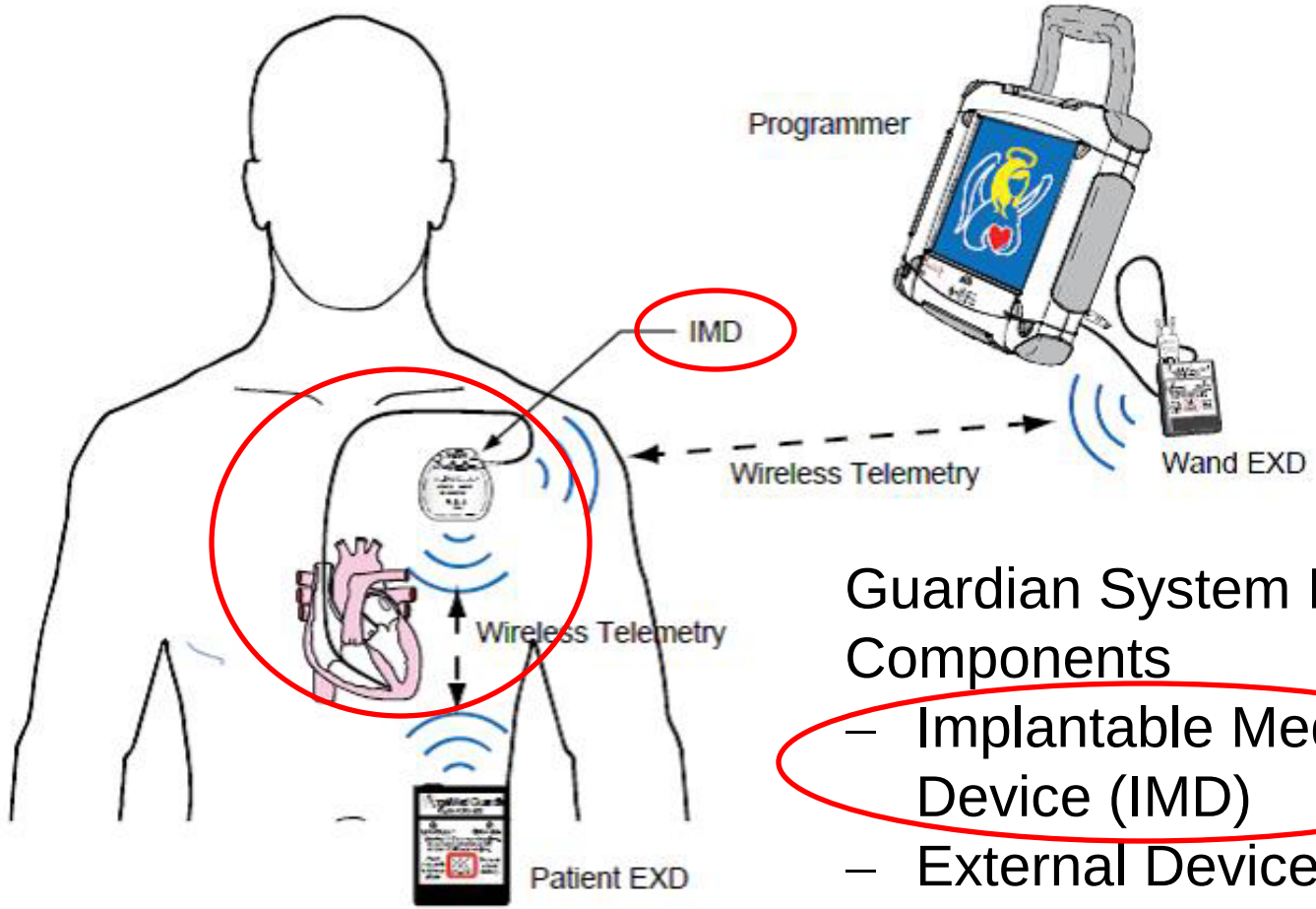
U.S. Public Health Service
Division of Cardiovascular Devices
Office of Device Evaluation
Food and Drug Administration

March 16, 2016

FDA Presentations

- Introduction – LTJG Stephen Browning
- Statistical Presentation – Dr. Zhiheng Xu, PhD
- Clinical Presentation – Dr. Kimberly Selzman, MD
- Conclusion – LTJG Stephen Browning

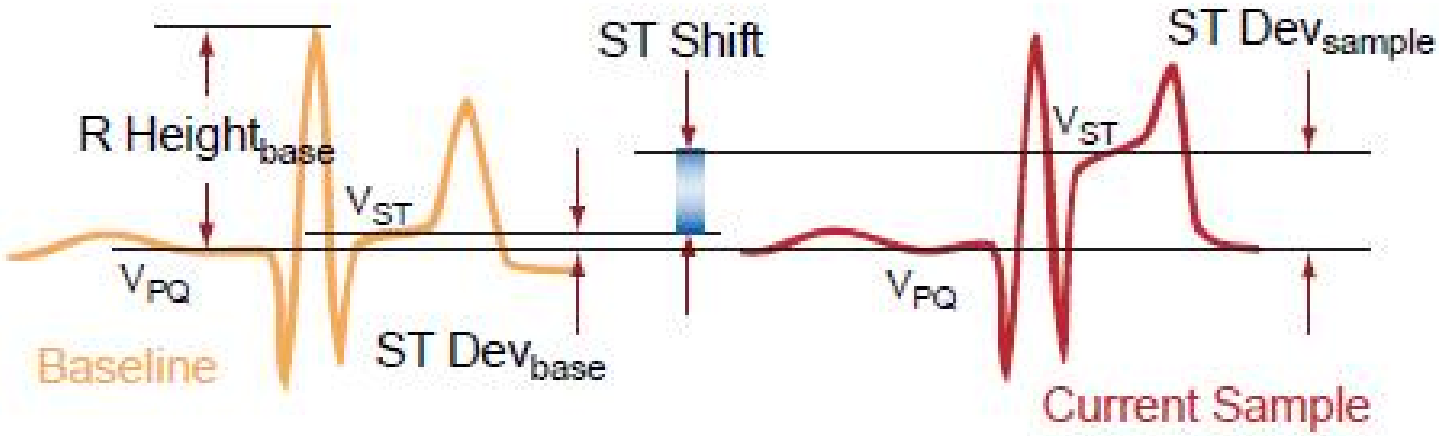
Physical Device Description



Guardian System Device Components

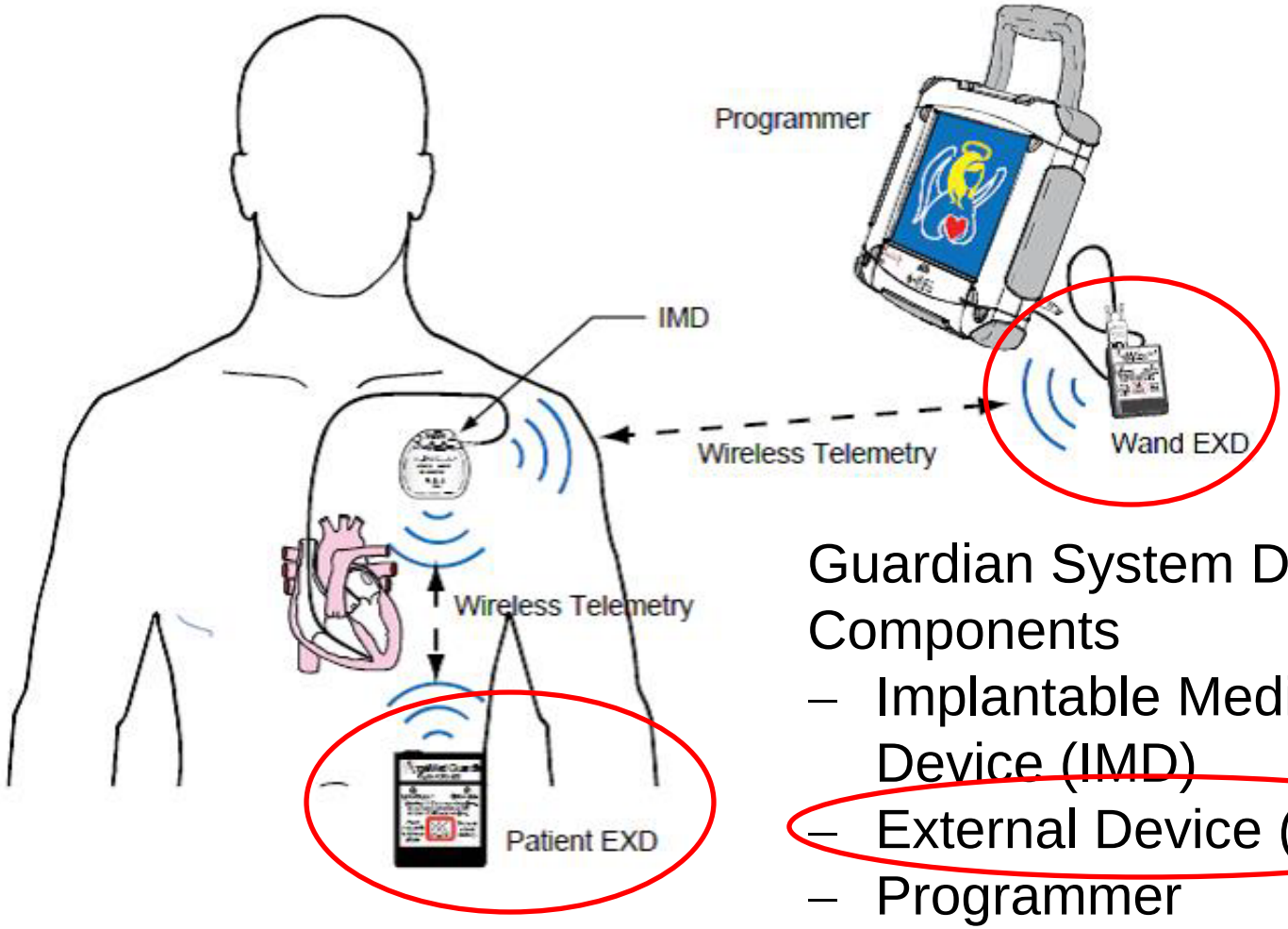
- Implantable Medical Device (IMD)
- External Device (EXD)
- Programmer

ST-Shift Measurement



- Collect electrograms (tip-can) every 90 seconds (30 seconds if previous electrogram was abnormal)
- Compare ST Deviation (ST and PQ segment difference) to a 24 baseline
- Six “shifted” beats → shifted electrogram
- Three consecutive shifted electrograms → possible ischemia and alarm
- Heart rate tracking (w/no alarm at high heart rates)

Physical Device Description



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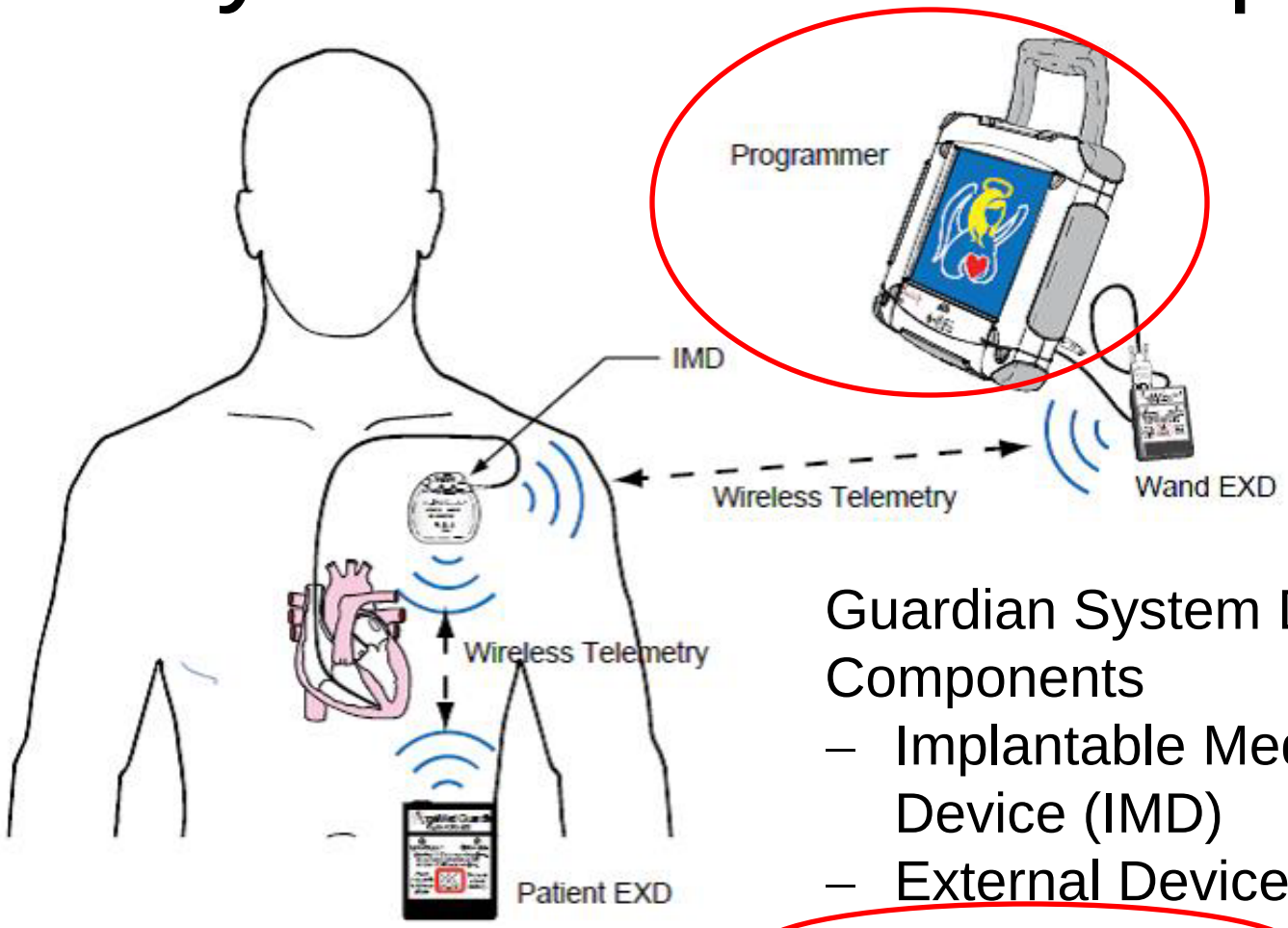

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- Implantable Medical Device (IMD)
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Proposed Indications for Use

The Guardian System is indicated to alert patients with prior acute coronary syndrome events to ST segment changes indicating acute coronary occlusion.

Guardian System alerts reduce the overall time-to-door from a detected acute coronary occlusion until presentation at a medical facility independent of patient-recognized symptoms.

Non-Clinical Testing

- Biocompatibility
- Sterility & Packaging
- Electrical Safety and EMC
- Human Factors risk assessment
- Software Validation and Documentation
- Mechanical and Electrical Device Integrity
- *In vivo* animal studies

Non-Clinical Testing is complete.

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Statistical Presentation

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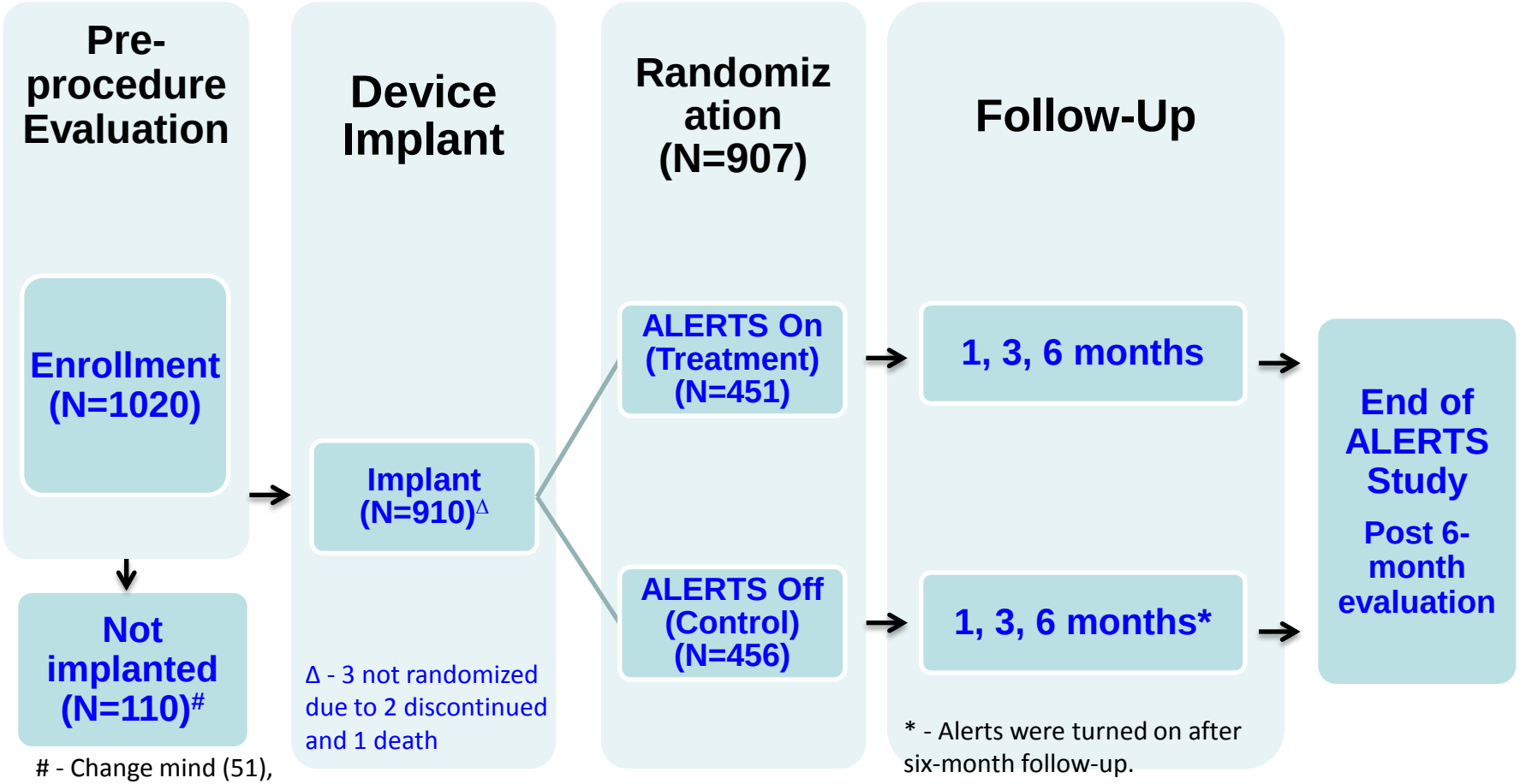
Division of Biostatistics
Office of Surveillance and Biometrics
FDA/CDRH

Outline

- ALERTS Clinical Trial Design
- Interim Analyses
- Primary Safety Endpoint
- Primary Effectiveness Composite Endpoint
  - Time-to-door >2 hours component
  - Death component
  - New Q-wave MI component
- Positive Predictive Value (PPV)
- Conclusion

ALERTS Clinical Trial



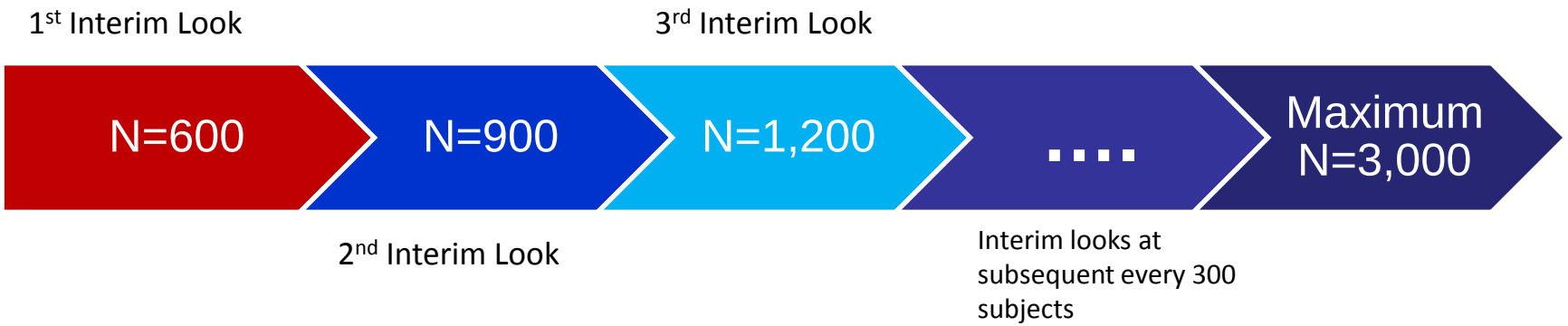
- Change mind (51), developed exclusion (35); unable to implant (8), other (15), death (1)

Study Population

- The ALERTS Clinical Study subject profile involved the following requirements:
  - Advanced Multi-vessel Coronary Disease
  - An index ACS event (MI, Unstable Angina or CABG) within six months of subject enrollment
  - Additional risk factors/co-morbidities (diabetes, TIMI risk score >3, or renal insufficiency)

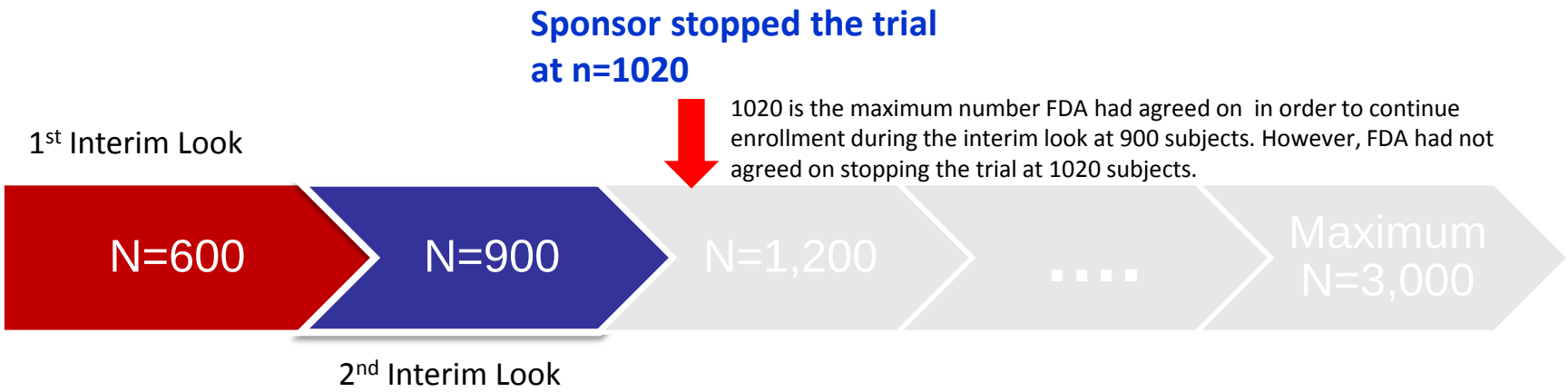
Prospective Bayesian Adaptive Design

Planned Interim Analysis



- Stop Enrollment if
  - *Pn > Sn (success bound)* or
  - *Pn < Fn (futility bound)*
- Otherwise, enroll another 300 subjects.
- *Pn*= Pr[$R_t < R_c$ | interim data]

Performed Interim Analyses



- *Assumption issue*
  - *New Q-waves come and go (contradictory to the stable Q wave assumption)*
- *Data quality issues*
  - *Incomplete or inaccurate data entry*
  - *Reporting delay*
- *Sponsor's decision: stop the trial at n=1020 even though interim analysis at N=600 and 900 have indicated that enrollment should continue*

Study Conduct Issue

- Sponsor's decision of enrollment termination is viewed by FDA as a significant **protocol violation**
  - Loss of power (the ability to claim the truly treatment success)
  - The operating characteristic of the trial is not the same as planned
  - The validity of the trial may be undermined from a compliance, data quality and trial integrity perspective
  - The Bayesian analyses on the primary and secondary endpoints may be compromised.
  - *Although FDA agreed to expand enrollment to 1020 subjects in order to cover the planned interim look at N=900, FDA did not agree to stopping the trial early. The interim looks showed that the trial should continue.*

Panel Question:

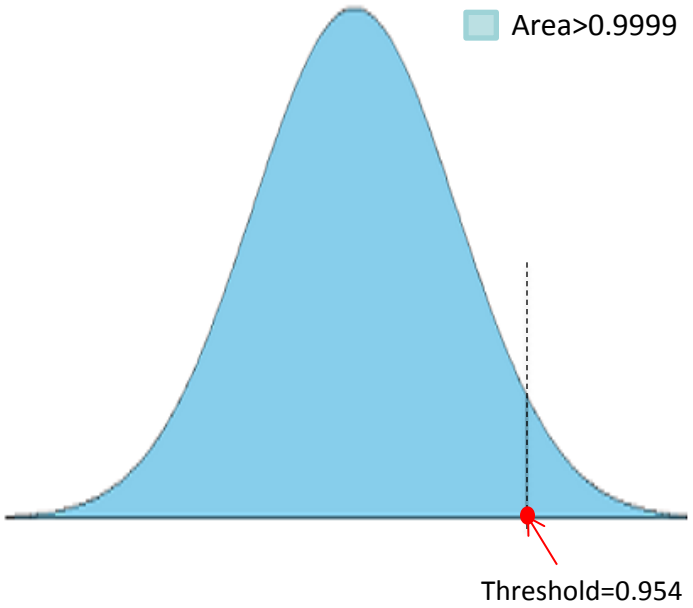
The panel will be asked to comment on study conduct issue of early termination of ALERTS clinical trial.

Primary Safety Endpoint

- Goal: >90% implanted subjects free of system-related complications at six months
  - System-related complication refers to any adverse event related to a successfully implanted system that requires a system revision (invasive intervention) to resolve.
- Success Criteria: $Pr(p>0.9 | data) > 0.954$
  - A high posterior probability in a Bayesian framework is analogous to a small p-value (e.g. $p<0.05$) in a Frequentist framework.
  - 0.954 was determined by trial and error in the simulation to achieve a type I error rate that is at most 0.05.

Primary Safety Endpoint Results

All Subjects with Successful Implant (N = 910)[1]	Primary Safety Endpoint
Event-free subjects	866
Subjects with events[2]	30
% Event Free	96.7% (866/896)
Posterior Probability *Pr(p>0.90|data)*[3]	>0.9999



1: 14 unobserved (no event but insufficient follow-up)
2: 30 subjects had 31 system-related complications
3: Significance threshold: **0.954**

Conclusion: Primary safety endpoint was met based on pre-specified protocol.

Caution should be given when interpreting safety data as study conduct issue of trial early termination.

Primary Effectiveness Endpoint

- Composite Endpoint
  - Cardiac or unexplained death, or
  - New Q-wave MIs, or
  - Time-to-door > 2 hours after detected thrombotic event
- Event Rate: R_t for treatment and R_c for control
  - Proportion of subjects who experience the event in 6 months
  - Patient-level analysis per protocol
- Success Criteria: $\pi = \Pr(R_t < R_c | data) > 0.983$

1. A high posterior probability in a Bayesian framework is analogous to a small p-value (e.g. $p<0.05$) in a Frequentist framework.
2. 0.983 was determined by trial and error in the simulation to achieve the overall type I error of the design not exceed 0.025.

Bayesian Model

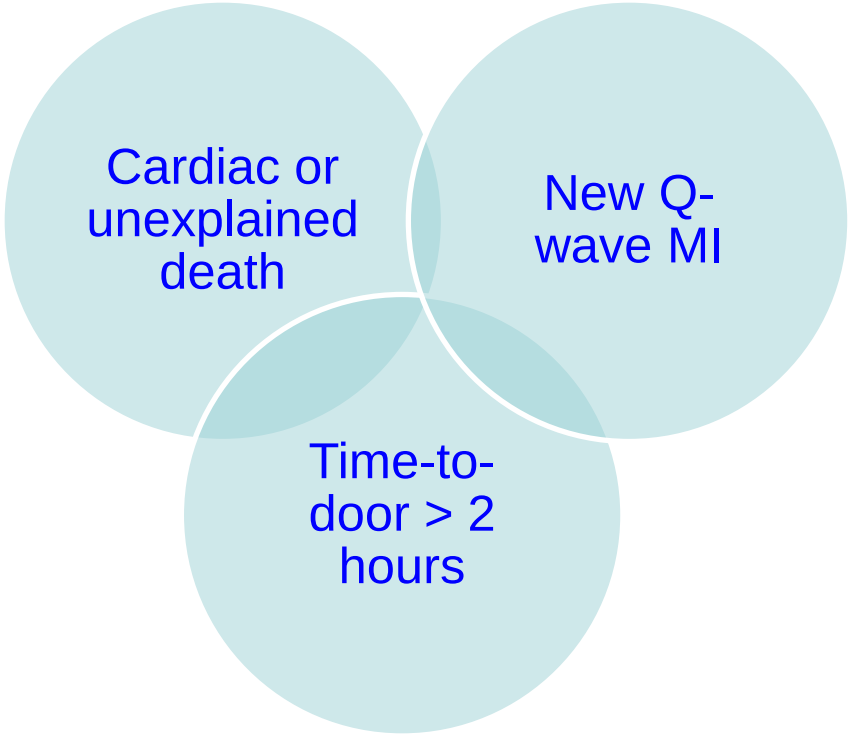
R_t ~ *Beta(1,1),*
R_c ~ *Beta(1,1)*

Posteriors
R_t ~ *Beta(1+* E_t*,1+* NE_t*),*
R_c ~ *Beta(1+* E_c*,1+* NE_c*)*

Posterior Probability of Event Reduction
$\pi = \Pr(R_t < R_c | data)$

R_t *:* treatment event rate
R_c *:* control event rate

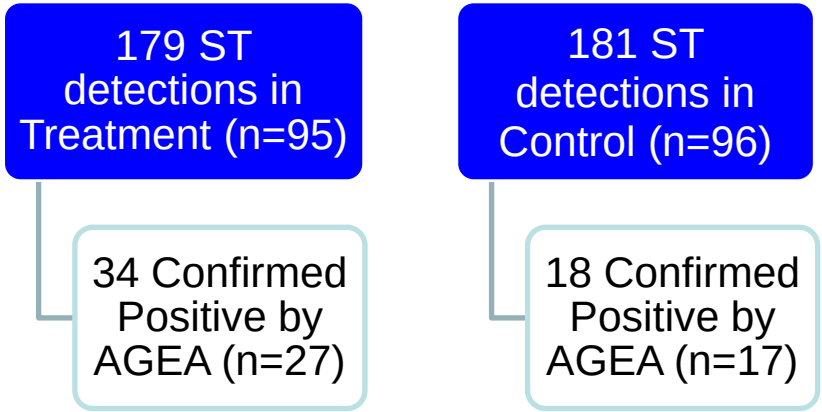
Primary Effectiveness Endpoint



- Composite endpoint: patients with any one of three components
- Will discuss each component individually

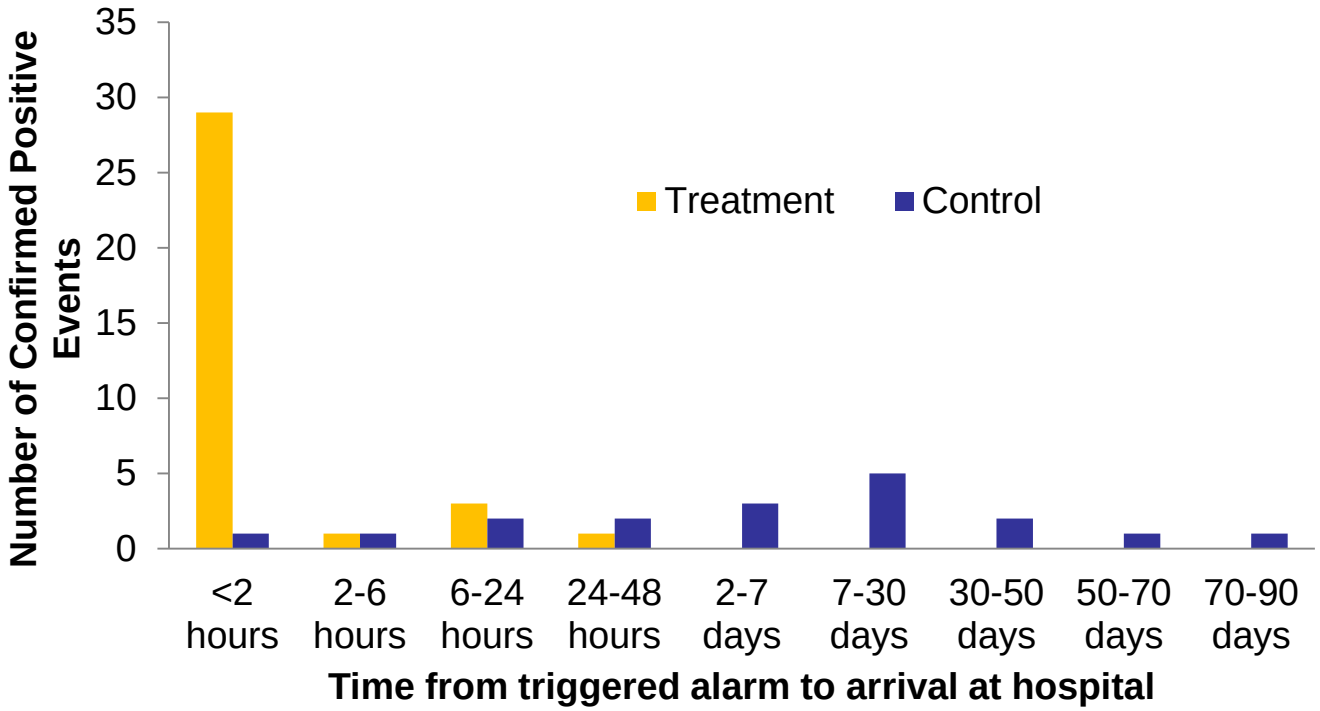
Time-to-door > 2 Hours Component

- Time-to-door: Time between ST shift detection and presentation for confirmation
- Confirmed positive event for ischemia by AGEA (either ST elevation on ECG, positive biomarkers, a positive stress test, or a positive angiogram)



n - number of subjects.
AGEA - ALERTS Group for Endpoint Adjudication (AGEA) Committee

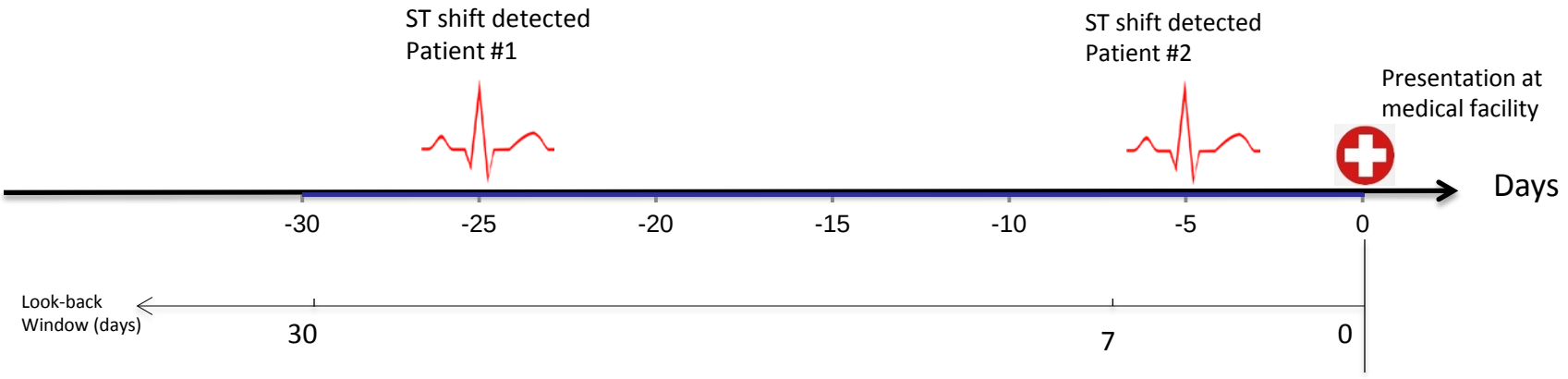
Time-to-door > 2 Hours Component



Question: What is the maximum allowable time for the time-to-door >2 hr events in the primary effectiveness endpoint?

Look-back Window

- Maximum allowable time between ST shift detection and the “late arrival” for a confirmed occlusive event
  - ST shift detection #1: time-to-door=25 days
  - ST shift detection #2: time-to-door=5 days
  - 7-day look-back window: one time-to-door>2hrs event (ST shift detection #2)
  - 30-day look-back window: two time-to-door>2hrs events (ST shift detection #1 and #2)



Time-to-door > 2 Hours

Look-back Window	Control (N=456)* n (%)	Treatment (N=451)* n (%)
7-Day	8 (1.8%)	4 (0.9%)
10-Day	9 (2.0%)	4 (0.9%)
30-Day	13 (2.9%)	4 (0.9%)
50-Day	15 (3.4%)	4 (0.9%)
70-Day	16 (3.6%)	4 (0.9%)
90-Day	17 (3.8%)	4 (0.9%)

* - Number of missing subjects in control (n=10) and treatment (n=12) for this component.

Statistical Analysis Issue

- Multiple look-back windows
  - No multiplicity adjustment was planned or conducted
    - The more hypothesis testing in a data set, the higher likelihood of getting significant result(s).
  - Neglecting multiplicity could lead to false declaration of significance and therefore spurious inference

Panel Question:

The panel will be asked to comment on statistical analysis issue of multiple look-back windows.

Death and New Q-wave MI Components

	Control (N=456) n (%)	Treatment (N=451) n (%)
Cardiac or Unexplained Death$^{\Delta}$	1 (0.2%)	3* (0.7%)
New Q-Wave MI$^{\#}$	14** (3.3%)	10 (2.4%)

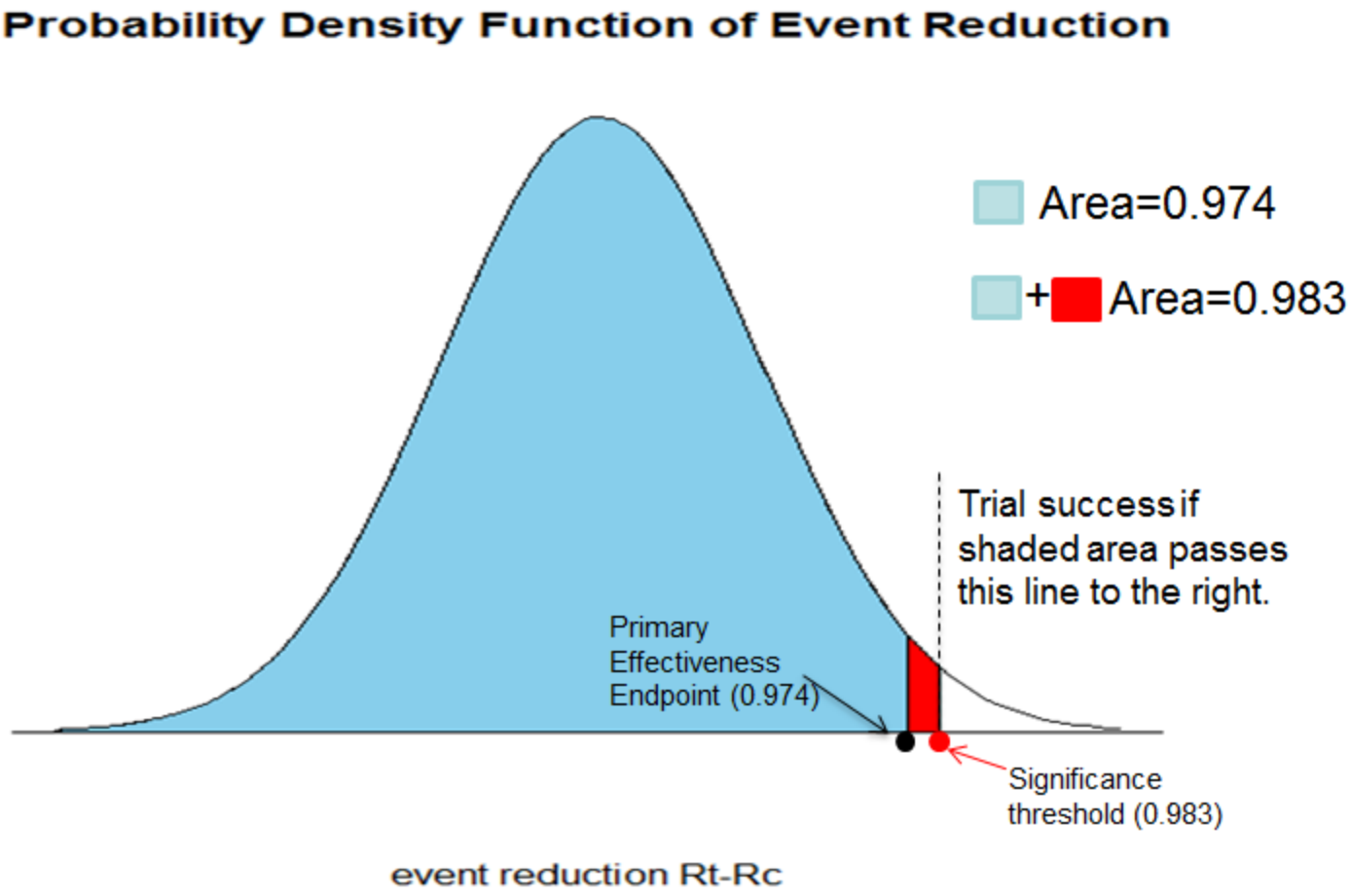
* - One treatment subject (042-005) had both death and time-to-door>2 hrs events.
** - Three control subjects (017-011, 062-019, 067-001) had both new Q wave MI and time-to-door >2 hrs events.
Δ - Number of missing subjects in control (n=9) and treatment (n=10) for death component.
- Number of missing subjects in control (n=29) and treatment (n=31) for new Q-wave component.

Primary Effectiveness Endpoint

Look-back Window	Control (N=456)# n (%)	Treatment (N=451)# n (%)	95% BCI (ON-OFF)	Posterior Prob. $\pi=P_r(R_{ON} < R_{OFF} \mid data)$*	Trial Success ($\pi>0.983$)
7-Day	21 (4.9%)	16 (3.8%)	(-3.93%, 1.67%)	0.7856	No
10-Day	22 (5.1%)	16 (3.8%)	(-4.22%, 1.48%)	0.8279	No
30-Day	25 (5.8%)	16 (3.8%)	(-5.02%, 0.84%)	0.9177	No
50-Day	27 (6.3%)	16 (3.8%)	(-5.55%, 0.43%)	0.9527	No
70-Day	28 (6.5%)	16 (3.8%)	(-5.82%, 0.24%)	0.9644	No
90-Day	29 (6.8%)	16 (3.8%)	(-6.06%, 0.03%)	0.9740	No

* - The significance threshold for the posterior probabilities of event reduction is **0.983**. The analysis is for completers only.
# - Number of missing subjects in control (n=28) and treatment (n=28) for the composite endpoint.

Conclusion: Primary effectiveness endpoint was not met.



R_t: treatment event rate
R_c: control event rate

New Q-wave MI: Single Baseline

- Single baseline: randomization ECG
  - pre-specified in SAP

Baseline at Randomization	1 Month Visit	3 Month Visit	6 Month Visit	New Q-wave MI (single)
–	X	X	X	Yes
–	–	X	X	Yes
–	–	–	X	Yes

X : present. – : absent

"Dual-baseline" Post-hoc Analysis

- Reliability issue at ECG baseline at randomization data
- Dual baseline: pre-implant ECG and randomization ECG
  - Proposed after the sponsor was unblinded but core lab who read all ECG was still blinded.

Baseline Pre-Implant	Baseline at Randomization	1 Month Visit	3 Month Visit	6 Month Visit	New Q-wave MI (single)	New Q-wave MI (dual)
–	–	X	X	X	Yes	Yes
–	–	–	X	X	Yes	Yes
–	–	–	–	X	Yes	Yes
X	**-**	**X**	**X**	**X**	**Yes**	**No**

X: present. – : absent

New Q Wave MI

Baseline Used	Control (N=456)*	Treatment (N=451)*
	n (%)	n (%)
Single – At Randomization	14 (3.3%)	10 (2.4%)
Dual – Pre-Implant and At Randomization	13 (3.0%)	7 (1.7%)

* - Number of missing subjects in control (n=29) and treatment (31) for new Q-wave MI.

"Dual-baseline" Post-hoc Analysis

Look-back Window	Control (N=456)# n (%)	Treatment (N=451)# n (%)	95% BCI (ON-OFF)	Posterior Prob. $\pi=P_r(R_{ON} < R_{OFF} \mid data)$*	Trial Success* ($\pi>0.983$)
7-Day	20 (4.7%)	13 (3.1%)	(-4.28%, 1.02%)	0.8833	No
10-Day	21 (4.9%)	13 (3.1%)	(-4.56%, 0.84%)	0.9110	No
30-Day	24 (5.6%)	13 (3.1%)	(-5.36%, 0.23%)	0.9637	No
50-Day	26 (6.1%)	13 (3.1%)	(-5.89%, -0.18%)	0.9812	No
70-Day	27 (6.3%)	13 (3.1%)	(-6.16%, -0.38%)	0.9870	Yes
90-Day	28 (6.5%)	13 (3.1%)	(-6.43%, -0.60%)	0.9908	Yes

* - The significance threshold for the posterior probabilities of event reduction is **0.983**. This analysis is for completers only.

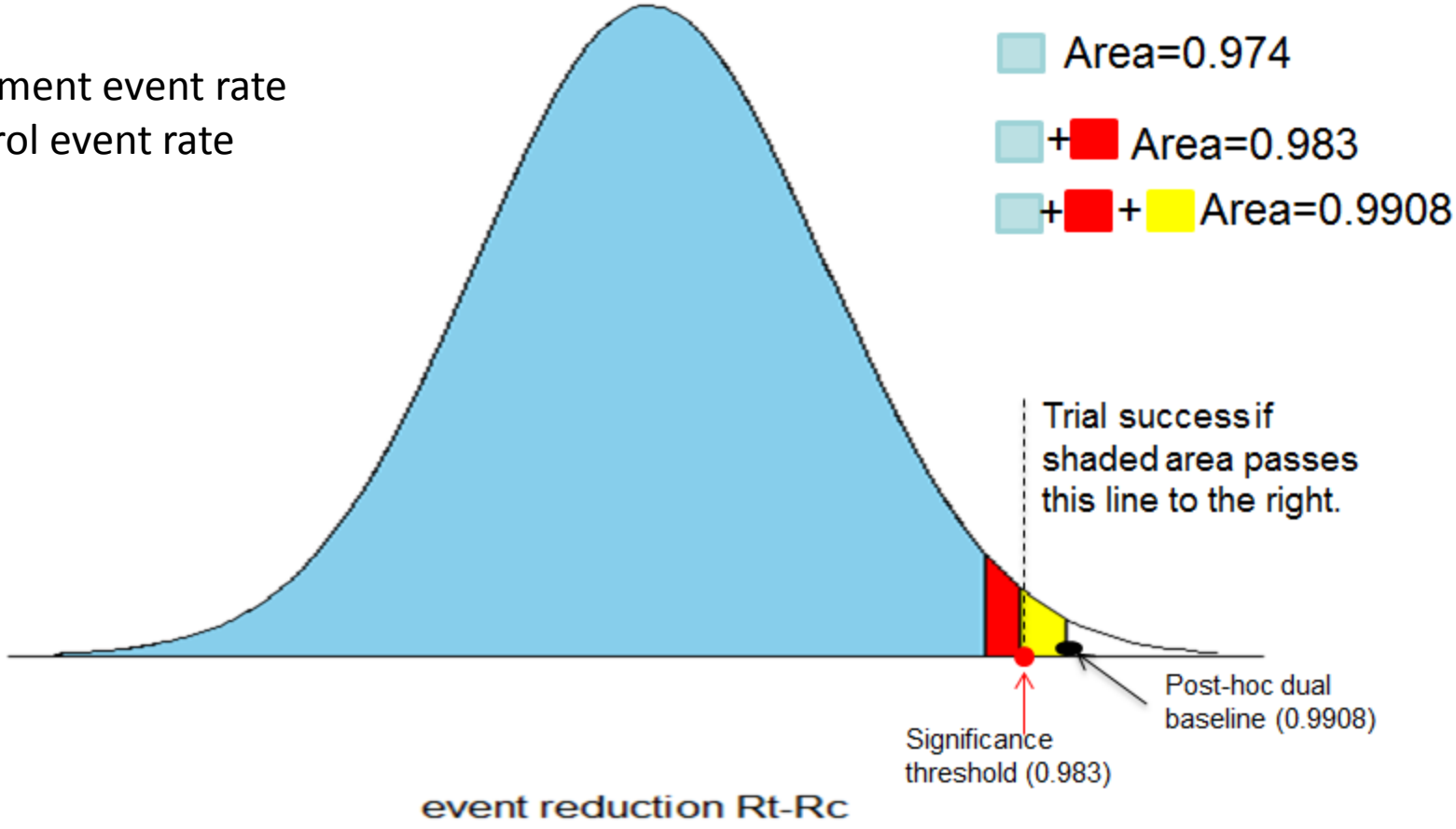
- Number of missing subjects in control (n=28) and treatment (n=28) for the composite endpoint.

Conclusion: "Dual-baseline" post-hoc analysis shows the primary effectiveness endpoint was met* with look-back windows of at least 70 days.

Note: Post-hoc analysis results should be interpreted with caution due to the nature of post-hoc.

Probability Density Function of Event Reduction

R_t: treatment event rate
R_c: control event rate



Note: post-hoc analysis results should be interpreted with caution due to the nature of post-hoc.

Post-hoc Analysis Issue

- "Dual baseline" post-hoc analysis
  - "Dual baseline" was proposed after data was unblinded and the risk of bias is high.
  - Event reduction could be artificially increased due to the use of "dual baseline".

Baseline	Composite Endpoint		
	R_c	R_t	$R_t - R_c$
Single	3.8%	0.9%	-2.9%
Dual	6.5%	3.1%	-3.4%

R_c: control event rate R_t: treatment event rate

Panel Question:

The panel will be asked to comment on post-hoc analysis issue of using dual-baseline.

Time-to-door: key secondary endpoint

- Binary outcome: time-to-door > 2 hours or not
  - Treatment event rate: 4 (0.9%)
- Continuous outcome: mean time-to-door
  - Treatment mean time 2.66 hrs (SD=5.3 hrs)

Look-back Window	Reduction in Events (time-to-door>2hrs)			Reduction in Time (mean time-to-door)		
	Control Time-to-door > 2 hrs (%)	Posterior Prob.	Success	Control Mean time-to-door (SD)	Posterior Prob.	Success
7-Day	8 (1.8%)	0.8614	No	52.33 (61.14)	>.9999	Yes
30-Day	13 (2.9%)	0.9840	Yes	322.35 (253.68)	>.9999	Yes
90-Day	17 (3.8%)	0.9978	Yes	664.48 (640.41)	>.9999	Yes

Conclusion: The results for time-to-door secondary end point is significant (>0.975) based on pre-specified study protocol. However, if this endpoint becomes the primary endpoint as the sponsor proposed in the IFU, then the significant threshold can't be determined post-hoc. Therefore the interpretation of this results should be taken with caution.

Device Diagnostic Performance

- Sensitivity, specificity, and negative predictive value (NPV) cannot be accurately calculated
  - Sensitivity = TP/ (TP+FN)
  - Specificity = TN/(FP+TN)
  - NPV=TN/(TN+FN)

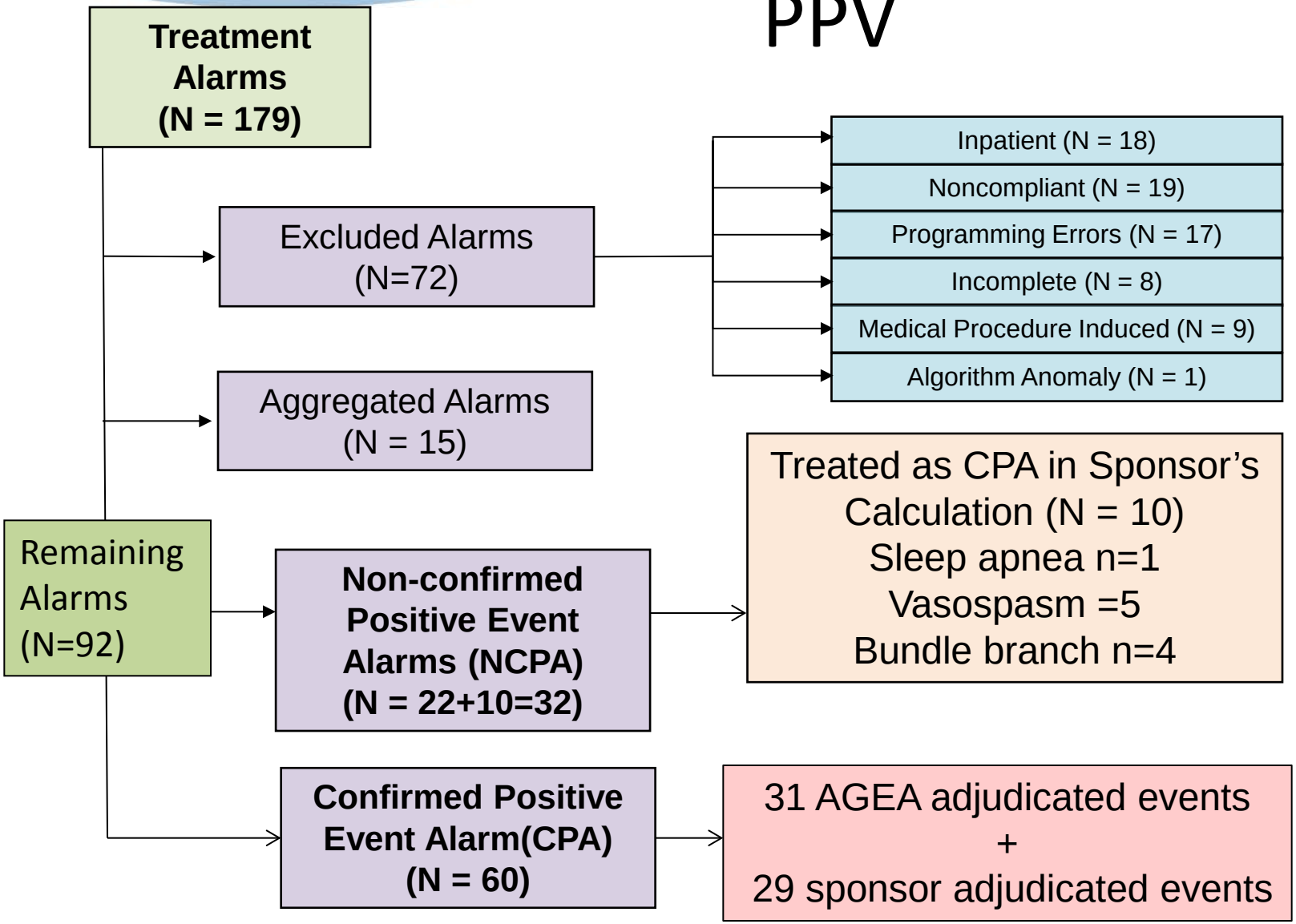
Device Alarm	True disease condition (ACS event)	
	Positive	Negative
Positive	True Positive (TP)	False Positive (FP)
Negative	False Negative (FN)	True Negative (TN)

False negatives (FN) and true negatives (TN) cannot be accurately determined for Control patients or Treatment patients who do not present due to an alarm

Positive Predictive Value (PPV)

- Alerts off for Control subjects
- PPV for alarms in treatment only (n=179)
  - True Positive (TP): CPA (Confirmed Positive Alarms)
  - False Positive (FP): NCPA (Non-confirmed Positive Alarms)
  - PPV= CPA/(CPA+NCPA)

PPV


Treatment Alarms (N = 179)
Excluded Alarms (N=72)
Inpatient (N = 18)
Noncompliant (N = 19)
Programming Errors (N = 17)
Incomplete (N = 8)
Medical Procedure Induced (N = 9)
Algorithm Anomaly (N = 1)
Aggregated Alarms (N = 15)
Remaining Alarms (N=92)
Non-confirmed Positive Event Alarms (NCPA) (N = 22+10=32)
Treated as CPA in Sponsor's Calculation (N = 10)
Sleep apnea n=1
Vasospasm =5
Bundle branch n=4
Confirmed Positive Event Alarm(CPA) (N = 60)
31 AGEA adjudicated events
+
29 sponsor adjudicated events

Positive Predictive Value (PPV)

	PPV Point Estimate*	PPV 95% CI**
FDA-Recommended Method	65.2% (60/92)	(54.2%, 74.9%)
Sponsor's Method	76.1% (70/92)	(67.0%, 85.2%)

* - Estimate Based on raw Counts

** - Estimate from GEE model to account for within patient correlation

Caution should be given when interpreting this result since more than 40% treatment alarms have been excluded from PPV analysis.

Panel Question:

The panel will be asked to comment on the concern when interpreting device diagnostic performance that 40% of alarms were excluded from the PPV analysis.

Statistical Conclusion

- The primary safety endpoint was met.
- The primary effectiveness endpoint was not met.
- Multiple study conduct issues result in difficulties in interpreting clinical data and analysis:
  - The sponsor's decision of enrollment termination is a significant protocol violation.
  - Multiplicity is not adjusted for multiple look-back windows on primary effectiveness endpoint.
  - The use of dual baseline could introduce potential bias and overestimate treatment effects.
  - Caution should be given to the PPV result since more than 40% treatment alarms have been excluded from PPV analysis.

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Angel Medical Guardian Device
ALERTS Trial
Clinical Review

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Division of Cardiovascular Devices
Office of Device Evaluation
Food and Drug Administration

March 16, 2016

FDA's Clinical Review: ALERTS Trial

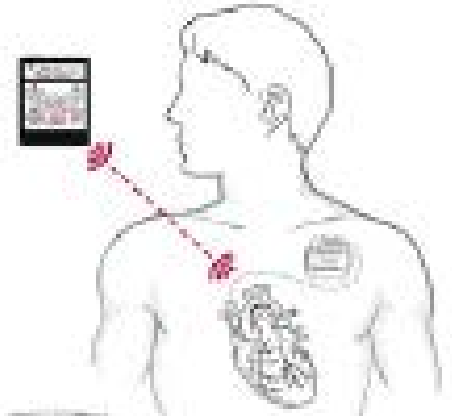
1. Safety Results
2. Effectiveness Results
   a) New Q wave MI
   b) Time to Door > 2 hours
3. Positive Predictive Value
4. Proposed IFU
5. Post Approval Study

The ALERTS Trial

- Prospective Bayesian RCT
- All subjects were implanted with the Guardian device
- Randomized to:
  - Alarm ON (treatment)
  - Alarm OFF (control)
- Primary endpoint:
  - Reduction in cardiac death,
  - New Q wave MI,
  - Delayed patient presentation for ACS

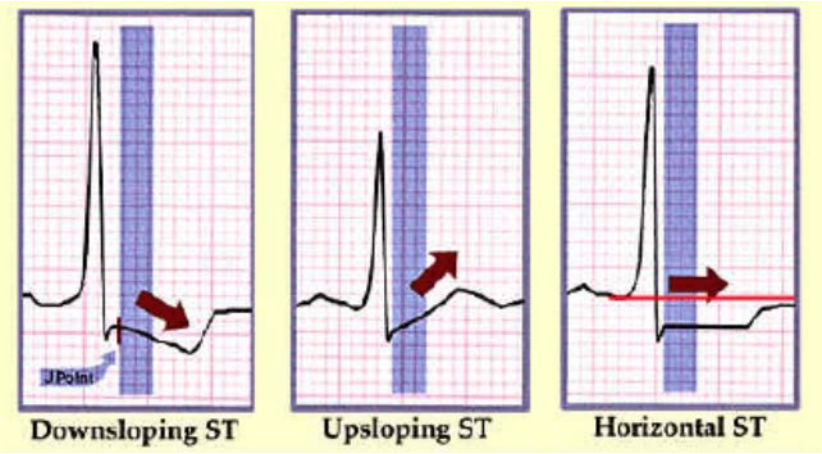
The Guardian Device

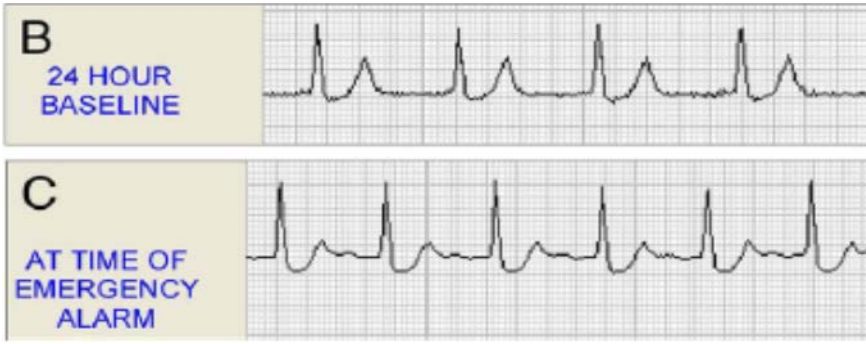
- Similar to a VVI pacemaker
- Continuously monitoring the intracardiac electrogram (EGM)
- Assessing changes in ST segment as an intracardiac ischemia monitor



Electrogram(EGM) vs ECG

- EGM ST changes traditionally for arrhythmia and rate detection
- EGM ST changes for ischemia detection is relatively new
- 2 prior ambulatory EGM studies (n=37)





Initial Clinical Results Using Intracardiac Electrogram Monitoing to Detect and Alert Patients During Coronary Plaque Rupture and Ischemia. Fischell et al. JACC 2010.

ALERTS Results: Demographics

Characteristic	Control (Off)	Treatment (On)
age	59	60
Female sex	34%	30%
Caucasian race/ethnicity	86%	87%
Prior STEMI, NSTEMI	**25% 28%**	**24% 28%**
Prior unstable angina	**44%**	**44%**
History of silent MI	6%	6%
Prior revascularization	97%	98%
LVEF	54%	54%
Diabetes, RI, TIMI>3	**49%, 16%, 3.6**	**46%, 18%,3.7**
History of smoking	69%	71%
BMI	32	32

Safety Results

Goal:>90% system-related complication free rate (CFR)

Event Type	Event s (n)	% of cohort
Infection	11	1.2%
Battery failures	2	0.2%
Pocket pain, erosion, protruding device	9	0.9%
Lead dislodgement, migration, malfunction	6	0.6%
Perforation	2	0.2%
Lead adaptor replacement	1	0.1%
TOTAL	**31**	**3.3%**

Comp. Free Rate =96.7%; posterior probability >0.9999

Primary Effectiveness Endpoint:

1. Cardiac/Unexplained death
2. Time to door > 2hours (using 90 day window)
3. New Q wave MI

Treatment (N=451)→N =439

Composite primary endpoint (n=16)

Control (N=456)→N=446

Composite primary endpoint (n=29)

Posterior Probability is 0.974 (<0.983)

Primary Effectiveness Endpoint: **Cardiac or Unexplained Death**

- 6 deaths total;
  - 4 were cardiac/unexplained;
    - Treatment Group: 3 deaths (0.7%)
    - Control Group: 1 death (0.2%)

Primary Effectiveness Endpoint: **New Q wave MI**

- New Q wave on ECG at 6 months
- New Q wave needs to be in an anatomic region with no prior Q wave
- Differs from Universal Definition of MI*
- Single Q waves may not represent a prior MI
  - Lead placement
  - Electrolyte imbalance

*Thygesen K, et al. ESC/ACCF/AHA/WTF Task Force for the Universal Definition of MI JACC 2012

Primary Effectiveness Endpoint: **New Q wave MI**

Serial over-read of ECGs to ensure Q waves persisted

Randomization	1 month	3 month	6 month
Absent	**Present**	**Present**	**Present**
Absent	Absent	**Present**	**Present**
Absent	Absent	Absent	**Present**

Primary Effectiveness Endpoint: New **Q wave MI: Dual Baseline**

Pre-implant	Randomization	1 month	3 month	6 month
Absent	Absent	**Present**	**Present**	**Present**
Absent	Absent	Absent	**Present**	**Present**
Absent	Absent	Absent	Absent	**Present**

7 new QWMIs developed the Q wave at 6 mo

Primary Effectiveness Endpoint: **new Q wave MI: dual baseline**

	Single baseline	Dual baseline
	New Q wave MI	New Q wave MI
Treatment n=10 (3.3%) →		Treatment n=7 (1.7%)
Control n=14 (2.4%) →		Control n=13 (3.0%)

Combined Primary Effectiveness Endpoint (90 day)

Single: Posterior probability=0.9740; <0.983

Dual: Posterior Probability=0.9908; >0.983

New Q wave MI Results:

1. The presence of a new Q wave on ECG may not be representative of a new interval Q wave MI
2. Even with the dual baseline approach, it is not clear that Q waves represent an interval MI
3. Dual baseline ECG serial read is a post hoc analysis

Effectiveness Results:
time to door > 2 hours

- Ischemic events were confirmed by;

  ECG, cardiac biomarkers, stress test, angio
- Time-to-Door: Time from device ST detection to presentation
- Look-Back Window: How many days between detection-to-presentation

  7-days → 90-days
- Presentation can be a protocol visit, ED visit

Time to Door > 2 hours Results: **Control**

18 events in 17 subjects → 17 events in 17 subjects Presented > 2 hours

6 angiograms in 6 subjects
- 3 PCI
- 1 CABG
- 2 CAD 58-69%

EKG: ST depression n=4
EKG: ST elevation n=1
Positive stress + EKG: ST elevation n=1
Pos. Biomarkers n=4
Positive stress test n=1

Time to Door > 2 hours Results: **Control**

18 events in 17 subjects → 17 events in 17 subjects Presented > 2 hours

6 angiograms in 6 subjects

- 3 PCI
  - 7.75 days
  - 4.5 days
  - 76 days
- 1 CABG
  - 3 days
- 2 CAD 58-69%
  - 5 hours, 6.5 hrs

Time to Door > 2 hours Results: **Control**

18 events in 17 subjects

17 events in 17 subjects
Presented > 2 hours

6 angiograms in 6 subjects
- 3 PCI
- 1 CABG
- 2 CAD 58-69%

11 Subjects with 11 positive tests:
- EKG: ST elevation n=1
- Positive Biomarkers n=4
- Positive stress test n=1
- Positive stress + EKG: ST elev. n=1
- EKG: ST depression or T wave n=4

Time to Door > 2 hours Results: **Treatment**

34 alarms in 27 subjects

29 alarms in 25 subjects < 2hrs

+

5 alarms in 4 subjects >2 hrs

23 alarms in 20 subjects

- 20 angiograms in 20 subjects
  - 10 PCI & 1 thrombolytics given
  - 6 no intervention; CAD present
  - 4 negative for significant CAD (-1 received lytics)

11 alarms

- EKG: ST elevation n=2
- EKG: ST depression n=1
- Pos. biomarkers or pos. stress test n=8

Time to Door > 2 hours Results: **Treatment**

34 alarms in 27 subjects

29 alarms in 25 subjects < 2hrs

+

5 alarms in 4 subjects >2 hrs

23 alarms in 20 subjects

- 20 angiograms in 20 subjects
  - 10 PCI & 1 thrombolytics given
  - 6 no intervention; CAD present
  - 4 negative for significant CAD (1 received lytics)

11 alarms in 10 subjects

- EKG: ST elevation n=2
- EKG: ST depression n=1
- Pos. biomarkers or pos. stress test n=8

Time to Door > 2 hours Results: **Treatment**

34 alarms in 27 subjects

29 alarms in 25 subjects < 2hrs

5 alarms in 4 subjects >2 hrs

- 1 Positive stress test
- 1 Positive enzymes
- 2 PCI*

(*1 PCI pt had 2 alarms)

Recalculating the Combined Effectiveness Endpoint (CEE)

Using 90 day window and dual ECG baseline

Control N=446 n(%) CEE	Treatment N=439 n(%) CEE	Post. Prob. CEE	Endpt. Met? (>0.983)
28 (6.5)	**13 (3.1)**	**0.9908**	**Yes**
25 (5.8)	13 (3.1)	0.974	No
24 (5.6)	13 (3.1)	0.963	No

Statistical Significance Threshold = 0.983

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24 (5.6)	**13 (3.1)**	**0.963**	**No**

Statistical Significance Threshold = 0.983

Time-To-Door : Key 2nd Endpoint

Look-back Window (days)		Reduction in events (binary: > 2hrs)			Reduction in time (continuous)		
		Time-to-door > 2 hrs (%)	Post. Prob.	Success	Mean Time-to-door hrs (SD)	Post. Prob.	Success
Control	7	8 (1.8%)	0.8614	No	52.33 (61.14)	>.9999	Yes
	30	13 (2.9%)	0.9840	Yes	322.35 (253.68)	>.9999	Yes
	90	17 (3.8%)	0.9978	Yes	664.48 (640.41)	>.9999	Yes
Treatment		4 (0.9%)			2.7 (5.3)		

Statistical Significance Threshold = 0.975

Time-To-Door : Key 2nd Endpoint

Look-back Window (days)		Reduction in events (binary: > 2hrs)			Reduction in time (continuous)		
		Time-to-door > 2 hrs (%)	Post. Prob.	Success	Mean Time-to-door hrs (SD)	Post. Prob.	Success
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	90	17 (3.8%)	0.9978	Yes	664.48 (640.41)	>.9999	Yes
Treatment		4 (0.9%)			2.7 (5.3)		

Statistical Significance Threshold = 0.975

Results: STEMI

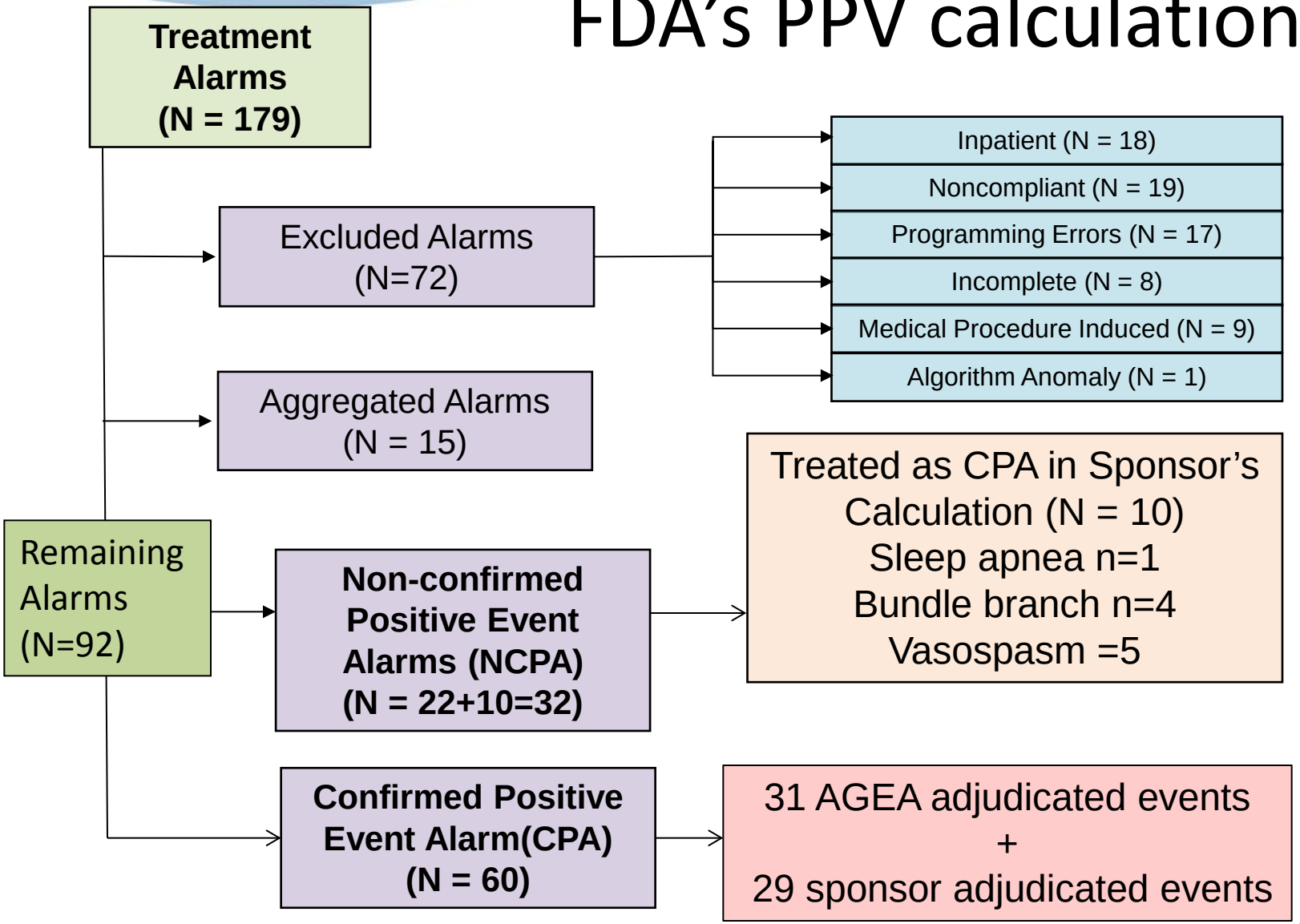
5 STEMIs; 3 treatment, 2 control

Time to presentation	Treatment Group (alarm status)
47 min **Prior**	Treatment (ON)
103 min **Prior**	Treatment (ON)
4 days **Prior**	Control (OFF)
15 min *After*	Treatment (ON)
13 hours *After*	Control (OFF)

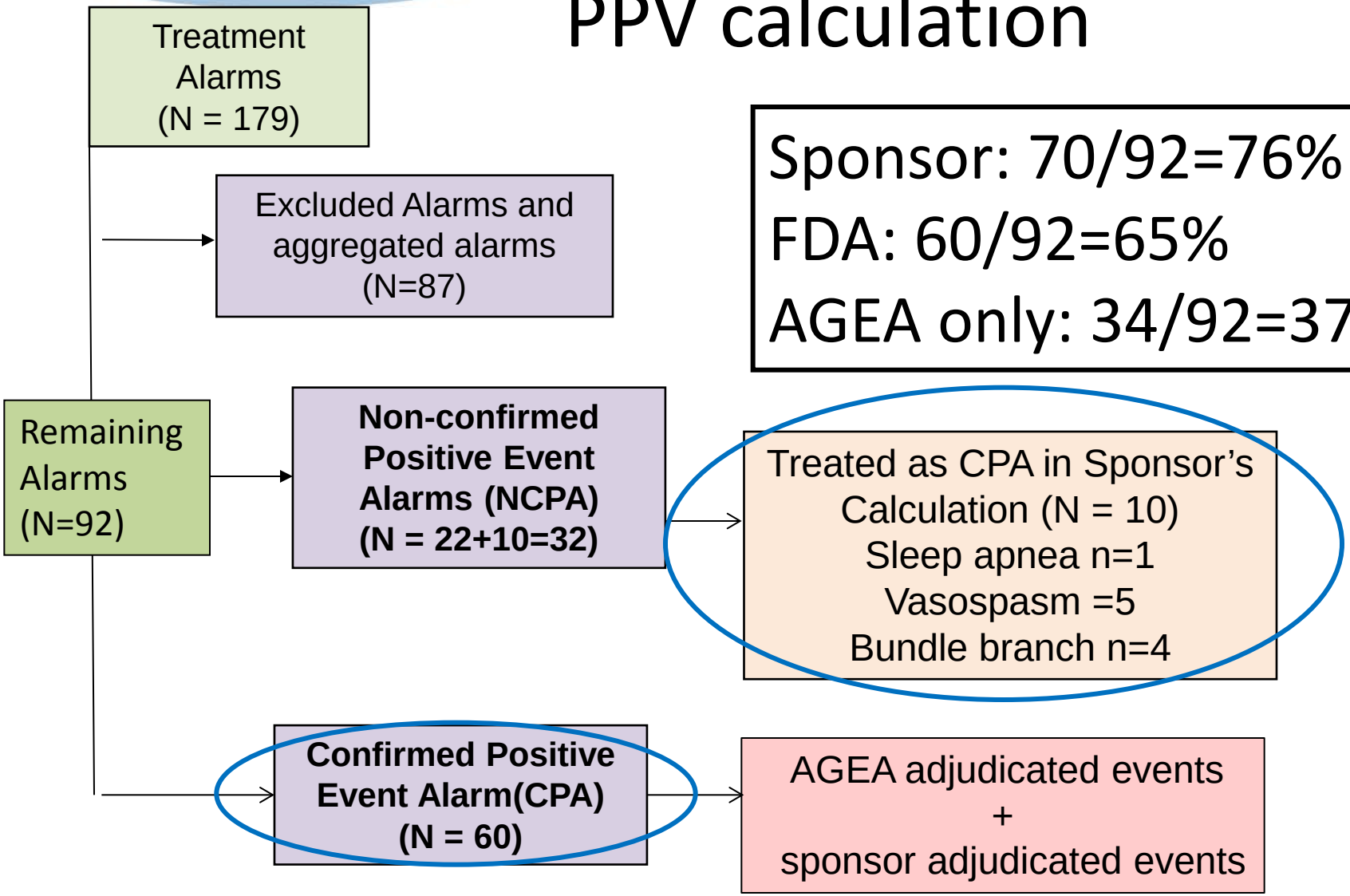
Positive Predictive Value (PPV)

- Calculated for Treatment subjects only
- The sponsor used the same 4 ischemia tests
  - ECG, biomarkers, stress, angiogram
- The sponsor adjudicated events for PPV
  - Includes all ST changes, T wave changes
  - Includes >50% stenosis and >20% change in stenosis
  - Include non ACS events
  - Uses both site and core lab data for angios

FDA's PPV calculation

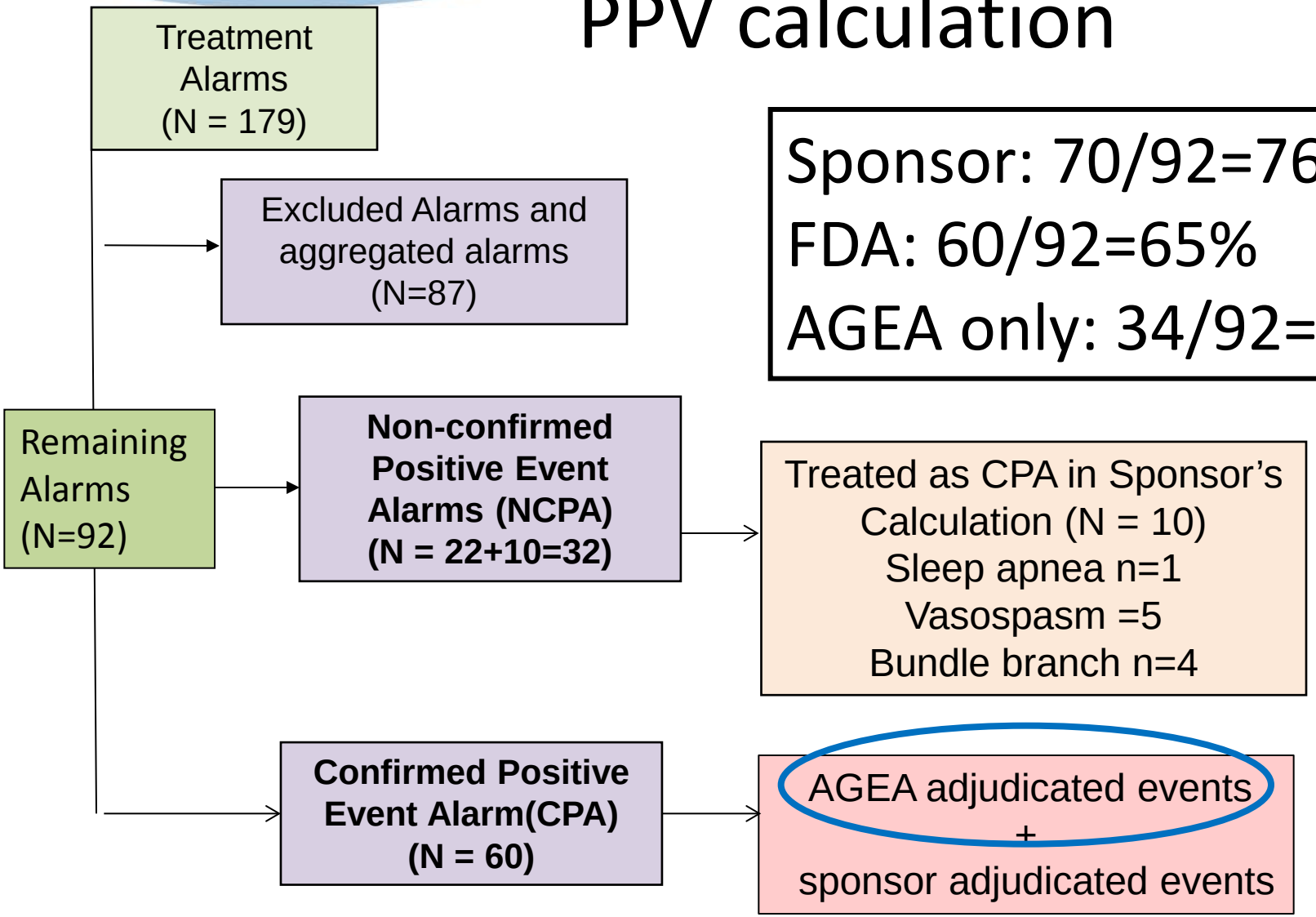


PPV calculation



Sponsor: 70/92=76%
FDA: 60/92=65%
AGEA only: 34/92=37%

PPV calculation



Sponsor: 70/92=76%
FDA: 60/92=65%
AGEA only: 34/92=37%

False Negative Rate

- Unable to truly calculate the FNR
- FNR=FN/(FN+TP)
- Treatment Group:

  23 angiograms for symptoms

  FNR=23+X /[(23+X)+34] ≥ 40%
- This is a guestimate, but should not overestimate the true FNR

Indications for Use (IFU)

The Guardian System is indicated to alert patients with prior acute coronary syndrome events, to ST segment changes indicating acute coronary occlusion.

Guardian System alerts reduce the overall time-to-door from a detected acute coronary occlusion until presentation at a medical facility independent of patient-recognized symptoms.

Panel Question:

The panel will be asked if the ALERTS results support the proposed IFU and indicated patient population

Clinical Conclusions

1. The safety endpoint was met
2. The primary effectiveness endpt. was not met when using a 90 day window and the pre-specified ECG analysis
3. The primary effectiveness endpt. was met when using a 90 day window and a dual baseline ECG analysis
   a. This ECG analysis is post hoc
   b. Endpoint no longer met when 4 events are removed from the analysis

Clinical Conclusions

- Clinical utility is clearly demonstrated in some subjects
- However, many ST detections appear to correspond to possible ischemia in absence of ACS event
- Patients respond to the alarm; Benefit of alarm may depend on whether an acute ACS event is ongoing

FDA Presentations

- Introduction – LTJG Stephen Browning
- Statistical Presentation – Dr. Zhiheng Xu, PhD
- Clinical Presentation – Dr. Kimberly Selzman, MD
- Conclusion – LTJG Stephen Browning

Post Approval Study (PAS)

- Prospective
- Event driven
- Registry
- Sponsor proposes to collect;
  - Time-to door for qualified events
  - Patient emergency alarm compliance
  - PPV
  - Measure EF at baseline and post ACS
  - Safety data for implant and replacement

FDA Conclusions

- Primary Safety Endpoint was met
- Primary Effectiveness Endpoint was not met
- Trial conduct and data analysis issues make clinical and statistical interpretation of the results difficult