The ProTECT III clinical trial

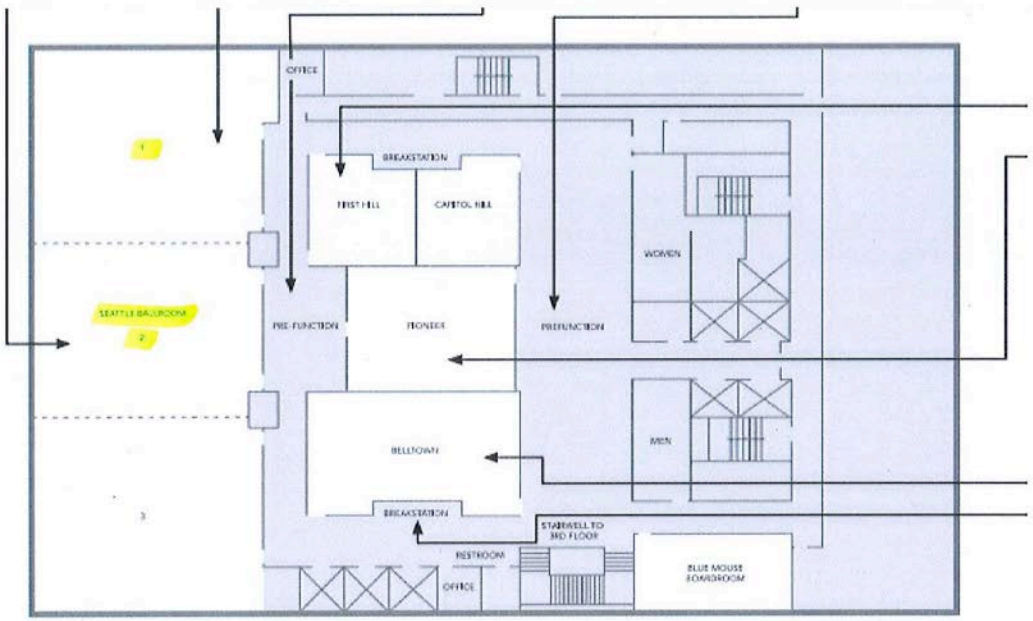
Investigators Meeting 2014

NIH – NINDS Award Numbers NS062778, 5U10NS059032, U01NS056975; National Center for Advancing Translational Sciences of the National Institutes of Health under Award Number UL1TR000454, the Emory Emergency Neurosciences Laboratory in the Department of Emergency Medicine Emory School of Medicine, and the Grady Memorial Hospital

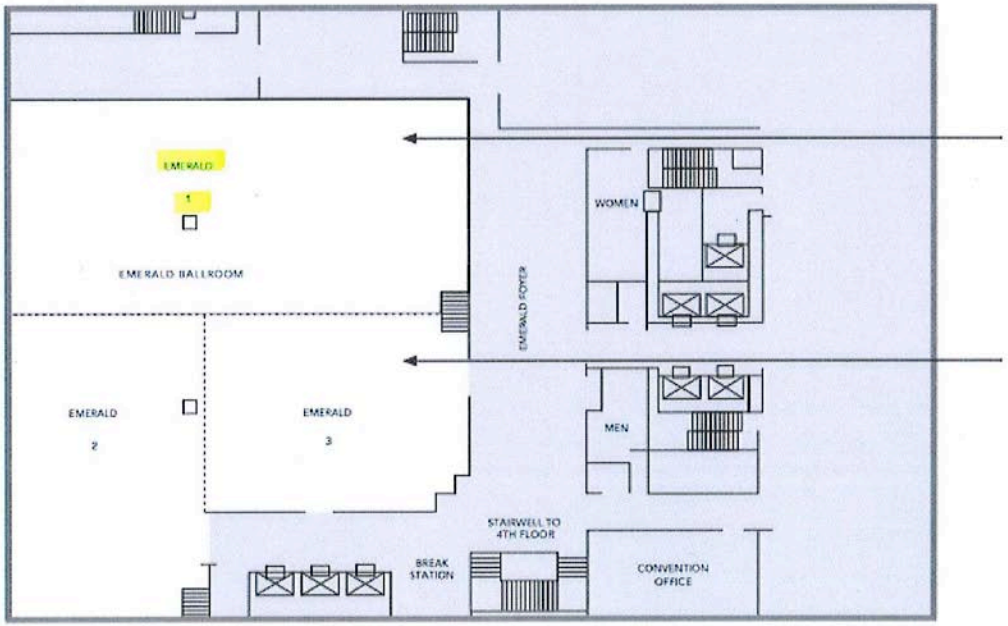
Seattle Washington Weather

Fri Sep 12	 Sunny	77° 54°	CHANCE OF RAIN: 0%	WIND: N at 9 mph Details
Sat Sep 13	 Sunny	81° 55°	CHANCE OF RAIN: 0%	WIND: N at 7 mph Details
Sun Sep 14	 Sunny	85° 57°	CHANCE OF RAIN: 0%	WIND: N at 8 mph Details

4TH FLOOR



3RD FLOOR




fRol!K
kitchen+cocktails

ProTECT III INVESTIGATORS' MEETING
Seattle, WA
September 12th, 2014

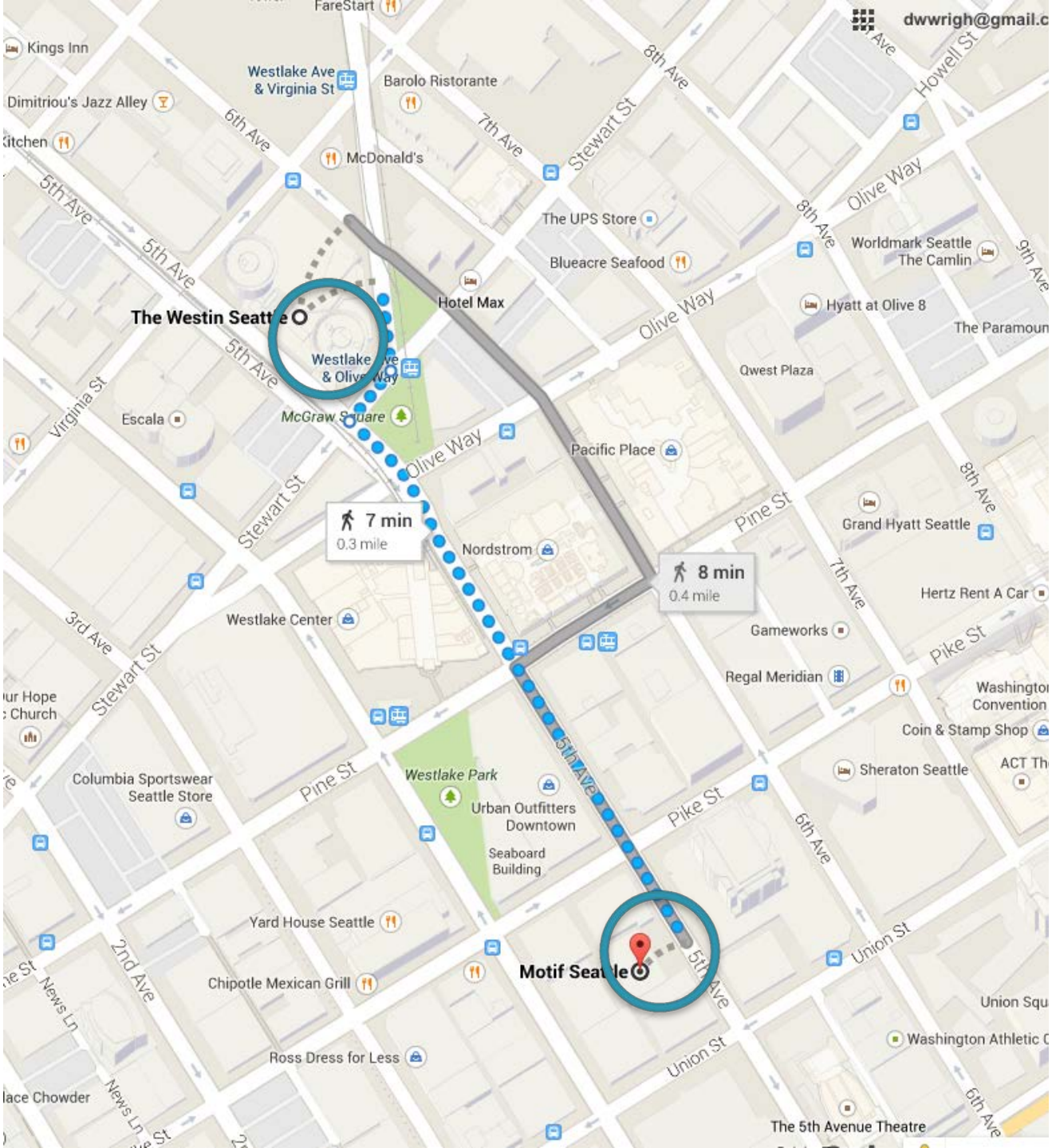
AGENDA

1:00-2:00	
2:00-2:20	Introduction
	• Welcome
	• Meeting Logistics
	• NCS logistics
2:20-3:10	Education/Training
	• EOS process
	• Public Disclosure - timing, templates, process
	• Press - how and when
	• Message
	• Financial Issues - Milestone document, invoice
3:10-4:05	Publication Process (Video-record)
	• Pub SOP
	• Process, procedures
	• Pub Submission Website
	• Ideas and Work groups
	• Data inquiries
4:05-5:00	ProTECT III Data Presentation
5:00-5:30	Q & A
5:30-6:00	Break
6:00-7:00	Cash Bar
7:00-9:00	Dinner - Awards and Presentations
9:00-until	Closure

Neurocritical Care Society ProTECT Presentation Logistics

Saturday 10:15 – 12:00 pm – Grand 3

D. Wright, G. Manley, D. Stein, M. Bell


FareStart
Kings Inn
Westlake Ave & Virginia St
Barolo Ristorante
Dimitriou's Jazz Alley
6th Ave
7th Ave
Stewart St
8th Ave
Howell St
McDonald's
5th Ave
The UPS Store
Olive Way
Worldmark Seattle The Camlin
Blueacre Seafood
Hotel Max
Hyatt at Olive 8
The Westin Seattle
Westlake & Olive Way
Qwest Plaza
Virginia St
Escala
McGraw Square
Pacific Place
7 min
0.3 mile
Nordstrom
8 min
0.4 mile
Grand Hyatt Seattle
Pine St
Hertz Rent A Car
Westlake Center
3rd Ave
Gameworks
Pike St
Regal Meridian
Coin & Stamp Shop
Sheraton Seattle
Columbia Sportswear Seattle Store
Westlake Park
Urban Outfitters Downtown
Seaboard Building
Yard House Seattle
Chipotle Mexican Grill
Motif Seattle
2nd Ave
Union St
Ross Dress for Less
The 5th Avenue Theatre

PUBLICATIONS

ProTECT III Publication Goals and Guidelines

GOAL

Publications – General Principles

- Inclusivity
- Productivity
- Novel ideas
- After initial and preplanned papers,
  - NETT PI's and Coordinators priority
  - First come, First serve

Version 4.0

ProTECT™ III

Progesterone for the Treatment of Traumatic Brain Injury

Trial Publication Protocol

Supported by:
National Institute for Neurological Disorders and Stroke

Project Number: 1U01NS062778
FDA IND #: 104,188

ProTECT Publications Committee

- David W. Wright, MD –ProTECT III PI (Chair)
- Yuko Palesch, PhD – PI of the ProTECT SDMC
- Sharon Yeatts, PhD –Unblinded Statistician ProTECT SDMC
- Vicki Hertzberg, PhD - Biostatistics, Emory University
- Geoff Manley, MD, PhD - University of California, San Francisco
- Robert Silbergleit, MD - NETT Clinical Coordinating Center
- Erin Bengelink – NETT ProTECT III Project Coordinator
- Kurt Denninghoff – Hub PI Representative (highest enrolling Hub)
- Art Pancioli, MD – Spoke PI Representative (highest enrolling spoke)
- Scott Janis, PhD – NINDS Scientific Program Officer

PPC Charge

- Set publication priorities for the ProTECT III trial data
- Review and approve all ProTECT III publications (manuscripts, abstracts, posters, presentations) prior to the public release of data
- Facilitate writing groups and approve or assign a designated leader
- Ensure correct interpretation and representation of ProTECT III data
- Ensure appropriate authorship designation and provide final ruling on disputes
- Track manuscript development and encourage timely submissions
- Evaluate outside requests for data use (prior to availability of public use data set)
- Approve the use of ProTECT III data for grant submissions

Publication Types

- Primary Hypothesis – Main Paper
  - Submitted to NEJM on Tue Sept. 9th
- Secondary Manuscripts – Preplanned Hypotheses
  - Neuropsych outcomes, NPOS, Transgressions, Imaging etc.
- Tertiary Hypothesis
  - Not preplanned, but related to the effect of Prog
- Quaternary and Newly Generated Hypothesis
  - Not preplanned, looking at any data, e.g. prediction models for mortality/morbidity, affect of confounder on outcome, etc.
- Ancillary Studies
  - BIO-ProTECT and PEER
- Methods papers
- Abstracts, Posters, Oral presentations

Acknowledgments

- Must have the following
  - *Research reported in this publication was supported by the National Institute Of Neurological Disorders And Stroke of the National Institutes of Health under Award Numbers NS062778, 5U10NS059032, U01NS056975, the General Clinical Research Center at Emory University, and the Grady Memorial Hospital. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or other supporting entities.*

- Others depending on manuscript

Authorship

- Guided by the International Committee of Medical Journal Editors (ICMJE) recommendations
  - Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
  - Drafting the work or revising it critically for important intellectual content; AND
  - Final approval of the version to be published; AND
  - Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
- In general, all members of the HWG that significantly contribute to the content of the manuscript should be included.
- ProTECT III publications will include the phrase "…*for the ProTECT III Trial Investigators*" at the end of the author list.
- All ProTECT III Trial Investigators (Hub and spoke) and coordinators will be named in the publication in a format that meets the journal of submission's guidelines.
- ProTECT III PI (usually listed as the last in the formal list), Central Coordinating Center PI, SDMC PI and manuscript statistician will also be included as authors

Other

- No ProTECT III data should be released to the public or non-ProTECT III entities unless prior approval is obtained from the PPC
- All data associated with ProTECT III, whether locally or centrally stored should be de-identified prior to release, sharing, or publication
- Hub investigators can publish their own data, notification of the PPC is encouraged.

Submission Process

1. **Submit Idea – Online WebPortal**
2. **Notify PPC /Chair**
   - Review within 2 wks
   - Prioritize request and ensure no overlap
3. **Form Hypothesis working group (HWG)**
   - Identify Lead/Chair
   - Team members/Authors
   - Develop hypothesis and detailed data request
4. **Submit detail to SDMC**
   - Allow 4 wk minimum if SDMC stats
   - If not SDMC stats, IDS provided (after Feb 2015)
5. **Write Drafts (8wks)**
   - Submit to PPC
   - 2 wks max to approve or request changes
7. **Submit to Journal**
   - Major changes – submit back to PPC post edits
   - Final Publication!

WebPortal

Publication Proposal

Date	
Originating Author	
E-mail	
Address	
Telephone	
Intended Audience	☐ Abstract ☐ Oral Presentation ☐ Lecture ☐ Manuscript ☐ Other
Event / Meeting / Publication / Journal of Interest	
Submission Deadline	☐ Deadline N/A
Date of Meeting	☐ Meeting N/A
Location	

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Section 2

Proposed Title

SDMC Data Analysis Required ○ Yes ○ No

Hypothesis / Questions of Interest:

Data Requested
- ☐ CRF - data point locations
- ☐ Ancillary data need (images, biomarkers)
- ☐ Other data source

Specific Explanation of Data Requested

Date Data Needed

Section 3

Hypothesis Writing Group (HWG) Members (if known):

Additional Members ○ Yes ○ No

Contact Information for the Writing Group Lead:

Same as Originator ○ Yes ○ No

Submit

Hypothesis Database

Originating Author	Proposed Title	Hypothesis 1	Hypothesis 2	Hypothesis 3
David W. Wright	The Effect of temperature and temperature control on patient outcome in the ProTECT III trial	Do patients who are hyperthermic (fever) have poorer outcomes, controlling for other infections	Does aggressive treatment of hyperthermia improve outcomes	Is there a correlation with temperature and ICP, MAP, CPP and other parameters
Pratik Doshi	The Impact of Hypothermia on patient outcomes in the ProTECT III trial	Do patients who present hypothermic have better outcomes than normothermic	Evaluation of temperature curve profile and outcome	
Michelle Biros	Unanticipated circumstances related to implementation of an EFIC Trial	Explore the unanticipated circumstances around implementation of EFIC - descriptive		
Kurt Denninghoff	Patterns and Comparisons of EFIC vs. Non-EFIC subjects in the ProTECT III trial	Are there specific differences between the EFIC enrolled subjects vs. the Non-EFIC enrolled subject.		
David Wright	Validation of the IMPACT Prediction Model using the ProTECT III Trial	The IMPACT Prediction Model will accurately predict overall mortality and morbidity of subjects in the ProTECT III trial	Other Prediction models	
Samir Belagaje	The Impact of Rehabilitation / Post Hospital Discharge Disposition on Outcomes in the ProTECT III Study	Subjects who went home or to acute Rehab had better outcomes than those who were discharged to a SNF	Was there an imbalance in the discharge disposition between 2 arms (ProgvsPlac) which could have served as a confounder	If, imbalance - did it affect overall results

Questions

- Neuropsych (NP) outcome and Prog
- NP outcome and other predictors
- NPOS
- Baseline characteristics and outcome, predictors
- Past history and outcome predictors (Baseline questionnaire)
- Medical history and confounders on outcome
- Transgression data, variability in management,
- Site specific management and outcome, medical care (e.g. early surgery), Ventric vs not and outcome, etc.
- Imaging questions, predictors of outcome, novel scoring methods, validating old scoring methods (Marshall, Rotterdam, Helsinki), CT reading guidelines, inter-rater reliability on reads
- NPOS, DRS, other measures
- ISS, AIS, CT and other injury severity questions, prediction of mortality, Compare predictive value of old ISS model, advanced ISS model, and Transgression models.
- Findings on baseline CT are predictive of elevated ICP in the first 24 hours
- Biomarkers and predictors
- A factorial analysis of baseline CT abnormalities will identify specific findings that correlate with baseline, 24 hour and 48 hour biomarker levels
- A new CT classification scheme can be created that is a better predictor of outcome than existing schemes (e.g. Marshall, Rotterdam and Abbrev Injury Scale)
- Relationship between findings on baseline CT and functional / neurocognitive outcome at 6 Months (control and treatment groups).
- Comparison of the ProTECT III outcomes vs. the IMPACT prediction model. (PROG tx vs. Placebo outcomes both compared to IMPACT scoring)
- Comparison of EFIC vs. Non-EFIC subjects
- Patterns and comparisons of refusal/withdrawals
- Neuro specific ICU versus a General trauma ICU
- WBC count and TBI. Does it go up? Other Serum markers of injury – correlate with outcomes
- Describe the evolution of baseline CT findings on subsequent imaging

ProTECT III

2014 Investigators Meeting

ProTECT™ III
Progesterone for Traumatic Brain Injury

ProTECT III PI – David W. Wright
ProTECT Project Manager – Mike Lunney
Statistician – Sharon Yeatts
Blinded Statistician – Vicki Hertzberg, Yuko Palesch
SDMC Statistical Center PI – Yuko Palesch
NETT PI – Bill Barsan, Rob Silbergleit
NETT ProTECT Site Manager – Erin Bengelink

21 Hubs Active
49 Spokes Active
38 Enrolled

NINDS # 1U01NS062778
FDA IND # 104,188
NETT 5U10NS059032,
U01NS056975

ProTECT™ III

A Phase III, double-blind, placebo-controlled randomized clinical trial

1. Blunt traumatic brain injury
2. GCS 4-12
3. Can initiate infusion within 4 hours of injury
4. Age ≥18 yrs

NINDS # 1U01NS062778
FDA IND # 104,188
IRB # 000-14409

Outcome

- Primary Outcome – GOSE sliding dichotomy at 6 months

If the patient's iGCS is:	If the iMotor Score is:	Then the favorable outcome is:
4-5	2-3	6 mo GOSE = severe, moderate, or good
6-8	4-5	6 mo GOSE = moderate or good
9-12		6 mo GOSE = good recovery

- Secondary Outcomes – DRS, NP Battery
- Sample size – 842/1140 subjects

Trial Updates

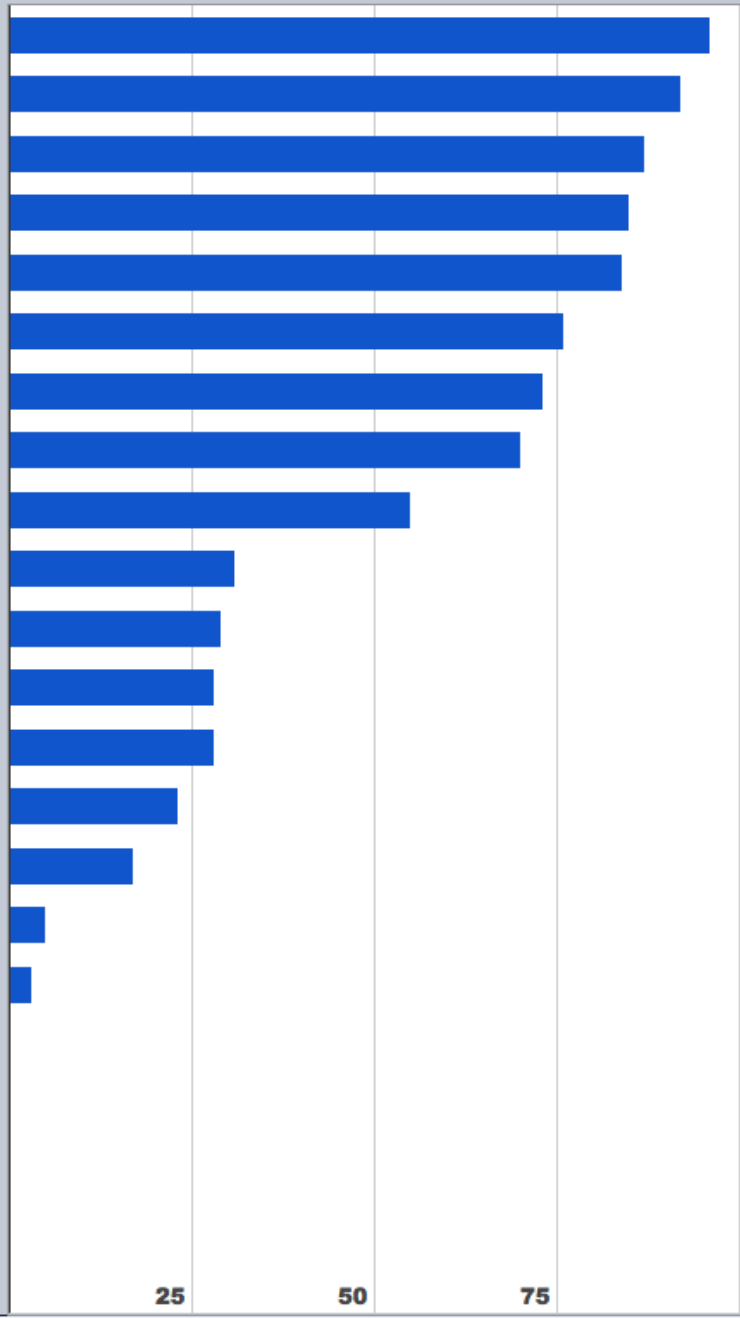
- Nov 1st 2013 – DSMB requested halting trial due to futility
- 882 Subjects enrolled
- Follow up continued – final May 2014
- Monitor/Data Cleaning May-July
- Database Locked July 30th

- CRFs posted: 259,301
- CRFs submitted: 76,949
- AEs coded: 3,028
- SAEs: 1,003

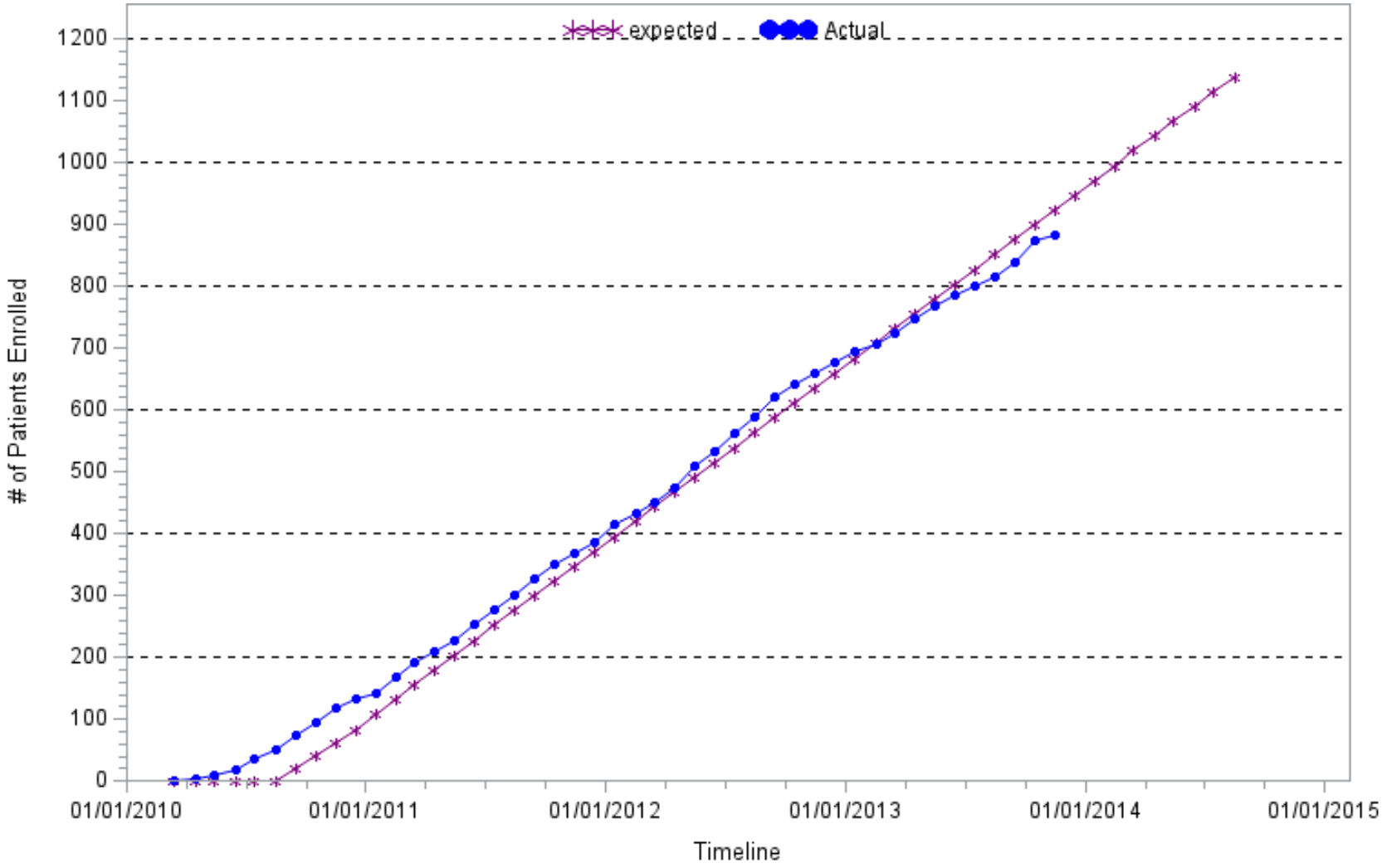
ProTECT Enrollment

Hub	Total	This week	Last 4 weeks	Sparkline (most recent 6 months)
Arizona	96	0	0	
Emory	92	0	0	
Stanford	87	0	0	
Cinci	85	0	0	
Minn	84	0	0	
Texas	76	0	0	
MCW	73	0	0	
U Penn	70	0	0	
Temple	55	0	0	
Oregon	31	0	0	
VCU	29	0	0	
UK	28	0	0	
Wayne	28	0	0	
UCSF	23	0	0	
HFHS	17	0	0	
NYP	5	0	0	
Maryld	3	0	0	
MGH	0	0	0	
Ohio St	0	0	0	
SUNY	0	0	0	
UCLA	0	0	0	
Pittsbg	0	0	0	

Total Enrollment (overall bar) Most recent 6 months (light blue bar)



Enrollment Rate

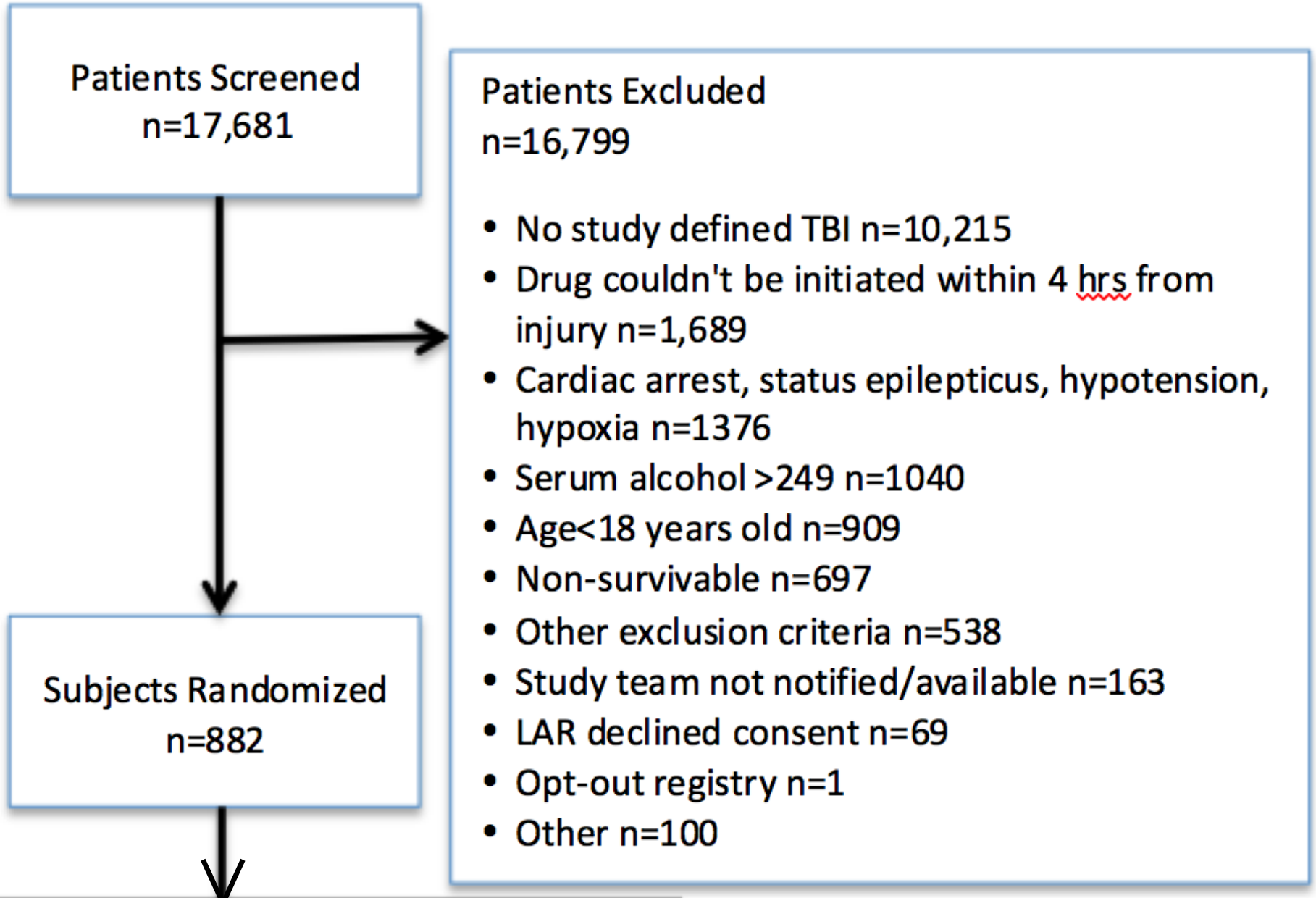


EFIC and Consent

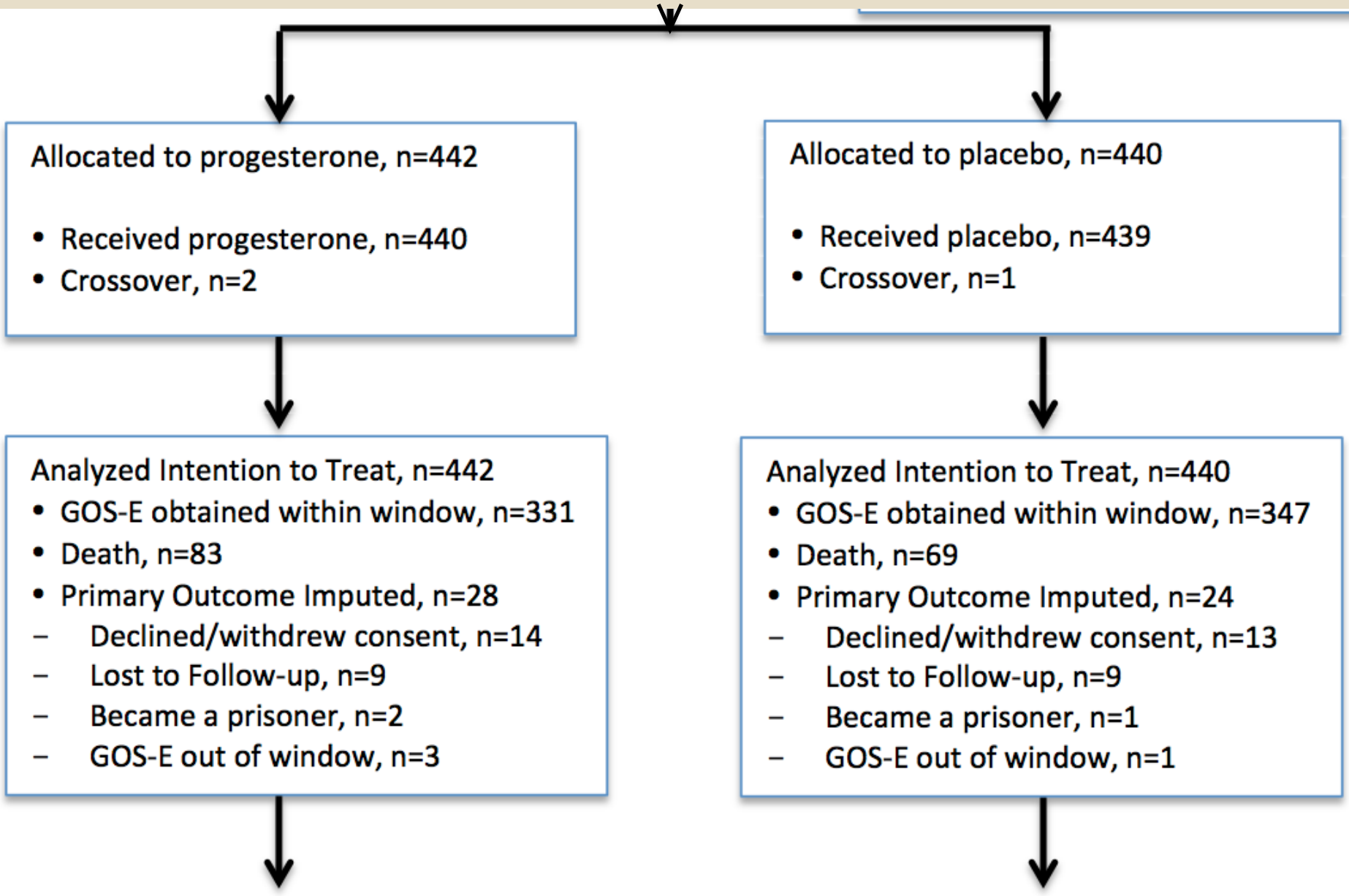
		Treatment A		Treatment B		All Groups	
		N	%	N	%	N	%
Total N		442	100.00	440	100.00	882	100.00
Enrolled Under	Exception from Informed Consent (EFIC)	299	67.65	316	71.82	615	69.73
	Consent	143	32.35	124	28.18	267	30.27

Initial Informed Consent Outcome		Treatment A		Treatment B		All Groups	
		N	%	N	%	N	%
All Enrolled Under EFIC		299	100.00	316	100.00	615	100.00
Consent Obtained		270	90.30	301	95.25	571	92.85
Final Consent Obtained by* *Denominator is number of subjects with consent obtained	Subject	56	20.74	67	22.26	123	21.54
	LAR	214	79.26	234	77.74	448	78.46
	Other					0	
Consent declined		10	3.34	9	2.85	19	3.09
Deceased, notification only		11	3.68	4	1.27	15	2.44
LAR unknown or unavailable		2	0.67	1	0.32	3	0.49
Notification about the study only		5	1.67	1	0.32	6	0.98
Other		1	0.33	0	0	1	0.16

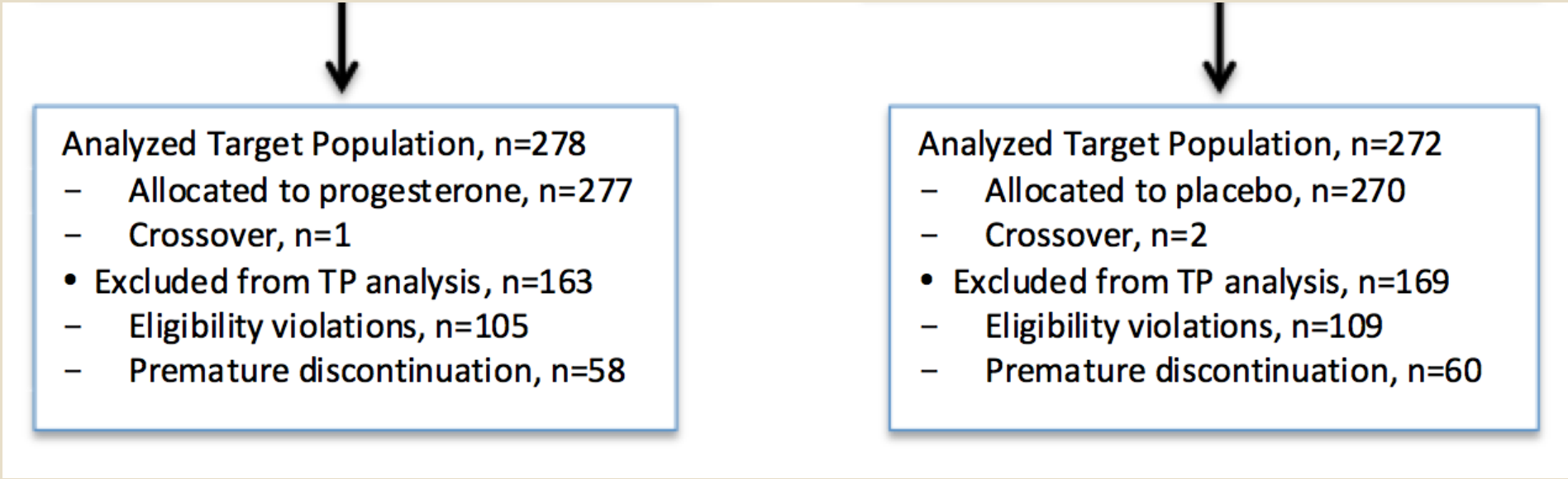
CONSORT Diagram



CONSORT Diagram – ITT



CONSORT Diagram - Target Analysis



Baseline Characteristics

Characteristic	Progesterone *(N=442)*	Placebo *(N=440)*	Total *(N=882)*
Age - Median (Min-Max)	36.5 (17.6-94.1)	34.4 (17.4-93.9)	35.5 (17.4-94.1)
Male - n(%)	324 (73.3)	326 (74.1)	650 (73.7)
African American - n(%)	70 (15.8)	64 (14.5)	134 (15.2)
Hispanic or Latino	61 (13.8)	64 (14.5)	125 (14.2)
Mechanism of Injury – n(%)			
Motor Vehicle Crash	159 (36)	163 (37)	322 (36.5)
Pedestrian Struck by Moving Vehicle	60 (13.6)	55 (12.5)	115 (13)
Motorcycle/scooter/ATV crash	78 (17.6)	91 (20.7)	169 (19.2)
Bicycle crash	23 (5.2)	23 (5.2)	46 (5.2)
Fall <3 feet	16 (3.6)	11 (2.5)	27 (3.1)
Fall >=3 feet	62 (14)	50 (11.4)	112 (12.7)
Assault	27 (6.1)	27 (6.1)	54 (6.1)
Blast injury	1 (0.2)	1 (0.2)	2 (0.2)
Unknown	3 (0.7)	3 (0.7)	6 (0.7)
Other	13 (2.9)	16 (3.6)	29 (3.3)

Baseline Characteristics - Severity

Index GCS (as Randomized)# - n(%)	Progesterone	Placebo	Overall
Moderate (iGCS 9-12)	129 (29.2)	125 (28.4)	254 (28.8)
Moderate to Severe (iGCS 6-8/iMotor 4-5)	234 (52.9)	238 (54.1)	472 (53.5)
Most Severe (iGCS 4-5/iMotor 2-3)	79 (17.9)	77 (17.5)	156 (17.7)
Injury Severity Score - Mean (SD)	24.7 (11.7)	24.1 (11.1)	24.4 (11.4)
AIS Head Score – n(%)			
No injury	12 (2.7)	19 (4.3)	31 (3.5)
Minor injury	7 (1.6)	6 (1.4)	13 (1.5)
Moderate injury	50 (11.3)	40 (9.1)	90 (10.2)
Serious injury	117 (26.5)	124 (28.2)	241 (27.3)
Severe injury	117 (26.5)	112 (25.5)	229 (26)
Critical injury	136 (30.8)	137 (31.1)	273 (31)
Non-survivable injury	1 (0.2)	0 (0)	1 (0.1)
Rotterdam CT Severity Grade – n(%)			
1	8 (1.8)	7 (1.6)	15 (1.7)
2	155 (35.1)	157 (35.7)	312 (35.4)
3	200 (45.2)	193 (43.9)	393 (44.6)
4	41 (9.3)	39 (8.9)	80 (9.1)
5	31 (7.0)	37 (8.4)	68 (7.7)
6	7 (1.6)	6 (1.4)	13 (1.5)

Baseline Characteristics – Time to treat

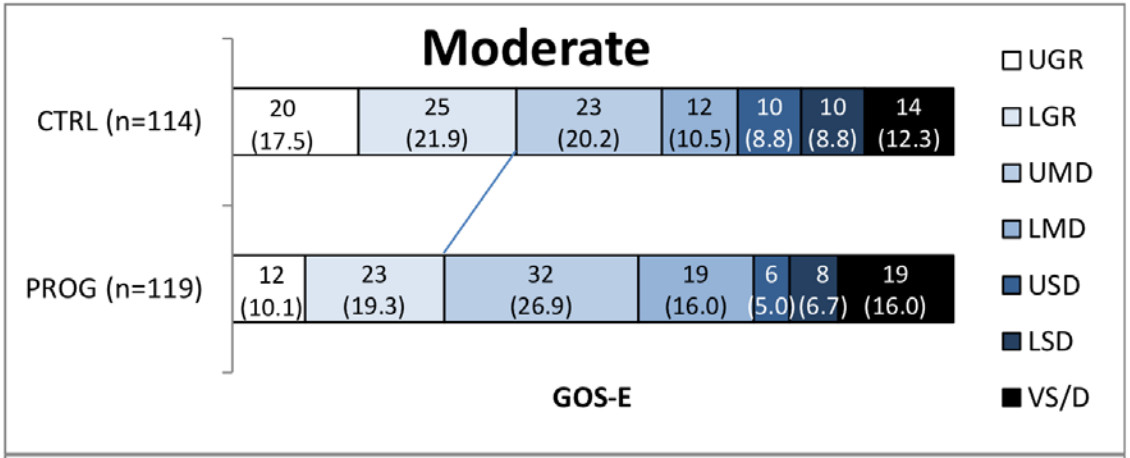
Time intervals in minutes – Mean (SD)	Progesterone	Placebo	Overall
Injury to ED Arrival	53.4 (30.3)	54.2 (27.2)	53.8 (28.8)
Injury to Randomization	173.2 (37.5)	173.0 (37.1)	173.1 (37.3)
Injury to Study Drug Initiation	219.9 (39.4)	216.4 (34.7)	218.1 (37.2)

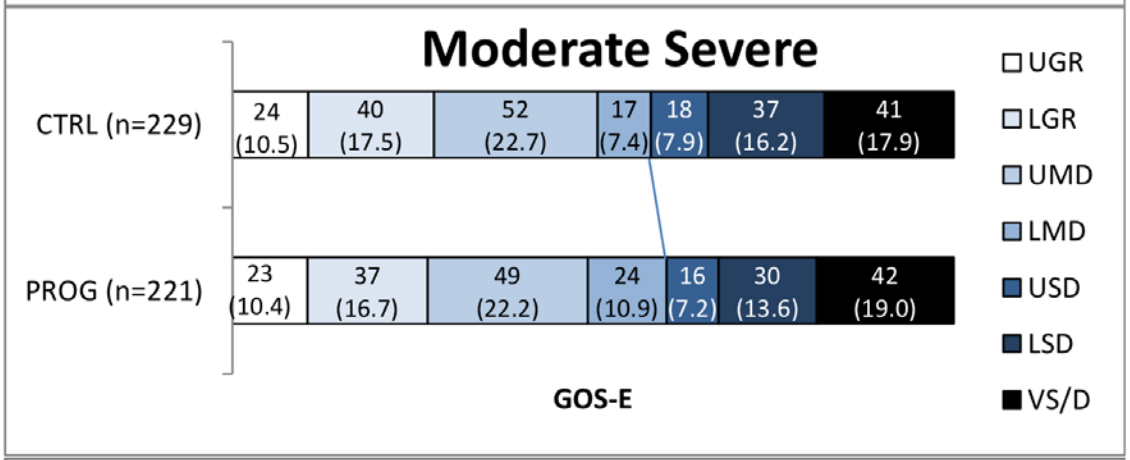
GOSE

	Progesterone *N=442* n (%)	Placebo *N=440* n (%)	Overall *N=882* n (%)	Unadjusted Risk Difference % (95% CI)
Primary Outcome				
Favorable	213 (48.2)	232 (52.7)	445 (50.5)	-4.5 (-11.1, 2.1)
Not Favorable	201 (45.5)	184 (41.8)	385 (43.7)	
Missing*	28 (6.3)	24 (5.5)	52 (5.9)	

Outcome by Severity

Outcome by initial injury severity	Progesterone	Placebo	Overall	
Moderate (iGCS 9-12)	*N=129*	*N=125*	*N=254*	
Favorable (GOS-E 7-8)	35 (27.1)	45 (36.0)	80 (31.5)	-8.9
Not Favorable	84 (65.1)	69 (55.2)	153 (60.2)	(-20.3, 2.5)
Missing*	10 (7.8)	11 (8.8)	21 (8.3)	
Moderate Severe (iGCS 6-8/iMotor 4-5)	*N=234*	*N=238*	*N=472*	
Favorable (GOS-E 5-8)	133 (56.8)	133 (55.9)	266 (56.4)	1.0
Not Favorable	88 (37.6)	96 (40.3)	184 (39.0)	(-8.0, 9.9)
Missing*	13 (5.6)	9 (3.8)	22 (4.7)	
Most Severe (iGCS 4-5/iMotor 2-3)	*N=79*	*N=77*	*N=156*	
Favorable (GOS-E 3-8)	45 (57.0)	54 (70.1)	99 (63.5)	-13.2
Not Favorable	29 (36.7)	19 (24.7)	48 (30.8)	(-28.1, 1.8)
Missing*	5 (6.3)	4 (5.2)	9 (5.8)	


Moderate
CTRL (n=114)
20 (17.5)
25 (21.9)
23 (20.2)
12 (10.5)
10 (8.8)
10 (8.8)
14 (12.3)
PROG (n=119)
12 (10.1)
23 (19.3)
32 (26.9)
19 (16.0)
6 (5.0)
8 (6.7)
19 (16.0)
GOS-E
UGR
LGR
UMD
LMD
USD
LSD
VS/D


Moderate Severe
CTRL (n=229)
24 (10.5)
40 (17.5)
52 (22.7)
17 (7.4)
18 (7.9)
37 (16.2)
41 (17.9)
PROG (n=221)
23 (10.4)
37 (16.7)
49 (22.2)
24 (10.9)
16 (7.2)
30 (13.6)
42 (19.0)
GOS-E
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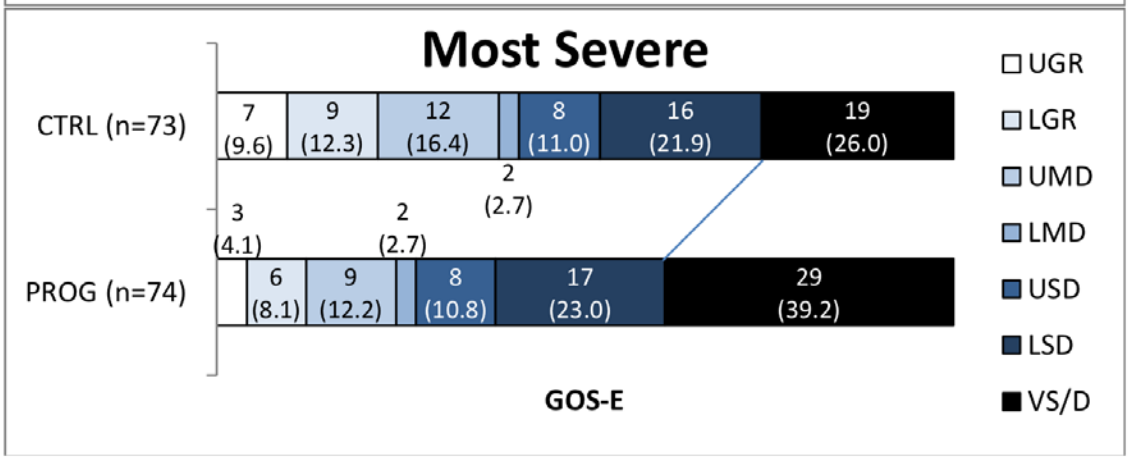
LSD
VS/D


Most Severe
CTRL (n=73)
7 (9.6)
9 (12.3)
12 (16.4)
2 (2.7)
8 (11.0)
16 (21.9)
19 (26.0)
PROG (n=74)
3 (4.1)
2 (2.7)
6 (8.1)
9 (12.2)
8 (10.8)
17 (23.0)
29 (39.2)
GOS-E
UGR
LGR
UMD
LMD
USD
LSD
VS/D

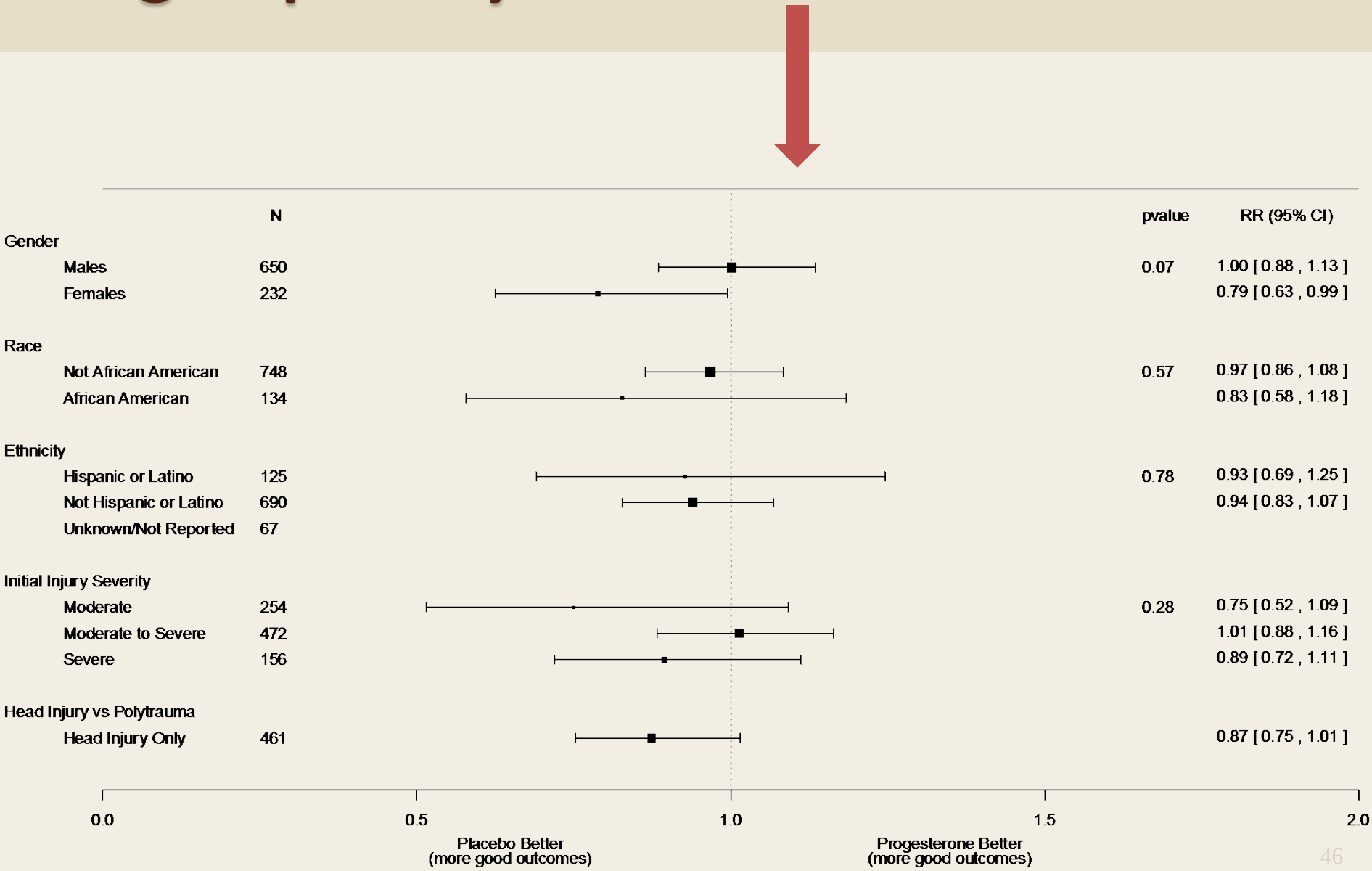
Outcome - Mortality

	Progesterone	Placebo	Overall
Mortality	83 (18.8)	69 (15.7)	152 (17.2)
Cause of Death: n (% of deaths)			
Neurological	53 (63.9)	49 (71.0)	102 (67.1)
Not Neurological	28 (33.7)	20 (29.0)	48 (31.6)
Other	2 (2.4)	0 (0.0)	2 (1.3)
Mortality by initial injury severity			
Moderate (iGCS 9-12)	19 (14.7)	14 (11.2)	33 (13.0)
Mod Severe (iGCS 6-8/iMotor 4-5)	37 (15.8)	39 (16.4)	76 (16.1)
Most Severe (iGCS 4-5/iMotor 2-3)	27 (34.2)	16 (20.8)	43 (27.6)

Adverse Events

	Progesterone	Placebo	Overall	*RR (95%CI)*
Specified Adverse Events	224 (50.68)	191 (43.41)	415 (47.05)	1.17 (1.01 - 1.34)
Myocardial infarction	5 (1.13)	5 (1.14)	10 (1.13)	1.00 (0.29 - 3.41)
Pulmonary embolism	10 (2.26)	13 (2.95)	23 (2.61)	0.77 (0.34 - 1.73)
Acute ischemic stroke	6 (1.36)	13 (2.95)	19 (2.15)	0.46 (0.18 - 1.2)
Deep venous thrombosis	50 (11.31)	40 (9.09)	90 (10.20)	1.24 (0.84 - 1.85)
Unexplained increased liver enzymes	18 (4.07)	14 (3.18)	32 (3.63)	1.28 (0.64 - 2.54)
Sepsis	9 (2.04)	9 (2.05)	18 (2.04)	1.00 (0.4 - 2.48)
Pneumonia	142 (32.13)	140 (31.82)	282 (31.97)	1.01 (0.83 - 1.22)
CNS infection	5 (1.13)	3 (0.68)	8 (0.91)	1.66 (0.4 - 6.9)
Phlebitis/Thrombophlebitis	76 (17.19)	25 (5.68)	101 (11.45)	**3.03 (1.96 - 4.66)**

Subgroup Analysis



Still Pending

- Neuropsychological Outcomes
- BIO-ProTECT results (Mike Frankel)
- Assessment of Transgressions/Impact


ProTECT
™
Thank you!

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