When Should RCTs Standardize Co-Interventions?

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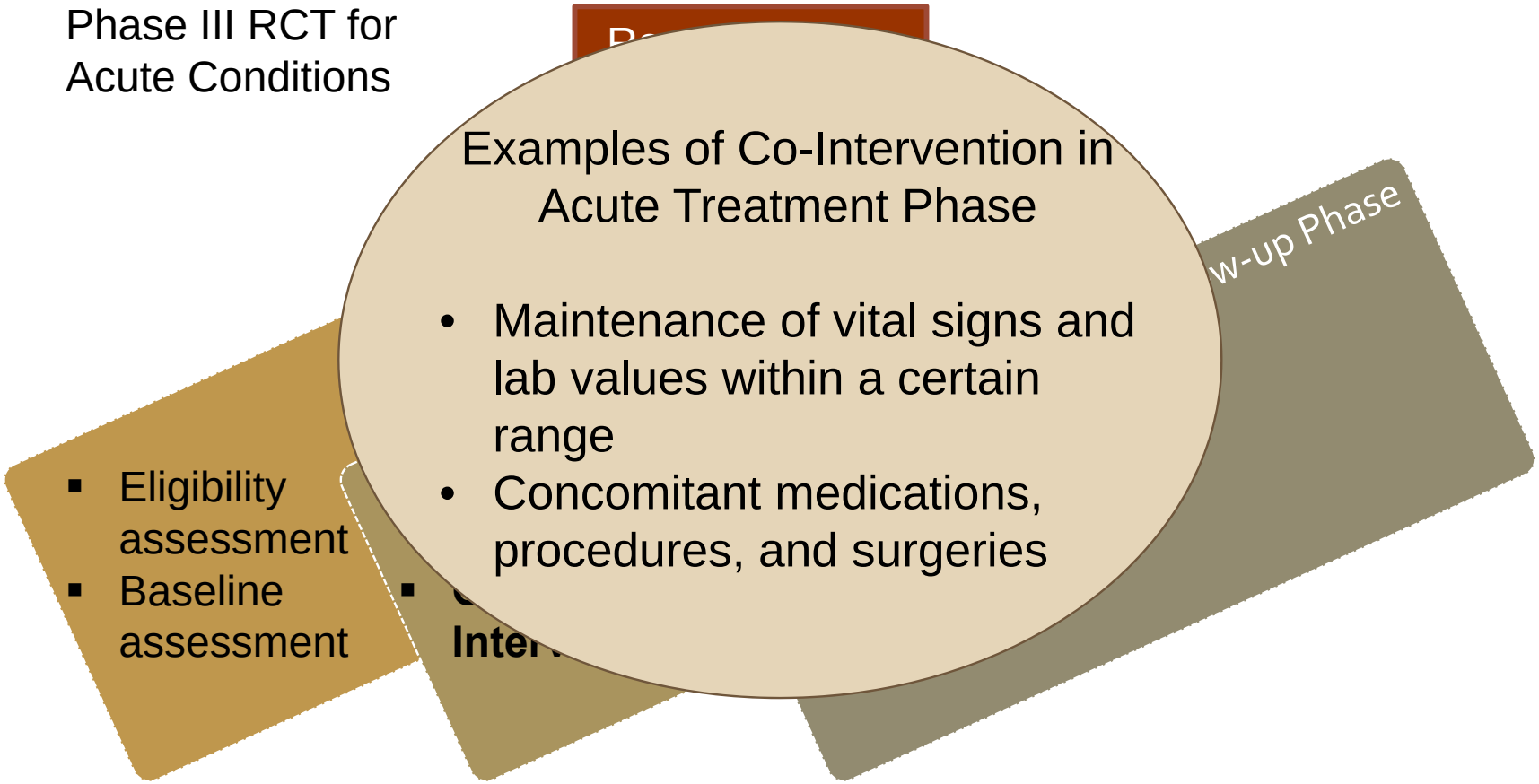
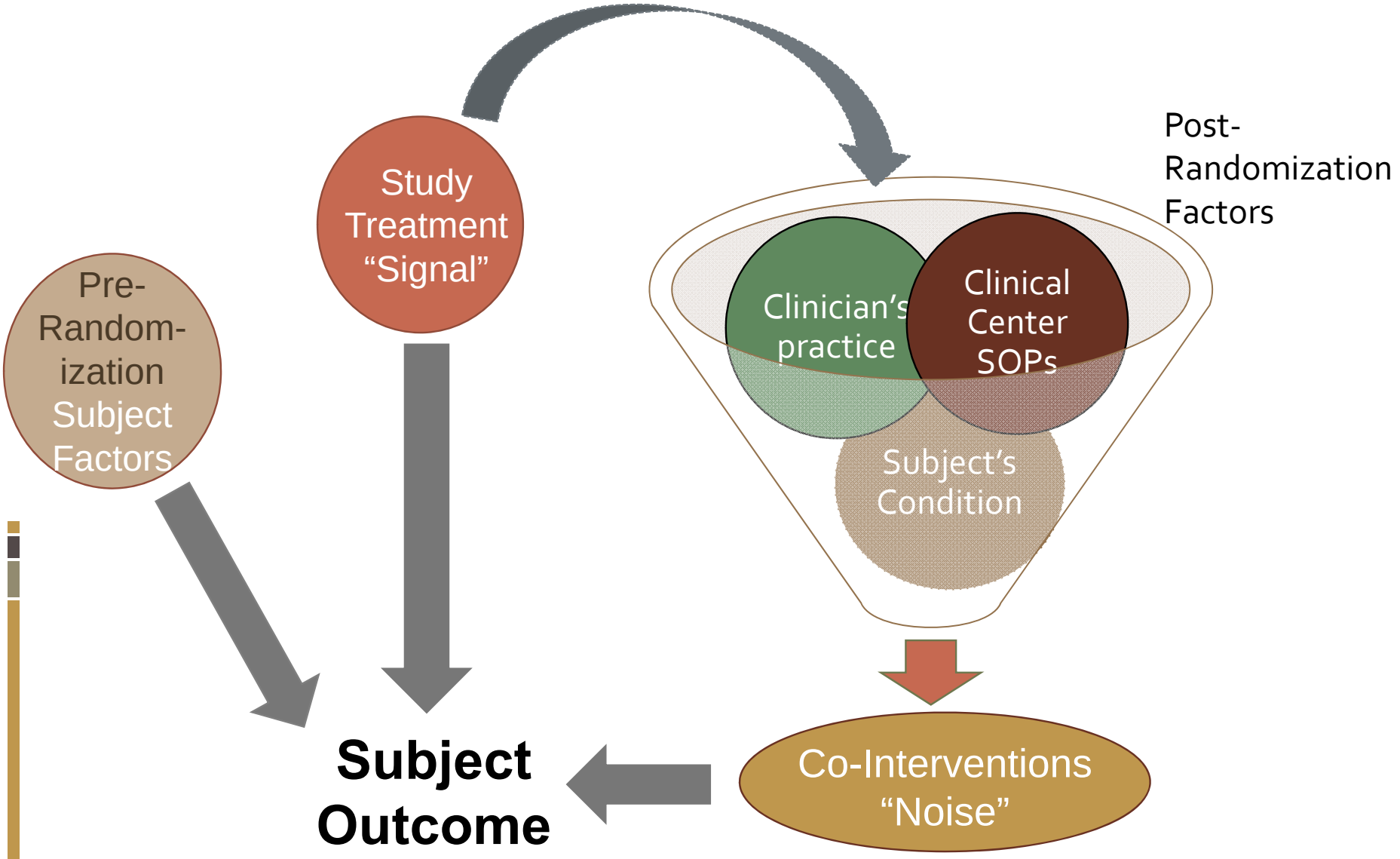
Definition / Context of Co-Intervention

Defn: Post-randomization clinical care, but not necessarily evidence-based

Context: Large multi-center Phase III RCT for Acute Conditions



Heterogeneity of Co-Interventions



a. Should we standardize co-interventions?

b. To what extent of standardization?

QUESTIONS:

Example 1: CLOTS-2 Trial

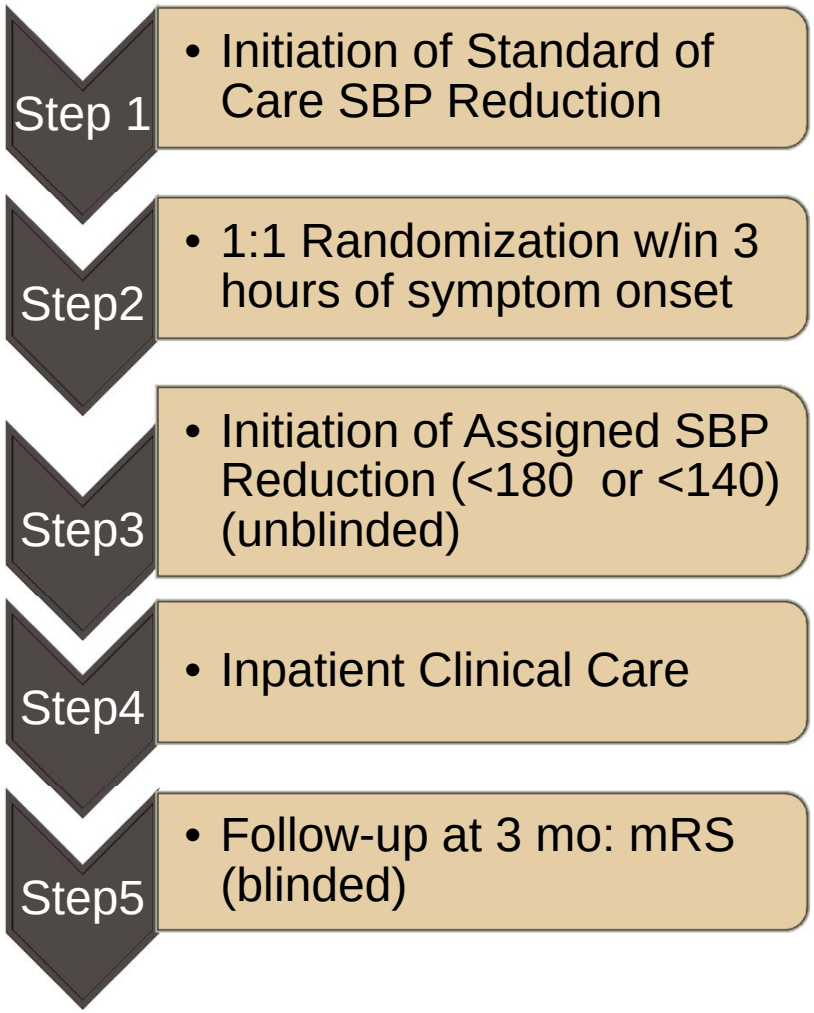
Clots in Legs or Stockings after Stroke

- **Aim:** Prevention of DVT in post-stroke immobile patients
- **Treatment:** thigh-lengths (TL) stockings vs below-knee (BK) stockings 24/7 during hospitalization (unblinded)
- **N:** 3,114
- **Sites:** 112
- **1^0 Outcome:** DVT on ultrasound scan at 30 days (blinded)
- **Co-intervention of interest:** anti-thrombotic drug use according to routine care (not standardized); intent to use these drugs were known prior to randomization
- **Results:** 6.3% (TL) vs 8.8% (BK), p=0.008 (signal detected)
- **Co-intervention Distribution:** 13% (TL) vs 13% (BK)

* CLOTS Trial Collaboration. *Annals of Internal Medicine* 2010;153:553-562.

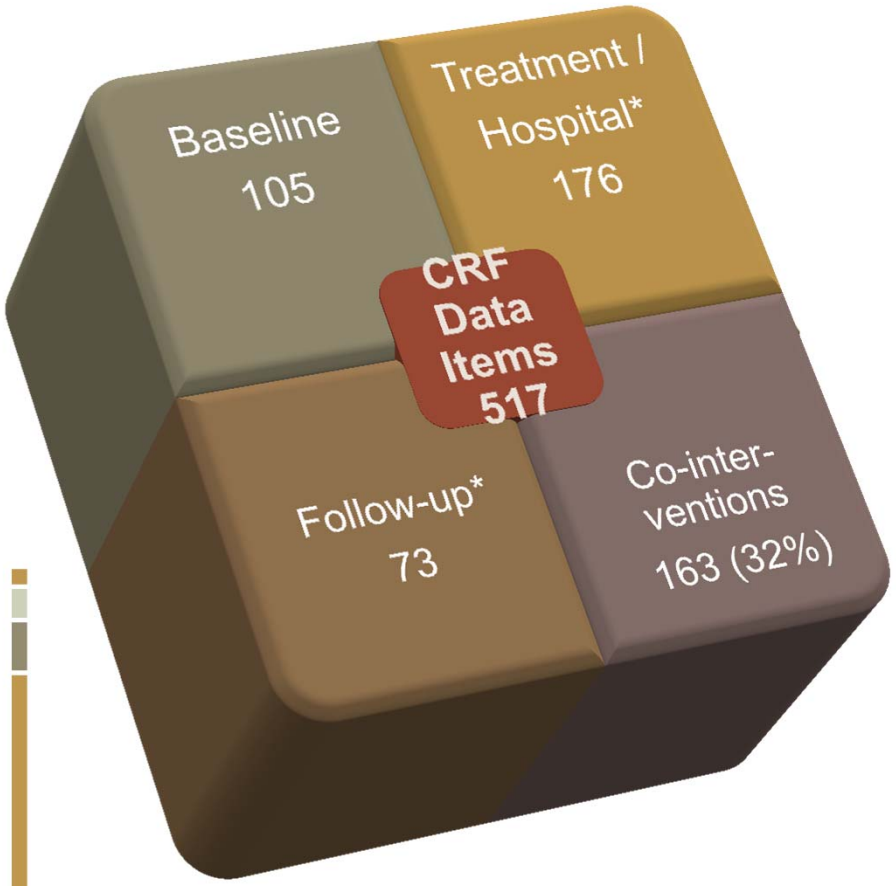
Example 2: ATACH II Trial

Antihypertensive Treatment for Acute Cerebral Hemorrhage



- **Aim:** Assess effect of intensive SBP reduction on functional outcome in ICH patients
- **Max N:** 1,280 (to date, 1)
- **Sites:** 100~150
- **Co-Intervention of interest:** Clinical management according to the AHA Guidelines during hospitalization (max 7 days); detailed in the protocol

ATACH II Co-Intervention Monitoring



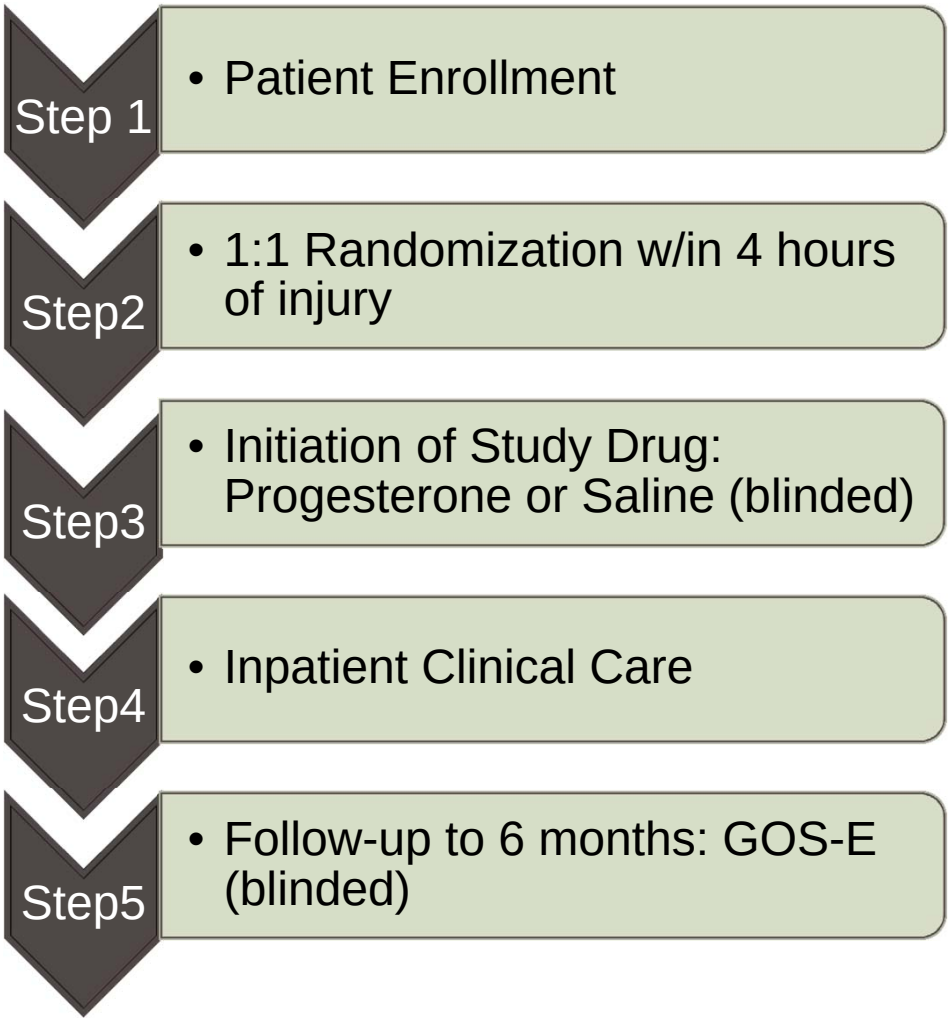
- Only certain key clinical parameters collected and data entered during hospitalization
- All baseline and inpatient data in the database reviewed by the external Independent Oversight Committee (IOC) for the first 3 subjects at each site
- Deviations ⇨ Discussions with the site; further review of random sample by IOC

*Exclude AEs, con-meds, con-procedures, central imaging

Example 3: ProTECT Trial

Progesterone for the Treatment of TBI

- **Aim:** Assess neuroprotective effect of progesterone in non-penetrating TBI patients
- **Max N:** 1,140 (to date, 220 randomized)
- **Sites:** ~25
- **Co-interventions of interest:** 13 key clinical parameters, HOURLY throughout hospitalization (max 30 days)



ProTECT Co-Interventions Monitoring (1)

- Any deviation - “transgression” - is collected and data entered on the Daily Checklist CRF, DAILY
- For each type of transgression: “Yes” on the Daily Checklist CRF triggers the Transgression CRF to be data entered DAILY

Transgressions

Pulse oximetry O_2 saturation < 90%
Arterial Blood Gas: PaO_2 < 100 mmHg
Arterial Blood Gas: $PaCO_2$ <35 or >45 mm Hg
Mean Arterial Pressure: MAP < 80 mmHg
Systolic BP <100mm Hg or >180mm Hg
CPP <60 mm Hg. Check n/a if not measured.
Glucose >180 mg/dl or <80 mg/dl
Temperature >38.3°C or <36.0°C (96.8° F)
ICP ≥ 20 mm Hg
INR > 1.4
Platelet count < 75 x 10^3 / mm^3
Hgb < 8 gm/dL
$PbtO_2$ <15 mmHg

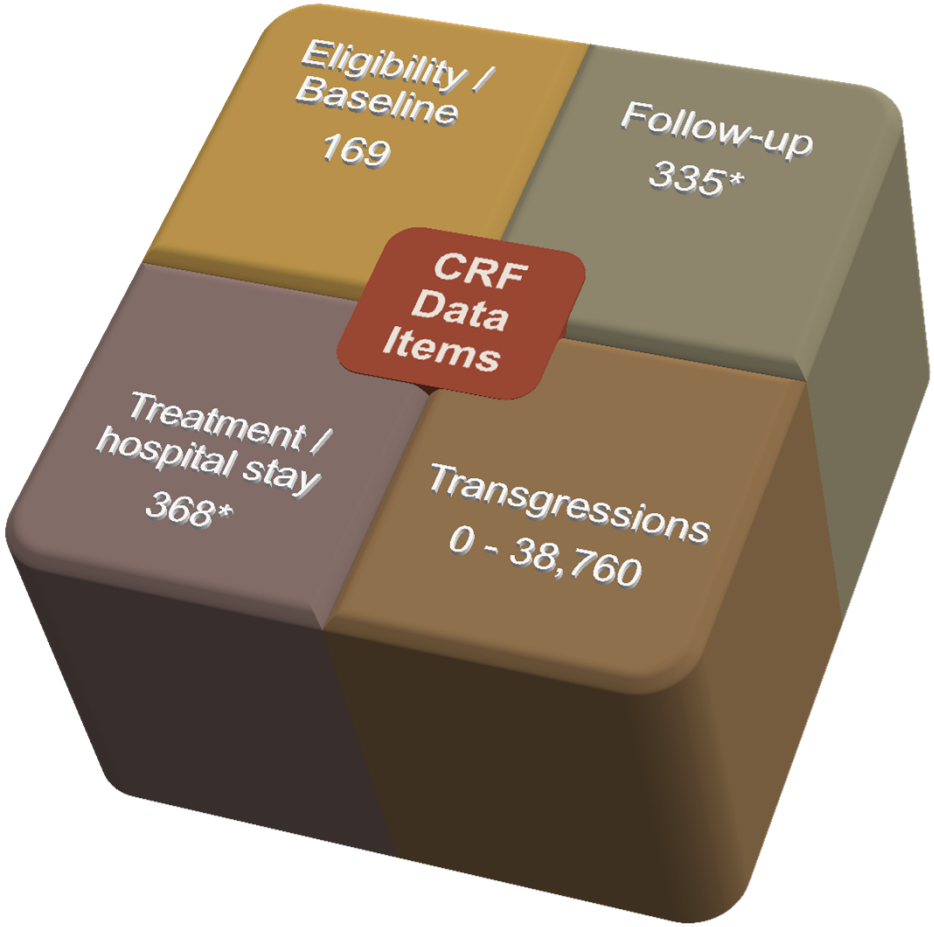
ProTECT Co-Interventions Monitoring (2)

Enter any instances where the study participant's oxygen saturation was < 90% for the previous 24 hour calendar day in the table below.									
1	Date of transgression:				___ ___ - ___ ___ ___ - ___ ___ ___ ___ (dd-mmm-yyyy)				
A. Hour	B. Status N=Normal A=Abnormal (complete QC and QD) U= Unknown	C. O_2 Sat (%)	D. Actions taken (Check all that apply)						E. Specify 'Other' intervention
			Sponta-neous recovery	Supple-mental O_2	Intuba-tion	Ventila-tion adjust-ment	Peep increase	Other (chest tube, etc.) - specify in next column	
00	__	___.__	☐	☐	☐	☐	☐	☐	
01	__	___.__	☐	☐	☐	☐	☐	☐	
02	__	___.__	☐	☐	☐	☐	☐	☐	
03	__	___.__	☐	☐	☐	☐	☐	☐	
04	__	___.__	☐	☐	☐	☐	☐	☐	

- The form has 24 rows
- Data reviewed DAILY by the Central Project Manager and the PI to determine whether they were clinically acceptable or not

ProTECT Co-Interventions Monitoring (3)

- Effort for a Clinical Site Study Coordinator to collect and enter transgression data: **10 min ~ 20+ hours per subject**
- Central Project Manager and PI daily reviews: **15~90 min per subject**
- # transgressions: **~8,000 in 219 subjects**
- Ave # of transgression data: **2,880 per subject ⇨ 77% (range: 100 to 11,620)**



*Exclude AEs, con-meds, con-procedures, central imaging

Thoughts on ProTECT

- How will we use all these co-intervention data?
- Will the Trial see the signal with less “noise”?
- If positive, can the Trial results be generalizable?
- Could we have considered stratifying randomization by co-intervention (like CLOTS-2)?
- Could we use EHR to transfer much of these data into the study database?
- Could we look for a smaller effect with larger N to compensate for the unequal application of co-interventions?

Summary

	Co-Intervention	Monitored/ Collected	Standardized?	Enforced?
CLOTS-2	Anti-thrombotic use	Y	N	N
ATACH II	Clinical care parameters	Y (some)	Y	Y (moderately)
ProTECT	Clinical care parameters	Y (OODLES)	Y	Y (strictly)

- Issue 1: Should we standardize co-interventions or do we rely on randomization to equalize their effect?
- Issue 2: How much do we monitor and enforce standardization?
- Consider feasibility of implementing rigid standardizations – e.g., will surgeons change their ways?
- Weigh the costs vs benefits - financial, stress/burden on trial staff
- Potential for trial fatigue – hindrance to recruitment, timely data collection and entry

ACKNOWLEDGEMENT

Codruta Chiuzan, Cassidy Conner, and Sharon Yeatts at MUSC for providing ProTECT Trial information

NIH R01 NS062778 (ProTECT Trial); and U01 NS062091 and U01 NS061861 (ATACH II Trial)

THANK YOU!

Society for Clinical Trials 32nd Annual Meeting
May 17, 2011