The Chilled Platelet Study (CHIPS): An Adaptive, Storage-duration Finding Trial

Advancing the Use of Complex Innovative Designs in Clinical Trials: From Pilot to Practice
Silver Spring, MD
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Disclosures

- Academic Affiliation and Employment
  - County of Los Angeles, Department of Health Services
  - Berry Consultants, LLC (multiple clients)
  - David Geffen School of Medicine at UCLA
  - Lundquist Institute for Biomedical Innovation
- Special Government Employee (inactive)
  - Food and Drug Administration/CBER
- Other
  - Statistical Editor, *JAMA*

CHIPS Facts

- Principal Investigators:
  - Philip C. Spinella, MD, University of Pittsburgh (lead)
  - Marie E. Steiner, MD, University of Minnesota
  - Nicole D. Zantek, MD, University of Minnesota
- Statistical Design and Implementation: Nick Berry, PhD, Anna Bosse, PhD, Liz Krachey, PhD, Roger J. Lewis, MD, PhD, Anna McGlothlin, PhD, Kert Viele, PhD, Berry Consultants, LLC
- Data Coordinating Center: John VanBuren, PhD (lead), Univ. of Utah
- Registration: https://www.clinicaltrials.gov/study/NCT04834414
- Funding: US Army Medical Research and Development Command (USAMRDC) through the U.S. Army Medical Research Acquisition Activity (USAMRAA)

Background: Platelet Storage and Availability

- In the US, platelet components are generally stored at 20 to 24 degrees C (room temperature platelets, RTP) for 5-7 days, depending on the storage container and measures to control bacterial risk (21 CFR 610.53(b)). … For RTP, the dating period is currently limited to 5 days unless dating is extended (up to 7 days) using an FDA cleared bacterial testing device labeled as a safety measure. [FDA BPAC 2019]
- Rural hospitals frequently are unable to maintain platelet availability
- The American Red Cross has 249 hospital customers (approx. 10% of total customers served) to whom RBCs are distributed but not PLTs. [Young PP, et al. Transfusion. 2020; 60:2474–2475]
- Longer storage duration, if safe, may increase platelet availability

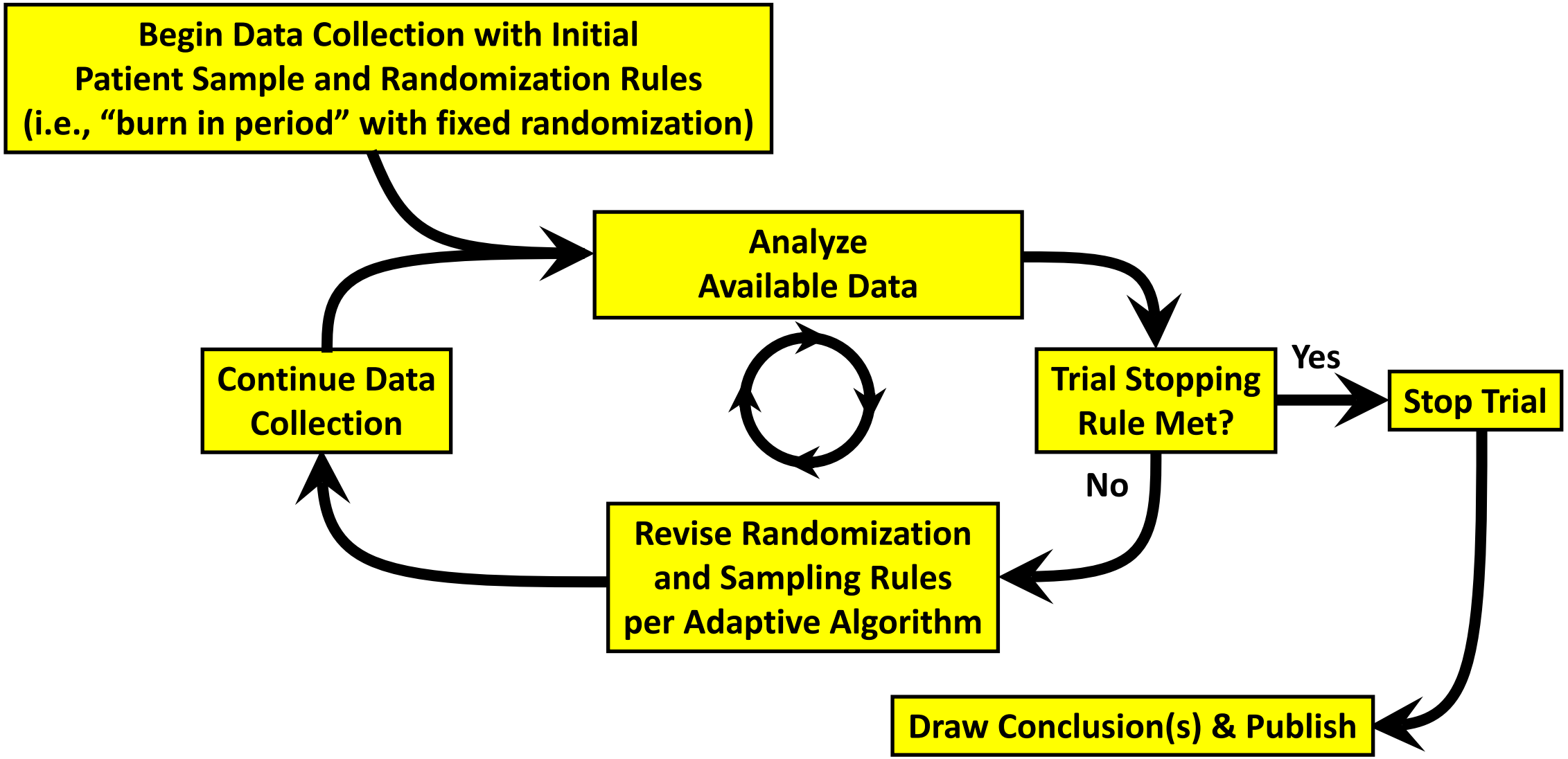
CHIPS Objectives

- Primary Objective:
  - Platelets stored at 4°C (CSP) are non-inferior (or superior) in hemostatic **efficacy** to standard, room temperature platelets stored at 22°C when transfused to adult and pediatric patients requiring complex cardiac surgery who are actively bleeding.
- Secondary Objectives:
  - To determine **maximum storage duration** (up to 21 days) at 4°C that maintains non-inferiority.
  - To demonstrate comparable **safety** of administration of platelets stored at 4°C versus platelets stored at 22°C to adult and pediatric patients requiring cardiac surgery who are actively bleeding.

Motivation and Advantages for Adaptive Design

- When designing a clinical trial there is substantial uncertainty (e.g., best measure of benefit, outcome event rates, best treatment or dose, best duration, responsive target population)
- Once patients are enrolled and at least some outcomes are known, information accumulates that reduces uncertainty
- Adaptive clinical trials are designed to take advantage of this accumulating information, by allowing modification to key trial parameters in response to accumulating information, and according to prespecified rules
- This can increase the probability of getting the right answer at the end of the trial or improve trial efficiency

The Adaptive Process for a Randomized Clinical Trial



CHIPS Design

- 2:1 (CSP:RTP) fixed randomization
- Primary endpoint: 5-level bleeding score (lower scores better)
- Arms
  - RTP considered a homogeneous treatment
  - CSP storage defined by the weighted mean storage duration of administered platelets
- Non-inferiority margin of 1 unit on bleeding score, with gated test for superiority—type I error control demonstrated by simulation
- Maximum storage duration for CSP adaptively changed according to prespecified rules
- Interim analyses every 200 participants, maximum sample size of 1000

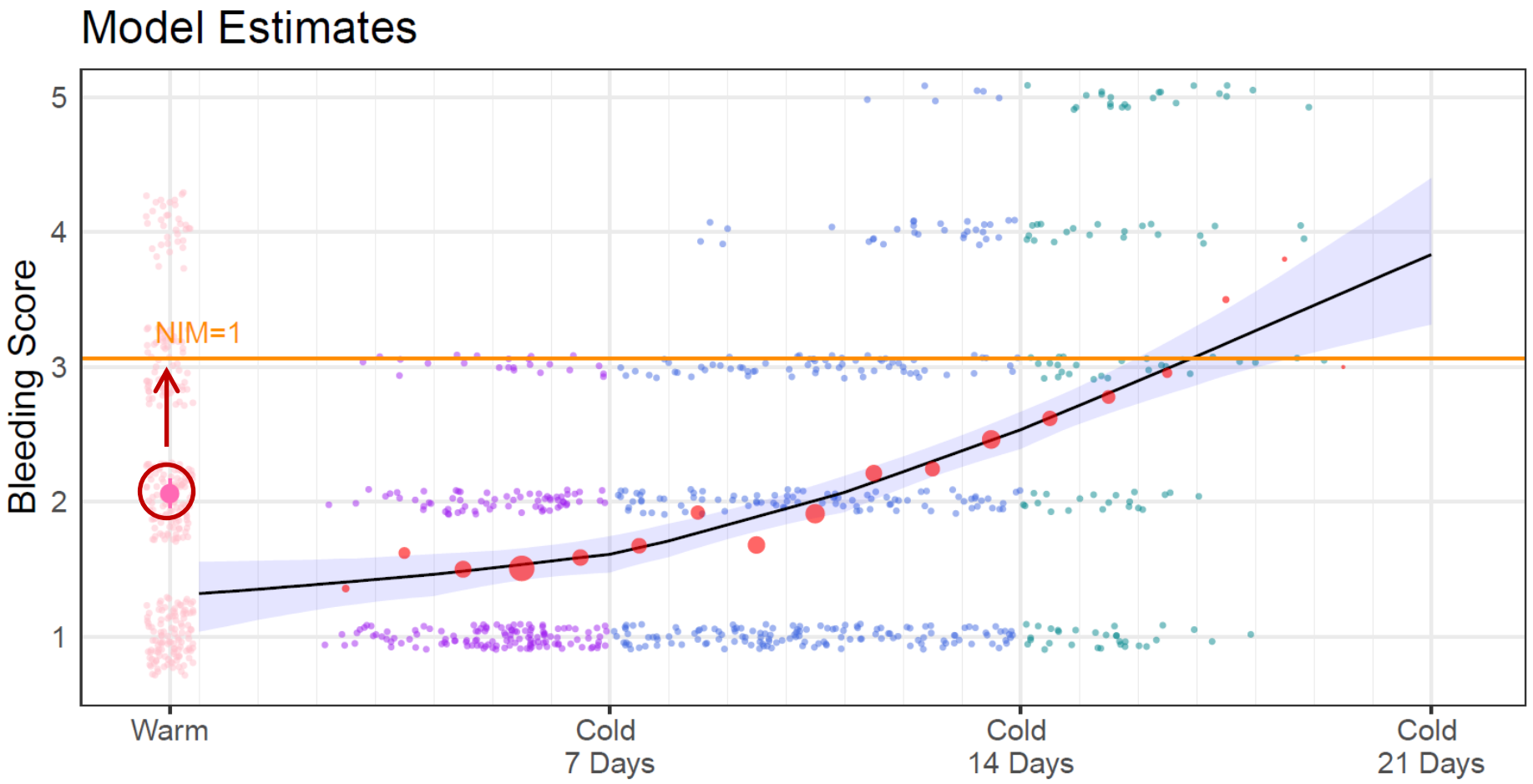
Basic Model, Hypotheses, Quantities of Interest

- True mean hemostatic efficacy score for CSP, as function of storage time: $\eta(x)$ where x is storage duration in days (smaller score is better)
- μ_{warm} true mean hemostatic efficacy score for RT platelets
- $\eta(x)$ modeled as monotonic piece-wise linear regression model
- Noninformative priors
- Hypotheses
  - H_0: No $\eta(x) < (\mu_{warm} + 1)$ for $x \geq 7$ days
  - H_1: At least one $\eta(x) < (\mu_{warm} + 1)$ for $x \geq 7$ days
- Final analysis: evaluate
  - $Pr(NI)_x = Pr(\eta(x) < (\mu_{warm} + 1)) > 0.975$ for $x \geq 7$ and if so, evaluate
  - $Pr(SUP)_x = Pr(\eta(x) < \mu_{warm} - \delta_x) > 0.983$ (corrections for multiplicities, model form)

Interim Duration Adaptation and Futility Rules

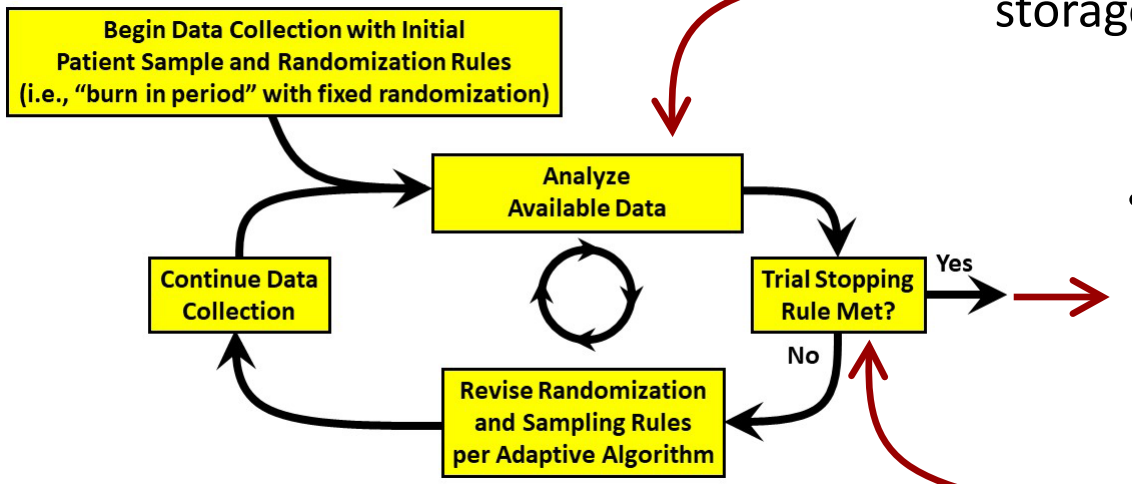
- Find the largest cold storage duration for which $\Pr(NI)_x > 0.33$, $X_{candidate}$
- If $X_{candidate} < 7$ days and $\Pr(NI)_7 < 0.10$ then stop trial for futility
- If $X_{candidate} \geq 7$ days then set new maximum storage duration as the minimum of
  - $X_{candidate}$
  - Current maximum duration + 5 days
  - 21 days
- Rules ensure no randomization unless probability of NI is at least 0.33, increases in duration ≤ 5 days of storage time, and maximum of 21 days
- No early stopping for success

Example Simulated Data



The Overall CHIPS Adaptive Design

- Initial maximum cold storage duration = 7 days
- First interim analysis after 200 participants enrolled and transfused

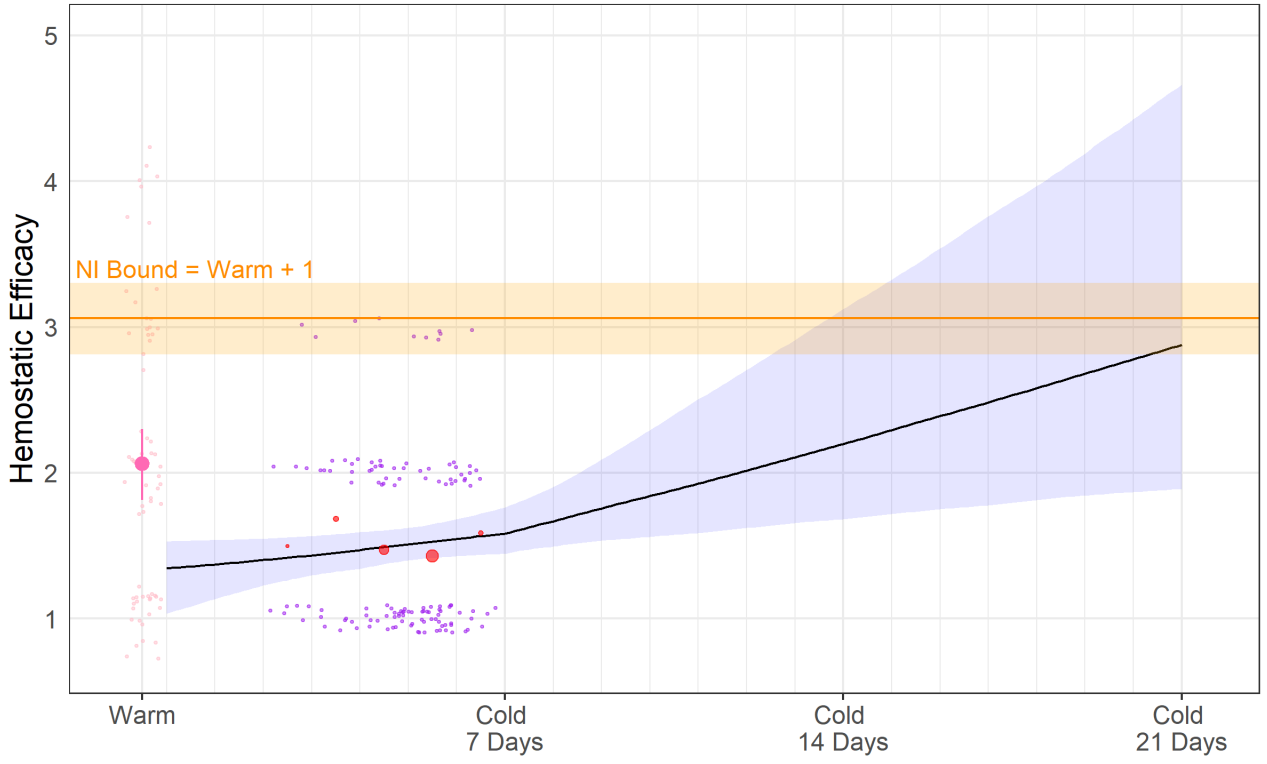


- Fit model for CSP efficacy as a function of cold storage duration
- If N = 1000
  - Evaluate $\Pr(NI)_x > 0.975$
  - If positive, evaluate $\Pr(SUP)_x > 0.983$
- Apply futility rules
- Revise upper limit for cold storage duration
- Next interim analysis after another 200 participants enrolled and treated

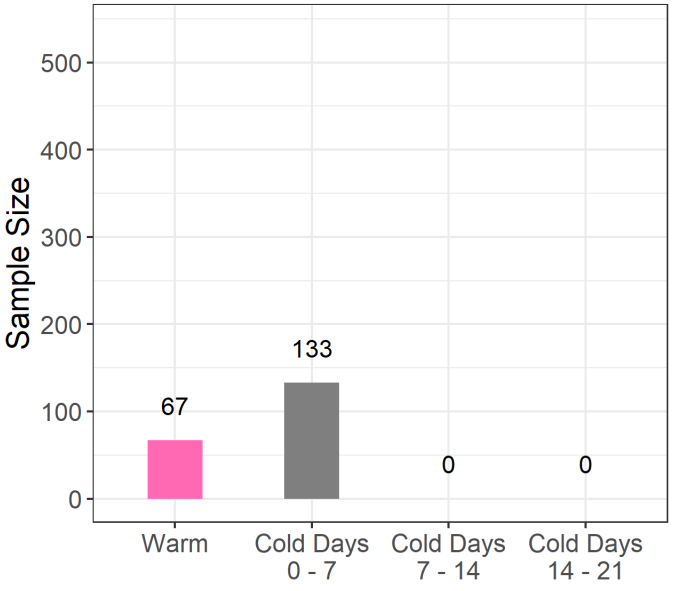
Example Trial

Interim 1, 200 Subjects Total

Model Estimates



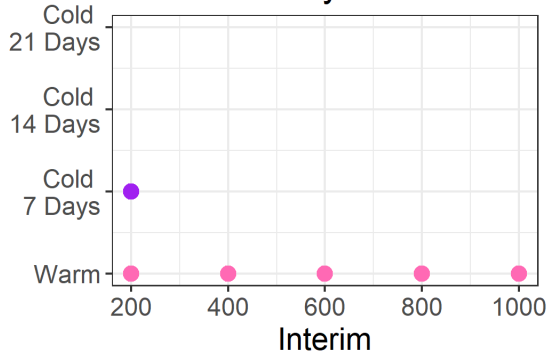
Overall Sample Size



Current Max Cold Days: 7

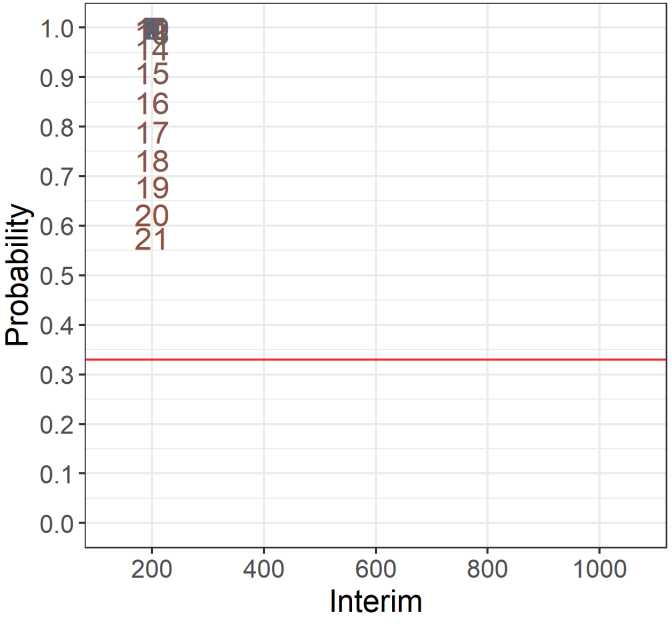
Interim Decision: Go to max allowed duration

Enrollment by Interim



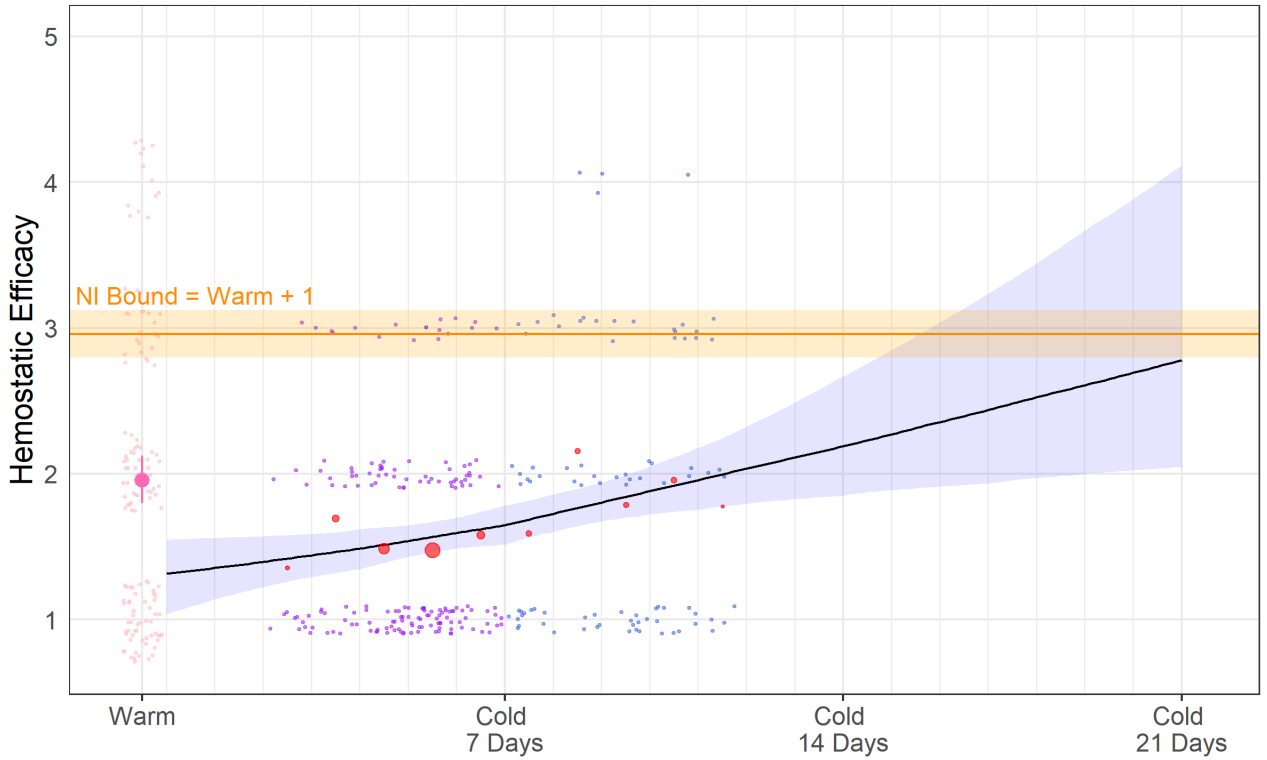
Cold Days	Mean	95% CI	Pr(NI)
Warm	2.06	(1.81,2.3)	NA
0	1.33	(1.04,1.53)	1.000
7	1.59	(1.44,1.76)	1.000
14	2.27	(1.68,3.12)	0.958
16	2.47	(1.75,3.54)	0.849
17	2.58	(1.78,3.76)	0.790
18	2.68	(1.81,3.97)	0.732
19	2.79	(1.84,4.19)	0.679
20	2.90	(1.87,4.42)	0.622
21	3.01	(1.89,4.66)	0.576

Pr(NI) for each duration

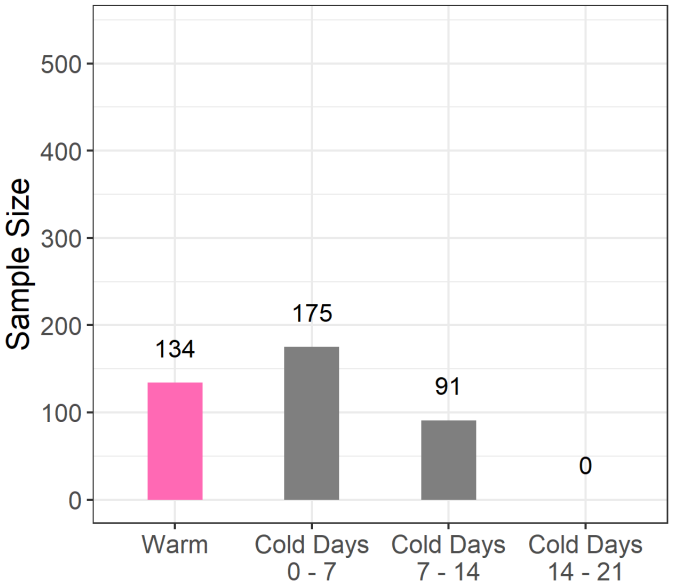


Interim 2, 400 Subjects Total

Model Estimates



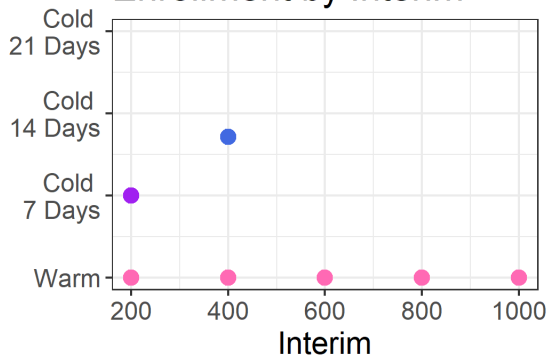
Overall Sample Size



Current Max Cold Days: 12

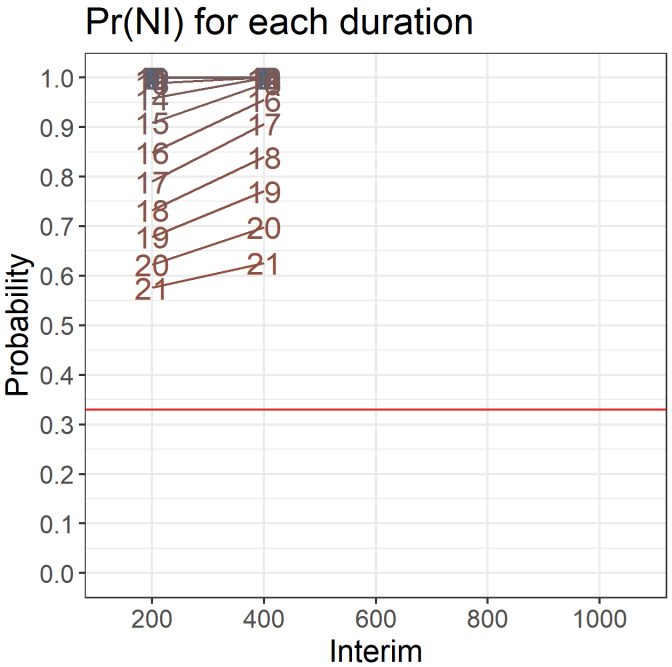
Interim Decision: Go to max allowed duration

Enrollment by Interim



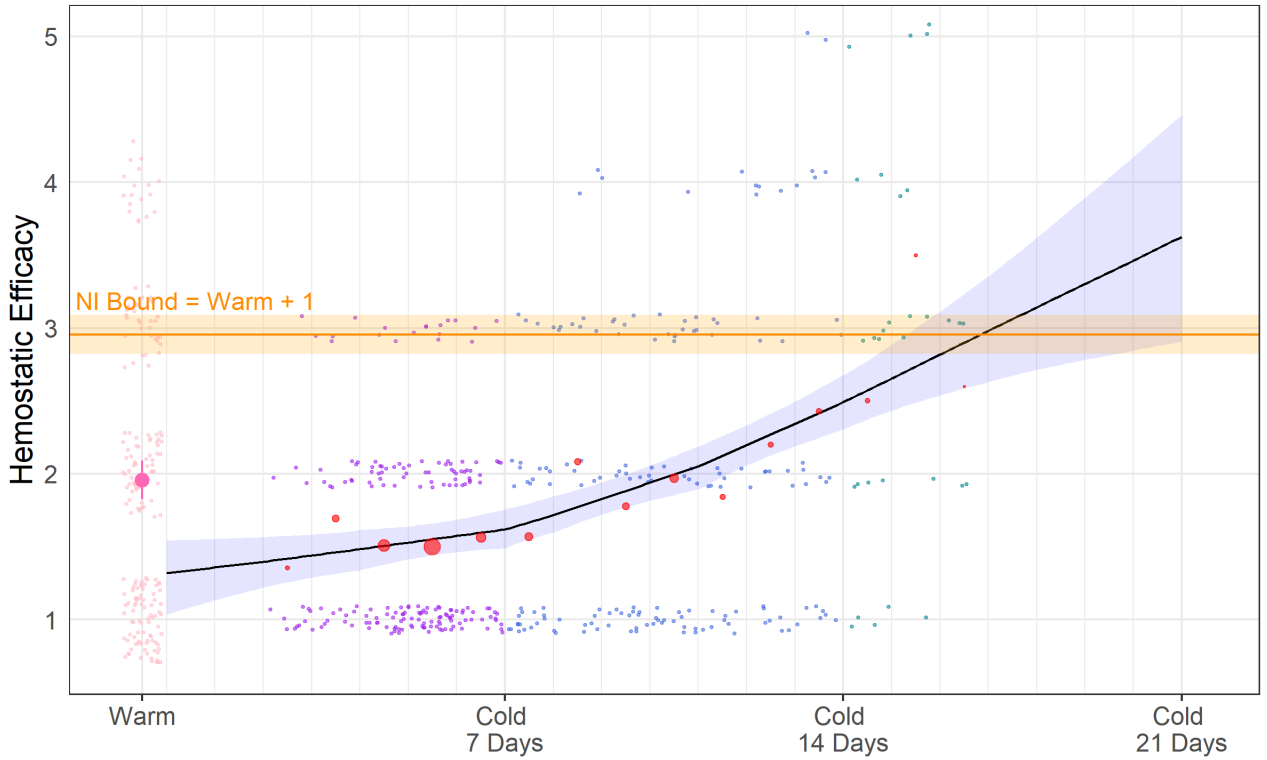
Cold Days	Mean	95% CI	Pr(NI)
Warm	1.96	(1.8,2.12)	NA
0	1.31	(1.04,1.55)	1.000
7	1.65	(1.51,1.78)	1.000
14	2.21	(1.85,2.67)	0.999
18	2.57	(1.97,3.44)	0.840
19	2.67	(2,3.67)	0.771
20	2.76	(2.02,3.89)	0.698
21	2.86	(2.05,4.12)	0.626

Pr(NI) for each duration

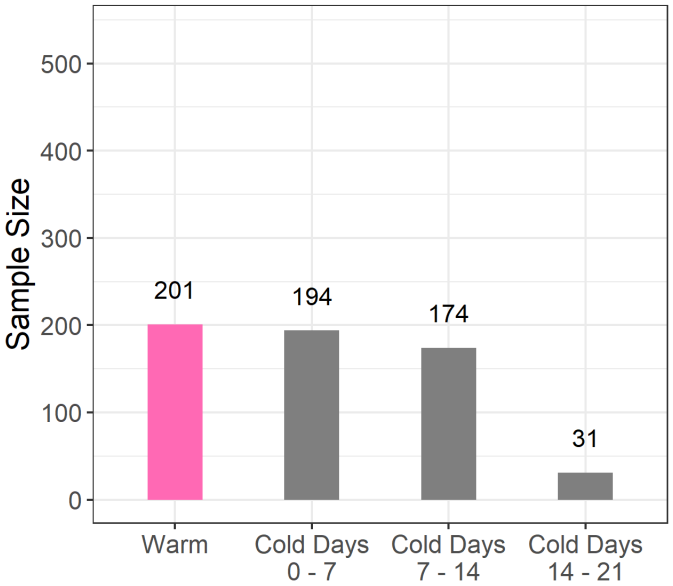


Interim 3, 600 Subjects Total

Model Estimates



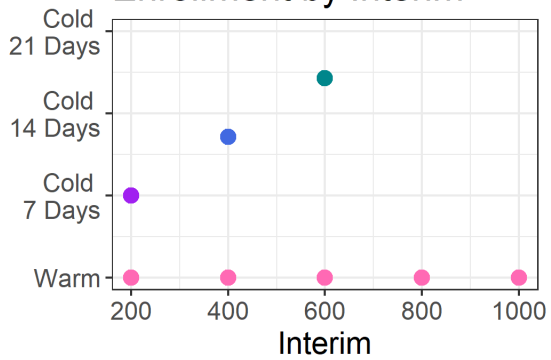
Overall Sample Size



Current Max Cold Days: 17

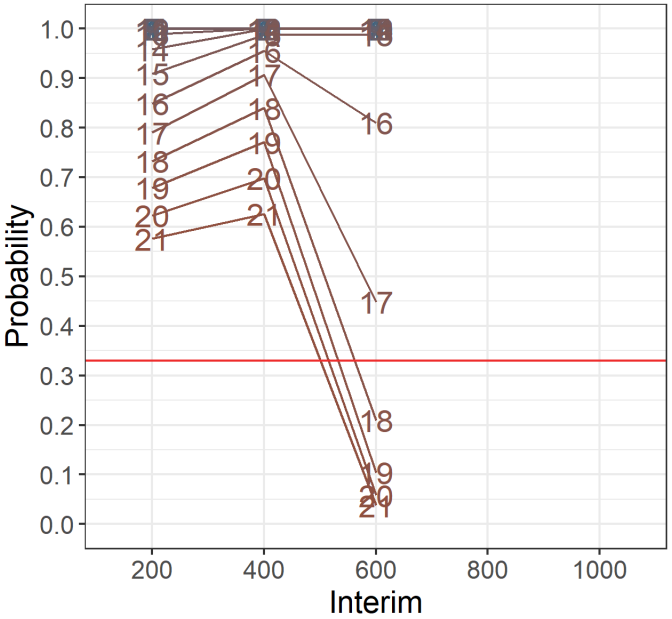
Interim Decision: Go to model chosen duration

Enrollment by Interim



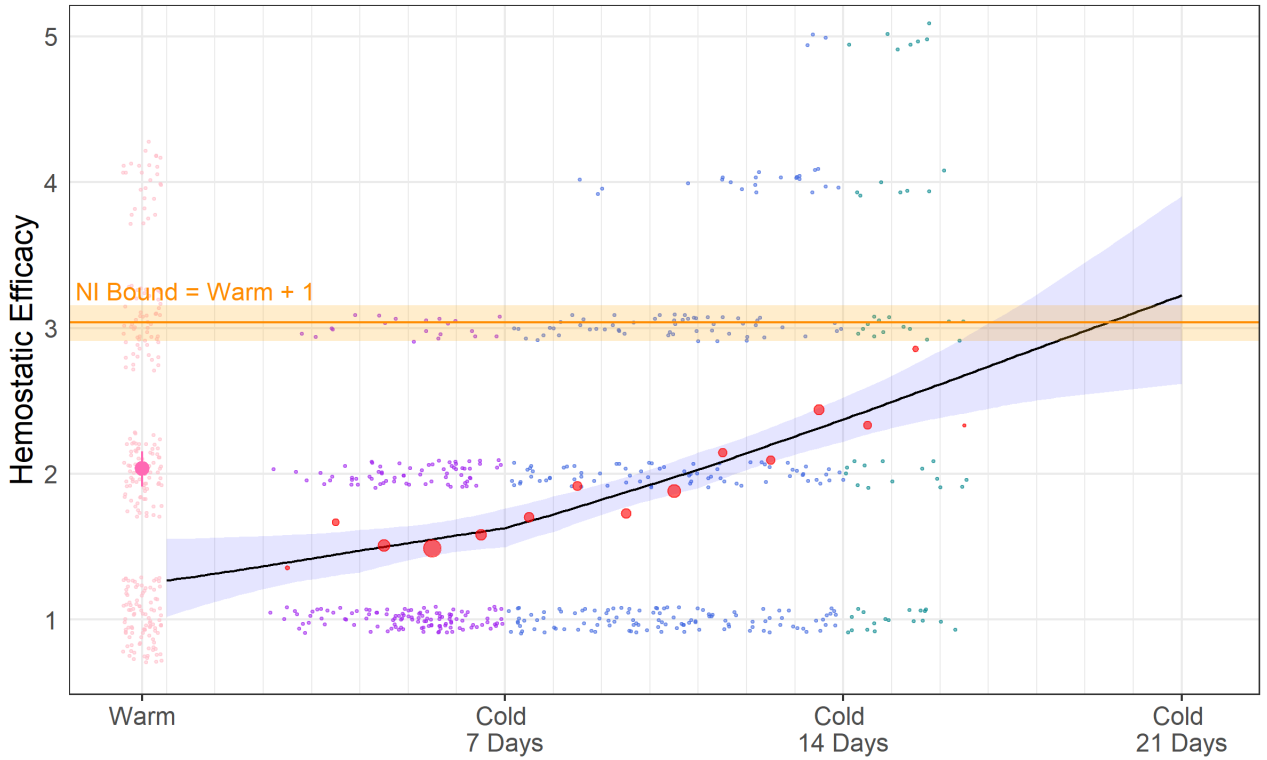
Cold Days	Mean	95% CI	Pr(NI)
Warm	1.96	(1.82,2.09)	NA
0	1.31	(1.03,1.54)	1.000
7	1.62	(1.49,1.76)	1.000
14	2.49	(2.3,2.68)	1.000
16	2.82	(2.54,3.11)	0.810
17	2.98	(2.63,3.35)	0.448
18	3.15	(2.71,3.62)	0.210
19	3.31	(2.78,3.89)	0.104
21	3.64	(2.91,4.46)	0.038

Pr(NI) for each duration

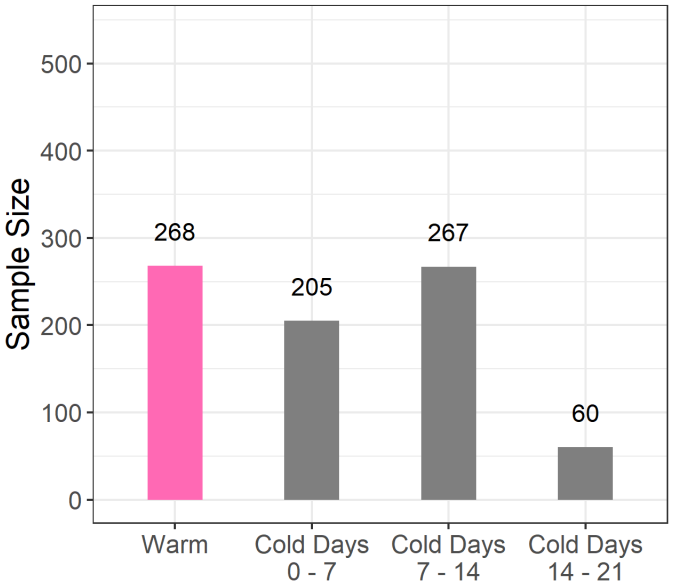


Interim 4, 800 Subjects Total

Model Estimates



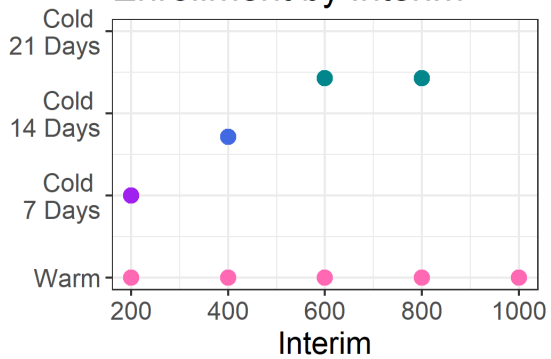
Overall Sample Size



Current Max Cold Days: 17

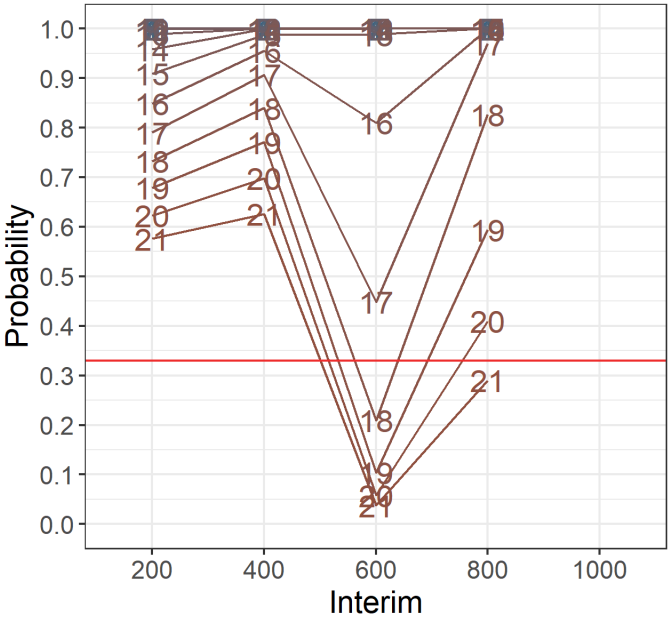
Interim Decision: Go to model chosen duration

Enrollment by Interim



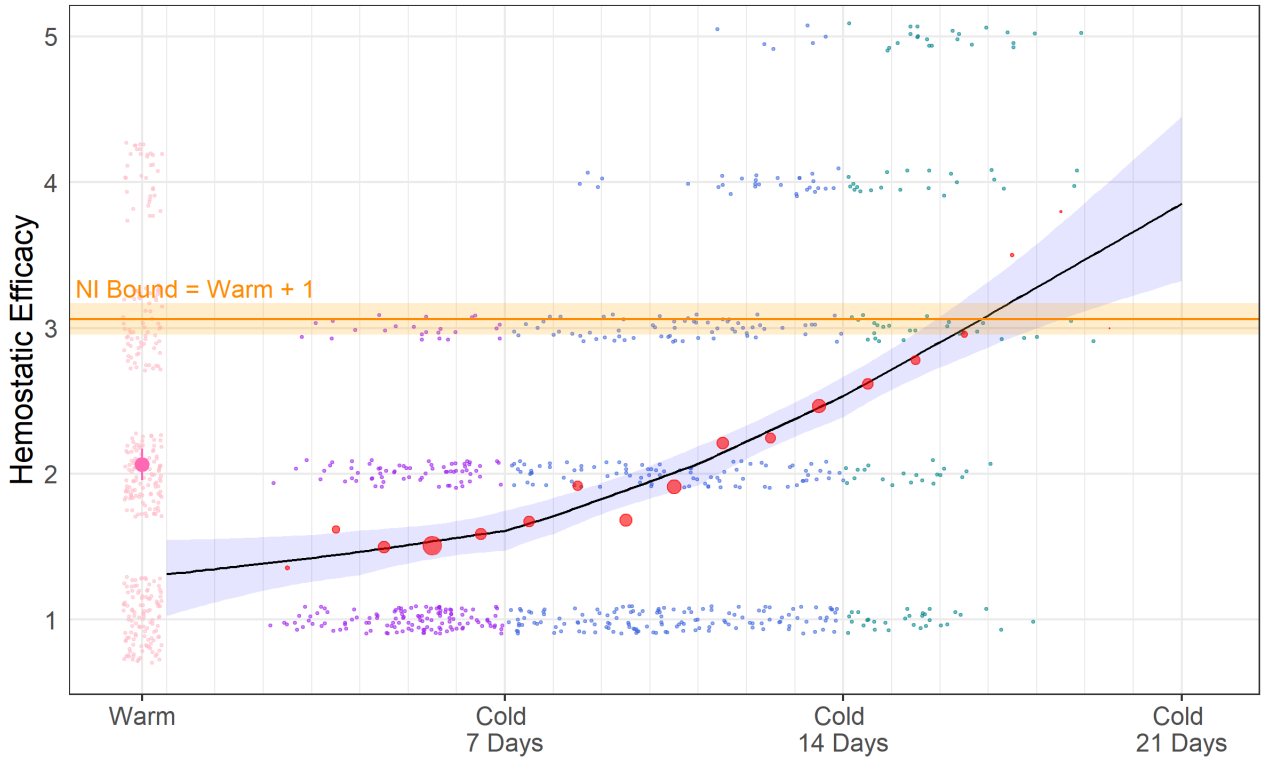
Cold Days	Mean	95% CI	Pr(NI)
Warm	2.04	(1.91,2.15)	NA
0	1.27	(1.02,1.55)	1.000
7	1.63	(1.5,1.76)	1.000
14	2.37	(2.22,2.52)	1.000
18	2.86	(2.5,3.23)	0.827
19	2.98	(2.54,3.45)	0.594
20	3.11	(2.58,3.67)	0.410
21	3.23	(2.62,3.9)	0.290

Pr(NI) for each duration

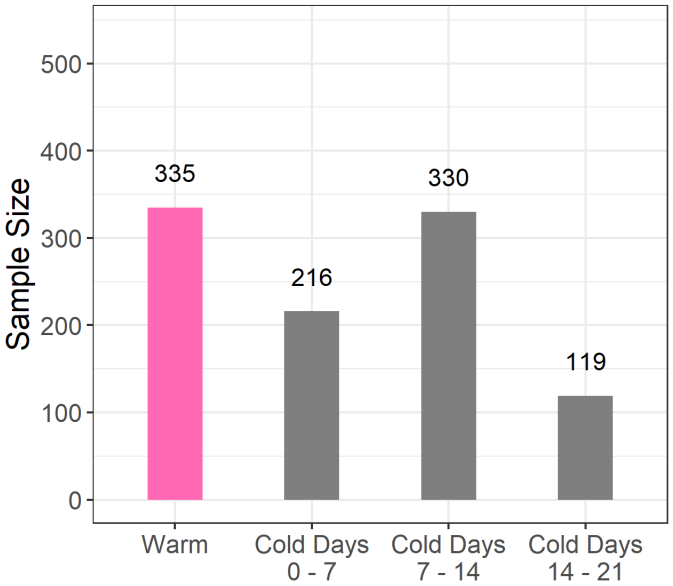


Interim 5, 1000 Subjects Total

Model Estimates



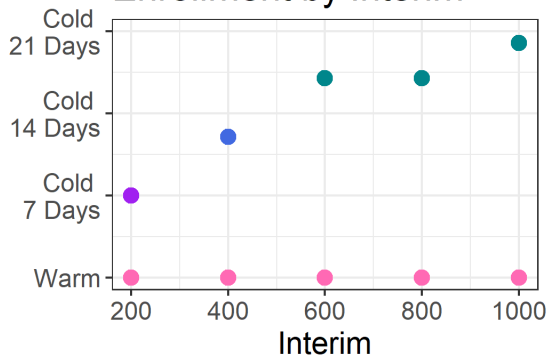
Overall Sample Size



Current Max Cold Days: 20

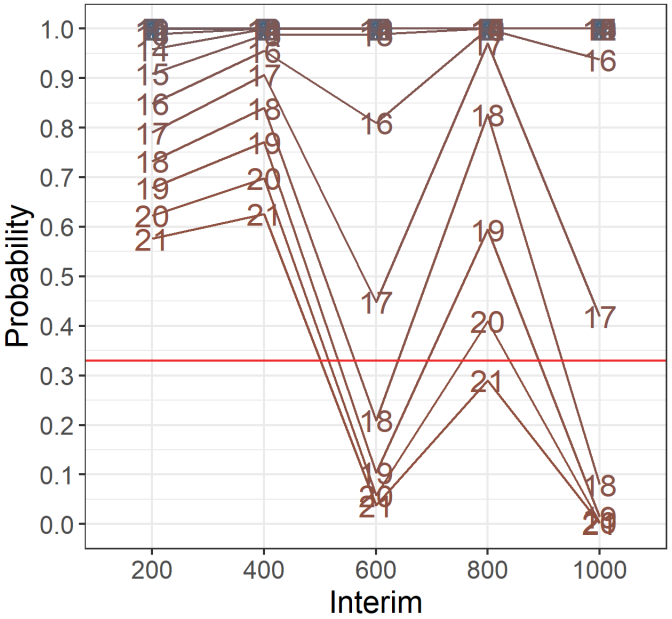
Interim Decision: final sample size

Enrollment by Interim



Cold Days	Mean	95% CI	Pr(NI)
Warm	2.06	(1.96,2.17)	NA
0	1.30	(1.03,1.55)	1.000
7	1.61	(1.47,1.75)	1.000
14	2.53	(2.39,2.66)	1.000
17	3.09	(2.87,3.32)	0.419
18	3.28	(3,3.58)	0.080
21	3.86	(3.32,4.45)	0.002

Pr(NI) for each duration



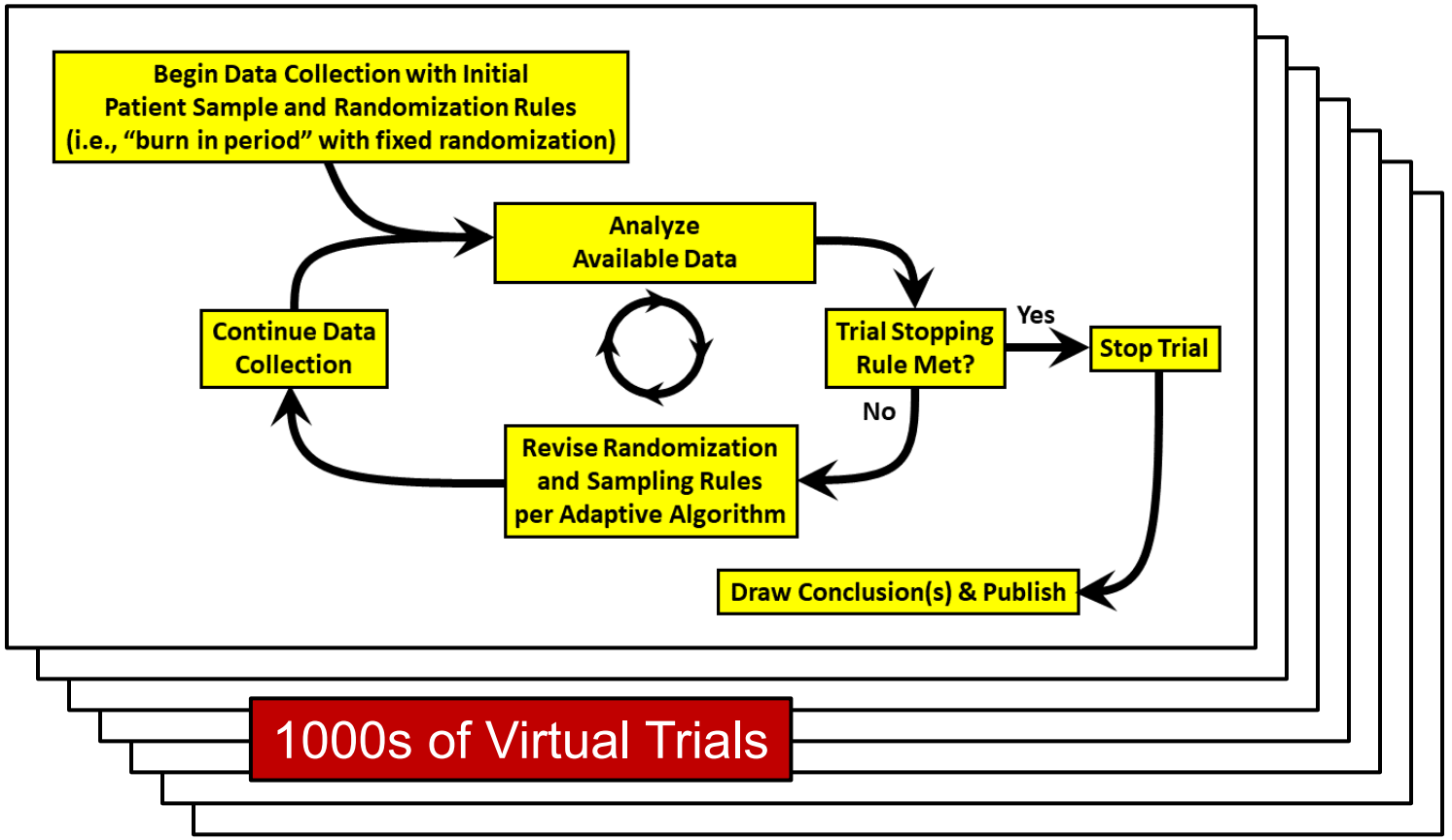
Primary Trial Analysis

At N = 1000 patients, we make our final conclusion. Possibilities:

- No cold storage duration of 7 or more days is non-inferior to warm
- Chilled platelets are non-inferior to warm stored platelets up to ***X*** days with possible values of X in range 7 to 21 days
- Maximum non-inferior duration is chosen to be the largest duration satisfying $\Pr(NI)_x > 0.975$
- If non-inferiority is demonstrated, then also evaluate $\Pr(SUP^*)_x > 0.983$, where SUP^* = adjusted super-superiority requirement

Trial Simulation

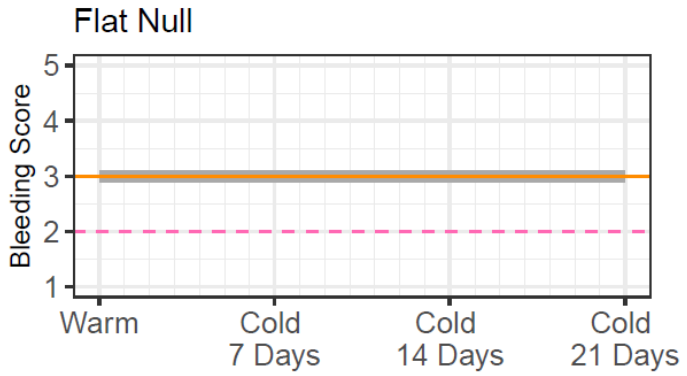
Assumed "reality" including population, accrual, efficacy, safety



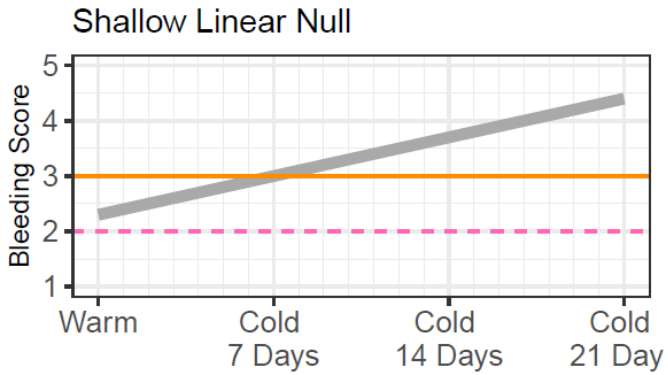
Single Example Trials

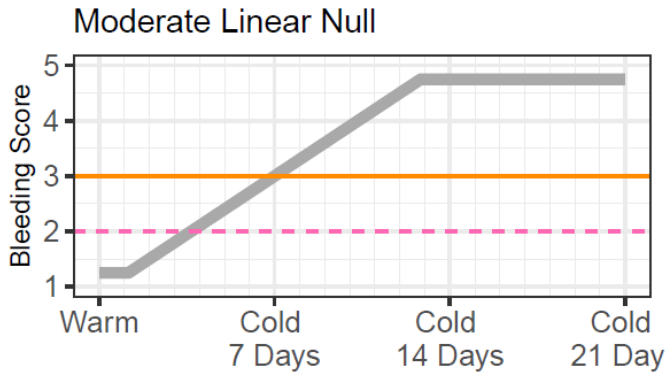
Operating Characteristics (e.g., error rates, sample size)

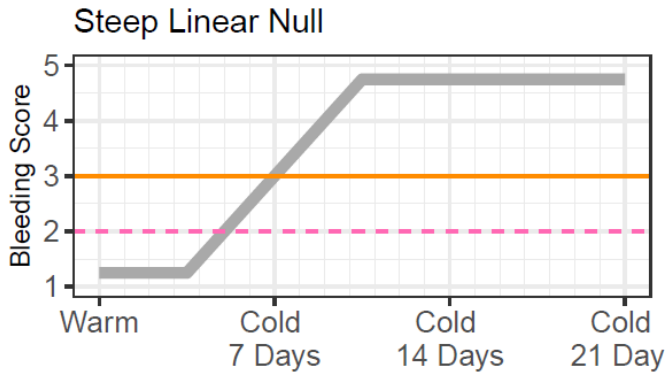
Type I Error Control

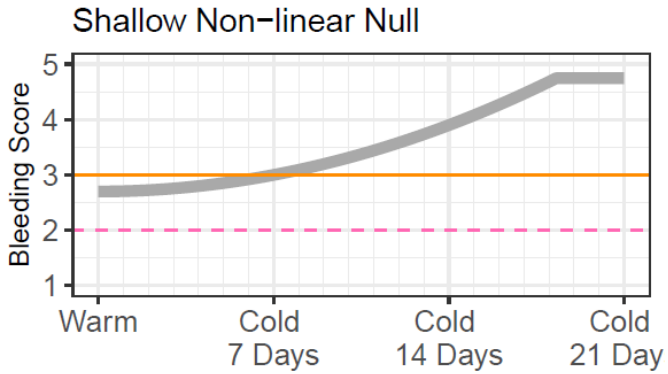


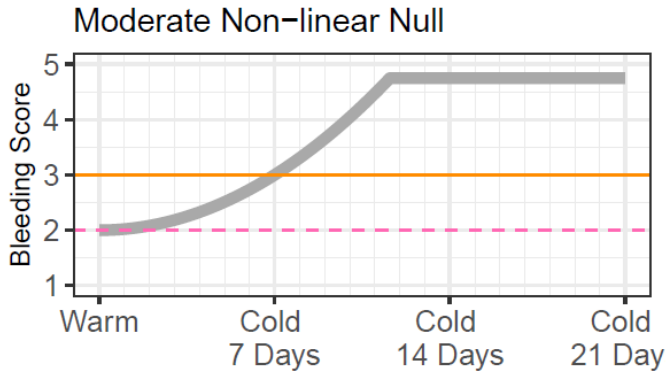
- Type I error was controlled under many different null scenarios
- Each of these scenarios has cold platelet efficacy exactly equal to NIM at 7 days.

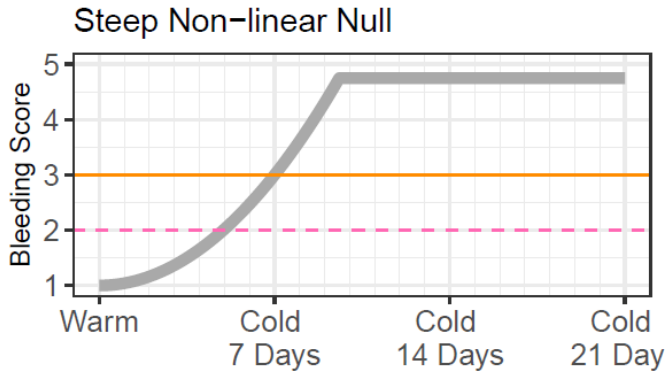




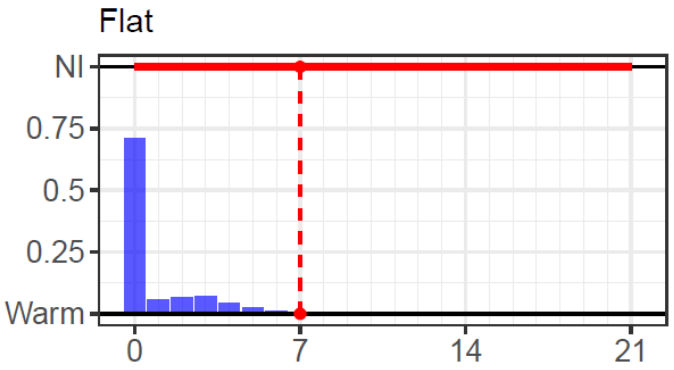


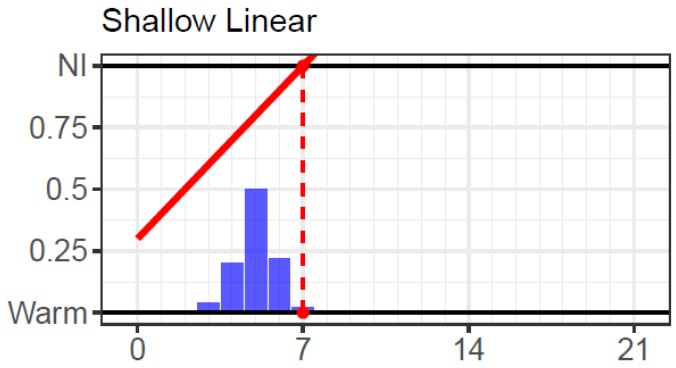


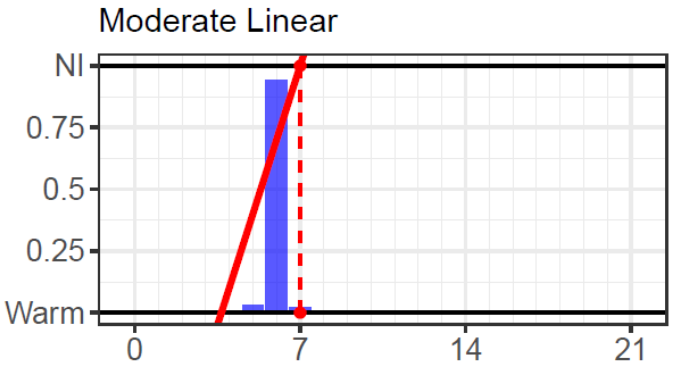


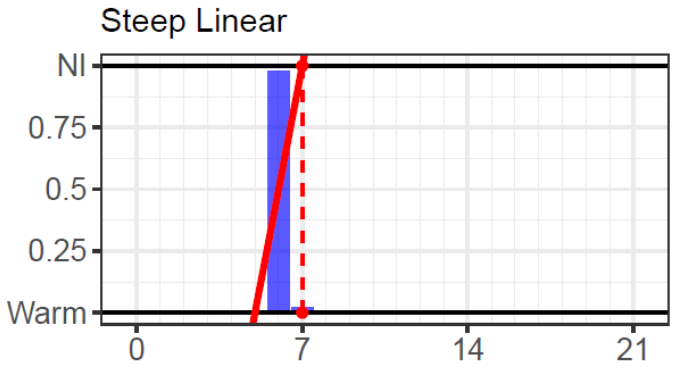


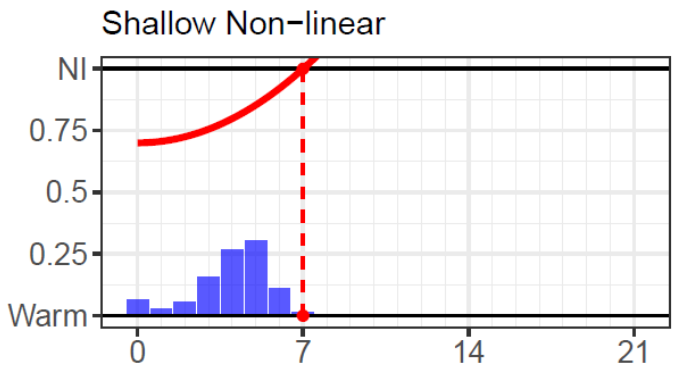
Type I Error Control (contd)

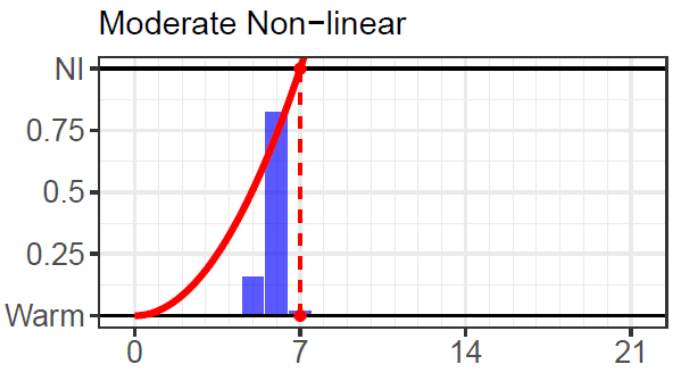


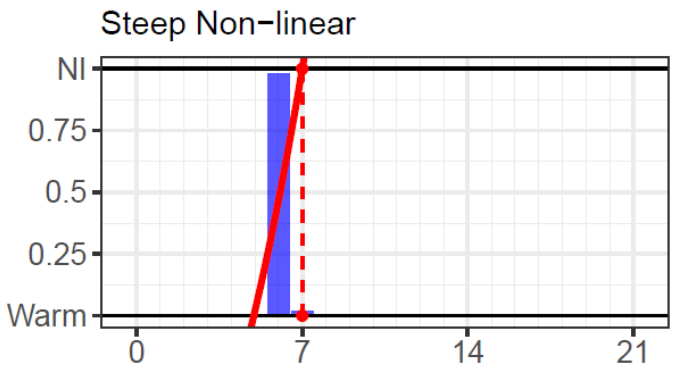








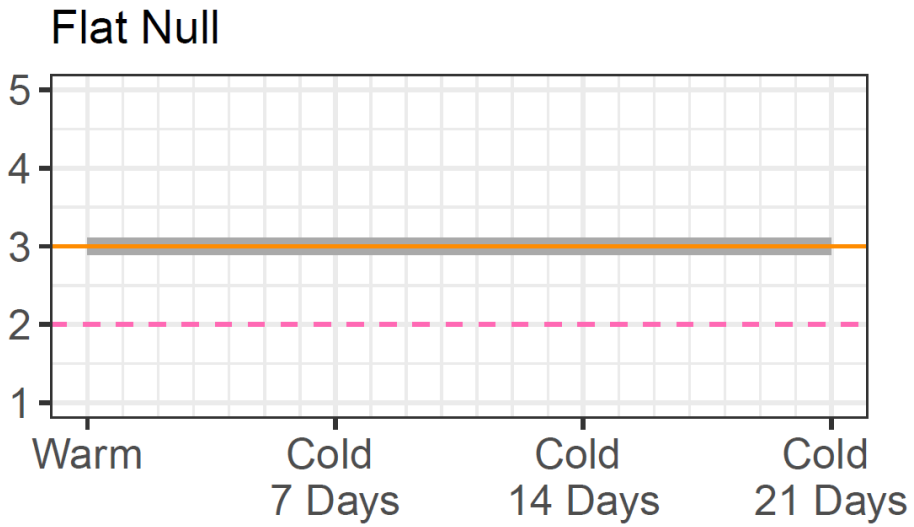




- Type I error was controlled under many different null scenarios
- Maximum cold storage duration reliably identified as < 7 days

Futility Rule Performance

- If at an interim analysis the probability that chilled platelets stored for 7 days are non-inferior to warm platelets is < 10%, then the trial will stop enrolling for futility
- In the null scenario in which cold stored platelet efficacy is equal to the non-inferiority cutoff of warm platelets, the trial stops at an early interim analysis ~ 50% of the time



Stops for futility at:

N = 200: 26%

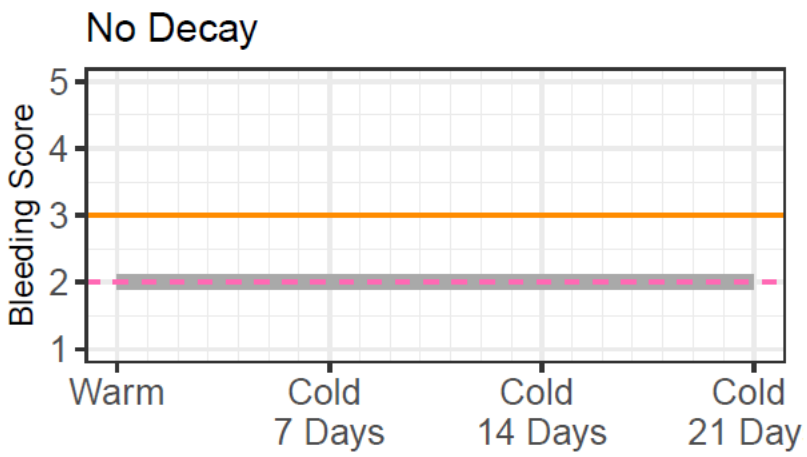
N = 400: 14%

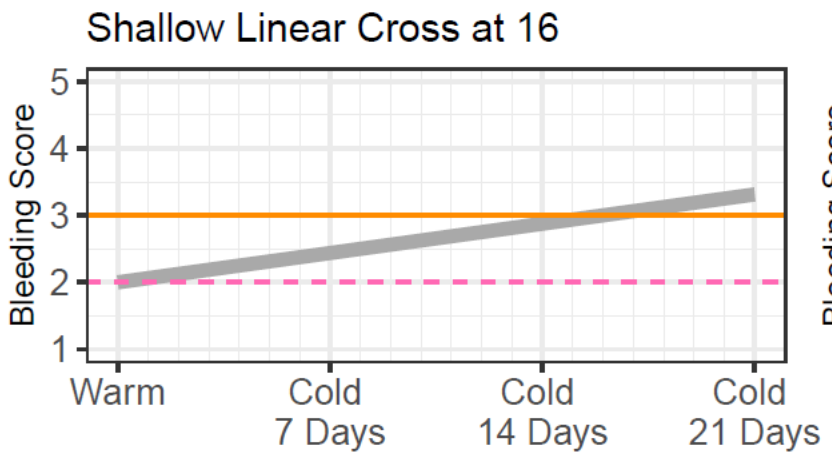
N = 600: 9%

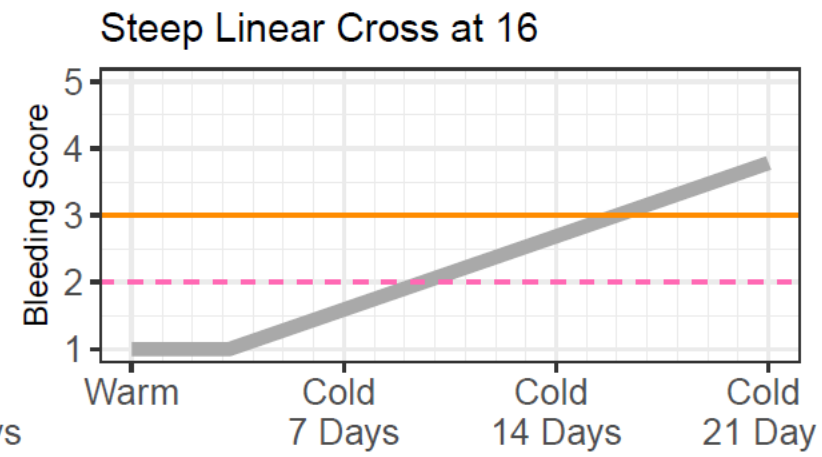
N = 800: 6%

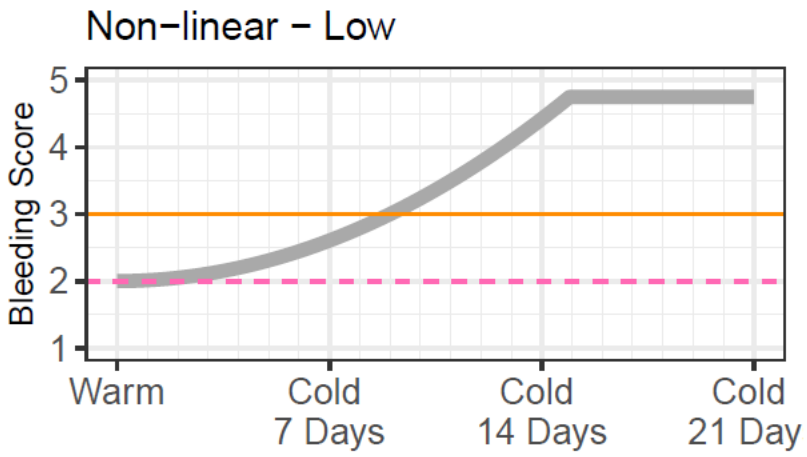
Continues to final analysis: 45%

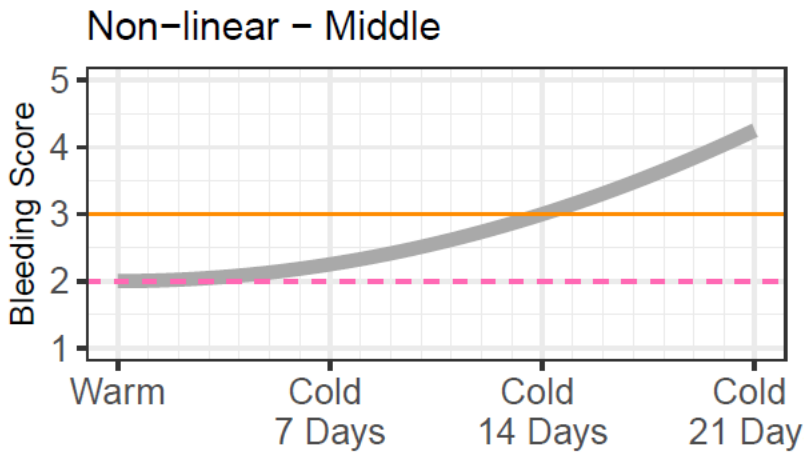
Alternative Scenarios

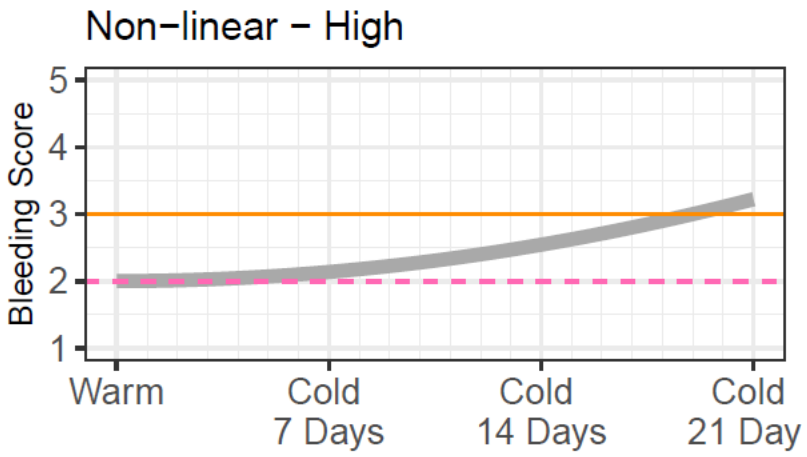




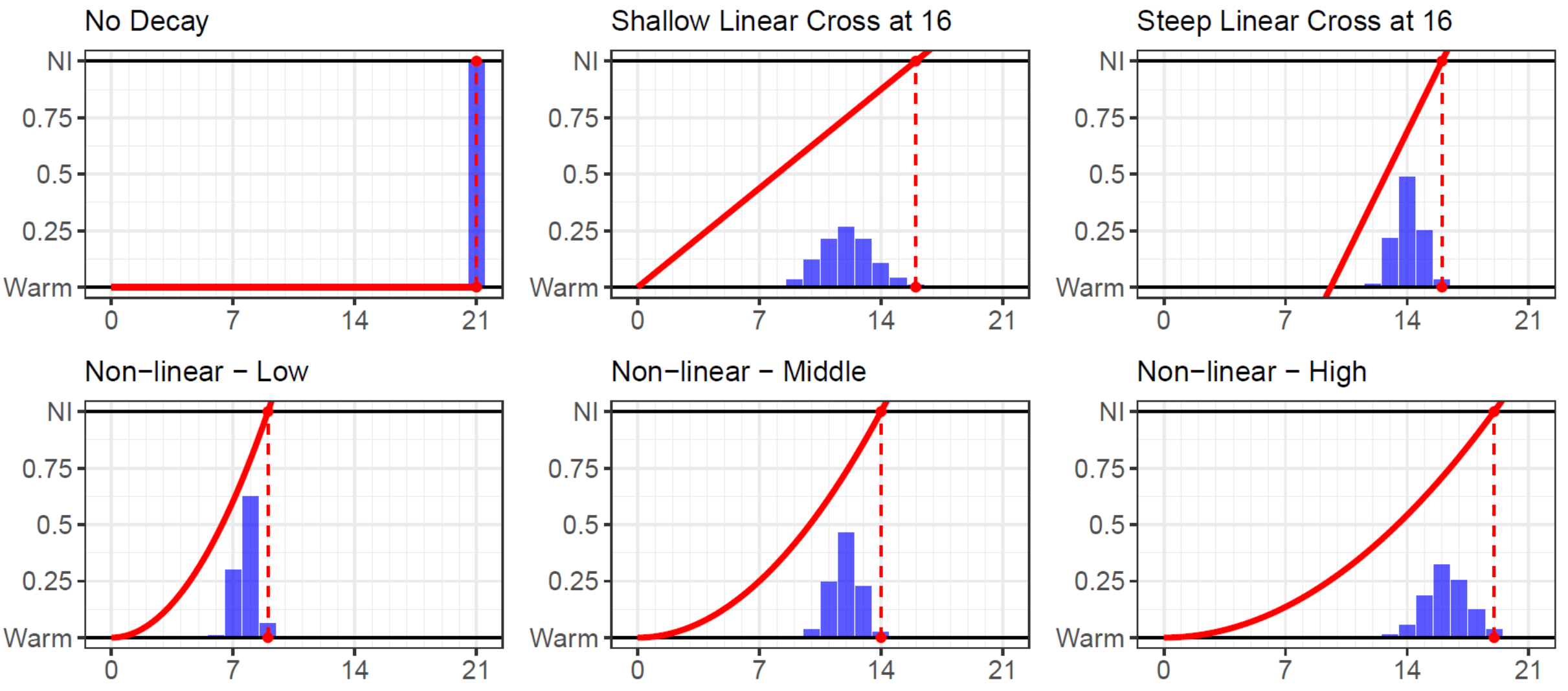








Duration Selection in Alternative Scenarios



Operating Characteristics Table

		1	2	3	4	5
	Scenario	Power	Inferior Patients	Within 3 Days	Sample Size	Over Crossing
Alternative	No Decay	1.000	0	1.000	1000	0.000
	Shallow Linear Cross at 16	1.000	15	0.156	1000	0.003
	Steep Linear Cross at 16	1.000	11	0.772	1000	0.001
	Non-linear - Low	0.991	64	0.991	1000	0.000
	Non-linear - Middle	1.000	33	0.719	1000	0.001
	Non-linear - High	1.000	12	0.414	1000	0.006
Null	Flat	0.008	25	0.036	663	0.004
	Shallow Non-linear	0.015	55	0.406	886	0.001
	Moderate Non-linear	0.017	75	0.990	964	0.000
	Steep Non-linear	0.018	78	1.000	843	0.000
	Shallow Linear	0.020	67	0.708	931	0.001
	Moderate Linear	0.020	74	0.999	970	0.000
	Steep Linear	0.018	73	1.000	891	0.000

1. Proportion with selected NI storage duration ≥ 7 days
2. Number of patients given platelets that were stored too long to be non-inferior
3. Proportion of simulations selecting a storage duration within 2 days of correct duration (e.g. 12, 13, or 14 if 14 is correct.
4. Mean sample size with stopping only for futility
5. Proportion of simulated trial that pick a storage duration that is too long, by any number of days

Comment in IND

U.S. FOOD & DRUG ADMINISTRATION

Our Reference: IND 19538

REMOVE CLINICAL HOLD
July 16, 2020

Washington University School of Medicine
Department of Pediatrics, Division of Critical Care
Attention: Philip C. Spinella, MD
CB 8116
660 South Euclid Avenue
St. Louis, MO 63110

Dear Dr. Spinella:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "Cold Platelets."

Please also refer to your amendments received June 19, 2020, July 6, 2020, and July 10, 2020.

You have satisfactorily addressed all clinical hold issues identified in our letter of February 5, 2020. We have removed the clinical hold and you may proceed with your study.

We have the following non-hold comments:

⋮

Statistical:

5. We recommend pre-specifying a minimum sample size requirement at or near the chosen maximum duration to help ensure that a reasonable number of subjects receive product stored at the maximum storage time. If you choose not to pre-specify a minimum sample size, please report the distribution of patients treated at each storage duration in the analysis.

If you have any questions, please contact the Regulatory Health Project Manager, LCDR Kimberly Bissohong, at Kimberly.Bissohong@fda.hhs.gov or (301) 796-5350.

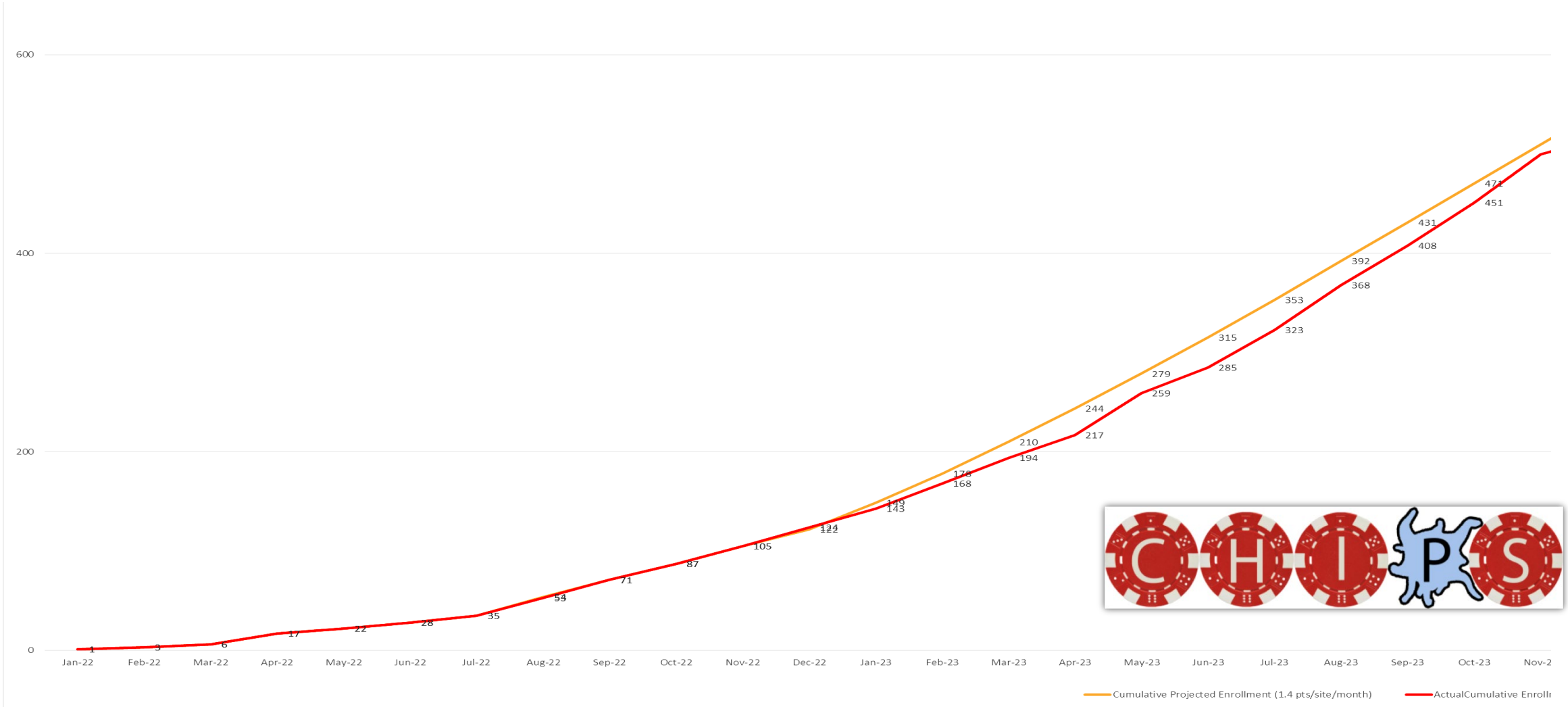
Sincerely,

Orieji Illoh -S

Digitally signed by Orieji Illoh -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Orieji Illoh -S, 0.9.2342.19200300.100.1.1=2000420941
Date: 2020.07.16 09:14:56 -04'00'

Orieji Illoh, MD
Director
Division of Blood Components and Devices
Office of Blood Research and Review
Center for Biologics Evaluation and Research

Enrollment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143
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168
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259
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285
353
323
392
368
431
408
471
451
Cumulative Projected Enrollment (1.4 pts/site/month)
ActualCumulative Enroll

Trial Progress

- Interim analyses conducted at N = 200, 400
- Enrollment at ~ 600
- Maximum current cold storage duration intended to be known only by those required to implement the trial (unblinding information)
- **External event**: FDA Guidance for CSP released in June 2023

FDA Guidance for CSP: June 2023

III. NOTICE OF EXCEPTIONS OR ALTERNATIVES

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a request to FDA under 21 CFR 640.120(a). Licensed establishments must report changes to their approved application in accordance with 21 CFR 601.12 as discussed in section V. of this guidance.

D. The Need for Additional Studies on CSP

At the November 2019 meeting of the BPAC (Ref. 35), the committee also recognized the need for additional data to support indications for use of CSP where conventional platelets are an available alternative. FDA is also not aware of well-controlled clinical studies supporting use of CSP for prevention of bleeding (prophylactic transfusion). An adaptive trial design in the setting of cardiac surgery, previously described in published literature (Ref. 36), was proposed and discussed at BPAC (Ref. 35) and is currently underway. (See, e.g., Ref. 37; the ongoing nature of this study has also been disclosed on participating sites' websites.) Additional studies of CSP manufactured using different procedures and devices, for example CSP prepared from platelets manufactured using pathogen-reduction devices or CSP prepared from Whole-Blood-derived platelets, would provide additional information. Sponsors and investigators planning such studies to support regulatory submissions for CSP are encouraged to contact FDA to discuss applicable regulatory pathways.

Response to FDA CSP Guidance of June 2023

- DSMB reviewed request from investigator team to increase maximum cold storage duration to 14 days, and approved that request on July 14, 2023
- At that time, the range of possible cold storage durations defined by the adaptive design would have been in the range of 7 to 12 days
- The June FDA guidance therefore indirectly lead to a temporary unblinding of the study team to the maximum cold storage duration, without “leaking” interim efficacy information
- Without the adaptive duration finding design, the investigator team would have always been unblinded to the maximum cold storage duration, but it would be *unrelated* to interim efficacy information

References

- Krachey E, Viele K, Spinella PC, et al. The design of an adaptive clinical trial to evaluate the efficacy of platelets stored at low temperature in surgical patients. J Trauma Acute Care Surg. 2018 Jun;84(6S Suppl 1):S41-S46. doi: 10.1097/TA.0000000000001876.
- Strandenes G, Sivertsen J, Bjerkvig CK, et al. A Pilot Trial of Platelets Stored Cold versus at Room Temperature for Complex Cardiothoracic Surgery. Anesthesiology. 2020 Dec 1;133(6):1173-1183. doi: 10.1097/ALN.0000000000003550.
- Zantek ND, Steiner ME, VanBuren JM, et al. Design and logistical considerations for the randomized adaptive non-inferiority storage-duration-ranging CHIlled Platelet Study. Clin Trials. 2023 Feb;20(1):36-46. doi: 10.1177/17407745221126423. Epub 2022 Dec 21.