PUBLIC HEALTH WEBINAR SERIES
ON BLOOD DISORDERS
BRINGING SCIENCE INTO PRACTICE

Inhibitor Prevention and Eradication:

From NHLBI SoS to the INHIBIT Trial

Public Health Webinar Series on Blood Disorders

Steven Pipe, MD and Margaret Ragni, MD, MPH

Inhibitor Formation

Incidence: 30% in severe hemophilia A

Mechanism: T-cell dependent B-cell response

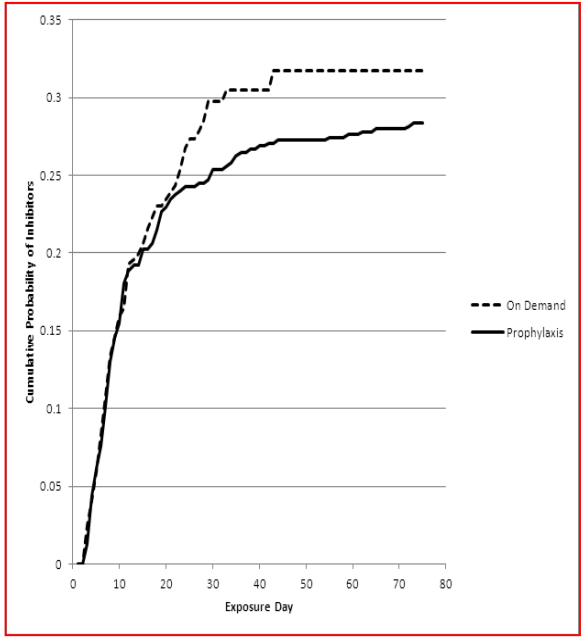
Target: Alloantibody to exogenous FVIII

Treatment: Bypass (rFVIIa, FEIBA)

Morbidity: Poorly controlled bleeding

- 2x hospitalizations
- 10x cost
- 3.5x mortality

Goal: Prevent and eradicate inhibitors



Gouw et al, 2013

Origins of the Workshop

- CDC's Division of Blood Disorders (DBD) has been committed to the goal of reducing the occurrence of inhibitors – the most significant and costly complication affecting people with hemophilia today
- March 2012 – First Inhibitor Summit
  - Multi-stakeholder engagement
  - Informed the integration of inhibitor surveillance into the Community Counts Registry for Bleeding Disorders Surveillance
    - Funded by the CDC through a cooperative agreement awarded to the American Thrombosis and Hemostasis Network in partnership with the U.S. Hemophilia Treatment Center Network
    - Collects information about key aspects of inhibitor development, treatment and outcomes
    - DBD Reference Laboratory developed the methodology for sensitive and specific inhibitor testing which is performed on all eligible Registry participants

Origins of the Workshop

- Jan 2017 – 2nd Inhibitor Summit
  - Need for collaboration across the entire US bleeding disorders community including key government, scientific, clinical and other bleeding disorders community stakeholders
  - Objectives:
  - Share information about the Registry and the current state of national inhibitor surveillance
  - Identify steps to maximize the accuracy and representativeness of national data on inhibitor occurrence
  - Determine the strategy to maintain the accuracy and validity of inhibitor testing methods
  - **Explore the need for a national, coordinated inhibitor science agenda**

Origins of the Workshop

- Subjects needed for studies in this area (primarily previously untreated patients) are a **precious resource** and efforts should be made to **coordinate studies** so that the **maximum benefit** can be obtained from each study subject
- Oversight to assure that only the **best science** is performed and funding for the studies should be adequate to cover the costs of obtaining high quality data
- **Multifaceted education and marketing activities** be directed to the patient community well in advance of upcoming trials to stimulate interest and participation
- Development of multi-disciplinary group working to develop and implement an **integrated scientific and public health agenda** as well as to establish definitions and common data elements
- Representatives from a **wide variety of disciplines** should be included to facilitate the generation of new ideas and approaches
- **Agreement from the bleeding disorder community** to proceed with regimented cooperative studies that have been appropriately vetted

Goal of the Workshop

To solicit hemophilia community-wide input into the development of a coordinated US- based blueprint for future basic, translational, and clinical research focused on FVIII immunogenicity and FVIII inhibitor prevention/eradication

Sabatino et al. (2019) *Haemophilia*. Origins and organization of the NHLBI State of the Science Workshop: Generating a national blueprint for future research on factor VIII inhibitors

Workshop Participation

More than 200 registered participants from 29 states and 9 countries, with half of registrants from academia and Hemophilia Treatment Centers (HTCs), 20% from industry, 18% from the Federal Government, and 8% representing patient advocacy. Participants who could not attend in person were able to participate in the workshop through videocasting.

Executive Steering Committee

- Executive Steering Committee (ESC) established
  - Workshop Co-Chairs: *Steve Pipe, Denise Sabatino*
  - NHLBI: *Keith Hoots, Donna Di Michele*
  - CDC: *Mike Soucie, Craig Hooper*
  - Community/Societies Representative*: Diane Nugent*

- Mandate:
  - Establish focus/leadership for Scientific WGs
  - Oversee the scientific WG activities
  - Develop the SOS Workshop agenda


National Heart, Lung, and Blood Institute
State of the Science Workshop
Factor VIII Inhibitors:
Generating a National Blueprint for
Future Research
National Institutes of Health
Bethesda, Maryland
May 15-16, 2018
Registration & Information
https://factorviiinhibitors.eventbrite.com

Infrastructure support
Leverage current national data collection efforts
Establish and optimize automated clinical and patient-entered data transfer
Use standard outcome measures across studies to allow data integration, including from international sources
Streamline protocols, contracting, and informed consent processes, including use of single IRBs
Centralize tracking of biorepository specimens and data for timely utilization
Resources/partnerships
Resource Hemophilia Treatment Centers for data entry and biospecimen collection
Optimize private-public collaborations and funding opportunities

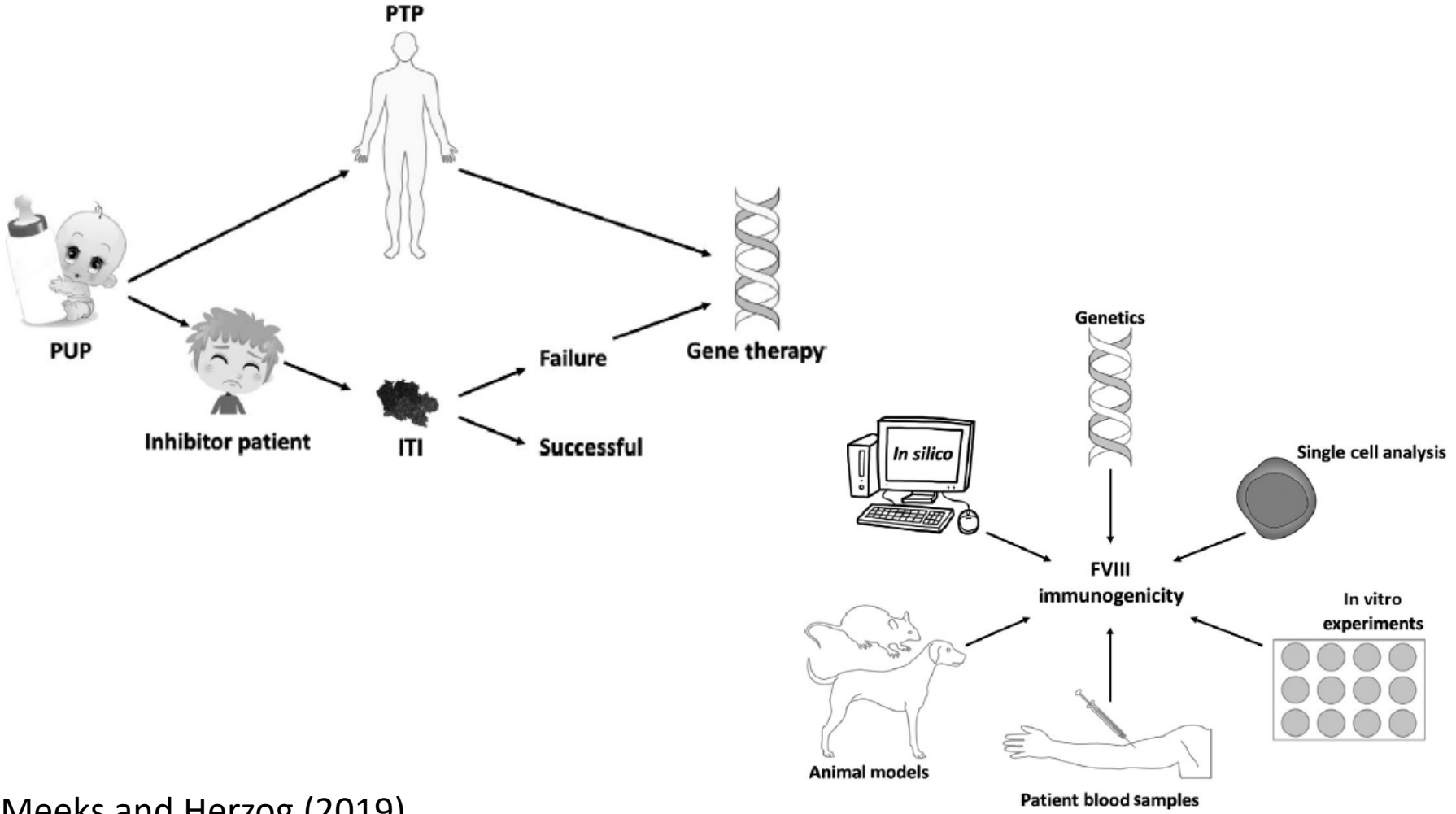
Konkle and Recht (2019) Haemophilia. The national blueprint for 21st century data and specimen collection and observational cohort studies: NHLBI State of the Science Workshop on factor VIII inhibitors

Patient engagement
Engage patients to identify patient-important outcomes in all stages of research
Build strong collaborative relationships with patient organizations to identify important research questions and disseminate new knowledge
Training opportunities
In human subjects, research and data sharing issues for researchers, clinicians, and participants
In study design and analysis, including epidemiology and data science and bioinformatics

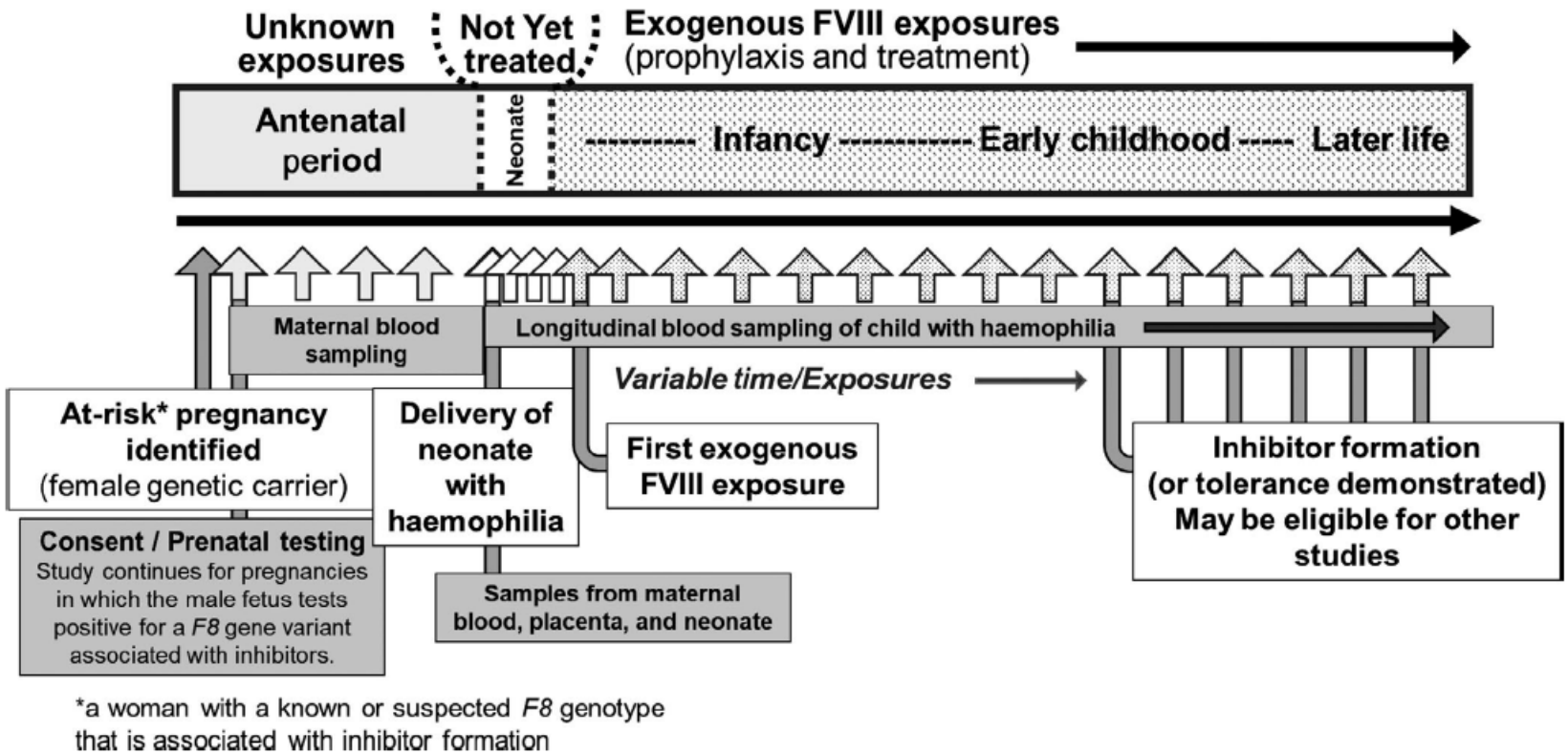
Konkle and Recht (2019) Haemophilia. The national blueprint for 21st century data and specimen collection and observational cohort studies: NHLBI State of the Science Workshop on factor VIII inhibitors

- Scientific Priorities
  - Activation signals and immune regulation that shape the response to factor VIII
    - Innate/early immune recognition of FVIII
    - Adaptive immune responses
    - Immune regulation and tolerance
  - Utility of non-animal models to help predict inhibitor formation
  - How the site of FVIII expression, its structure and VWF determine immunogenicity and tolerance
    - FVIII expressed in gene therapy
    - FVIII interactions with VWF
    - FVIII molecules with altered structure

Meeks and Herzog (2019) Haemophilia. The national blueprint for future basic and translational research to understand factor VIII immunogenicity: NHLBI State of the Science Workshop on factor VIII inhibitors

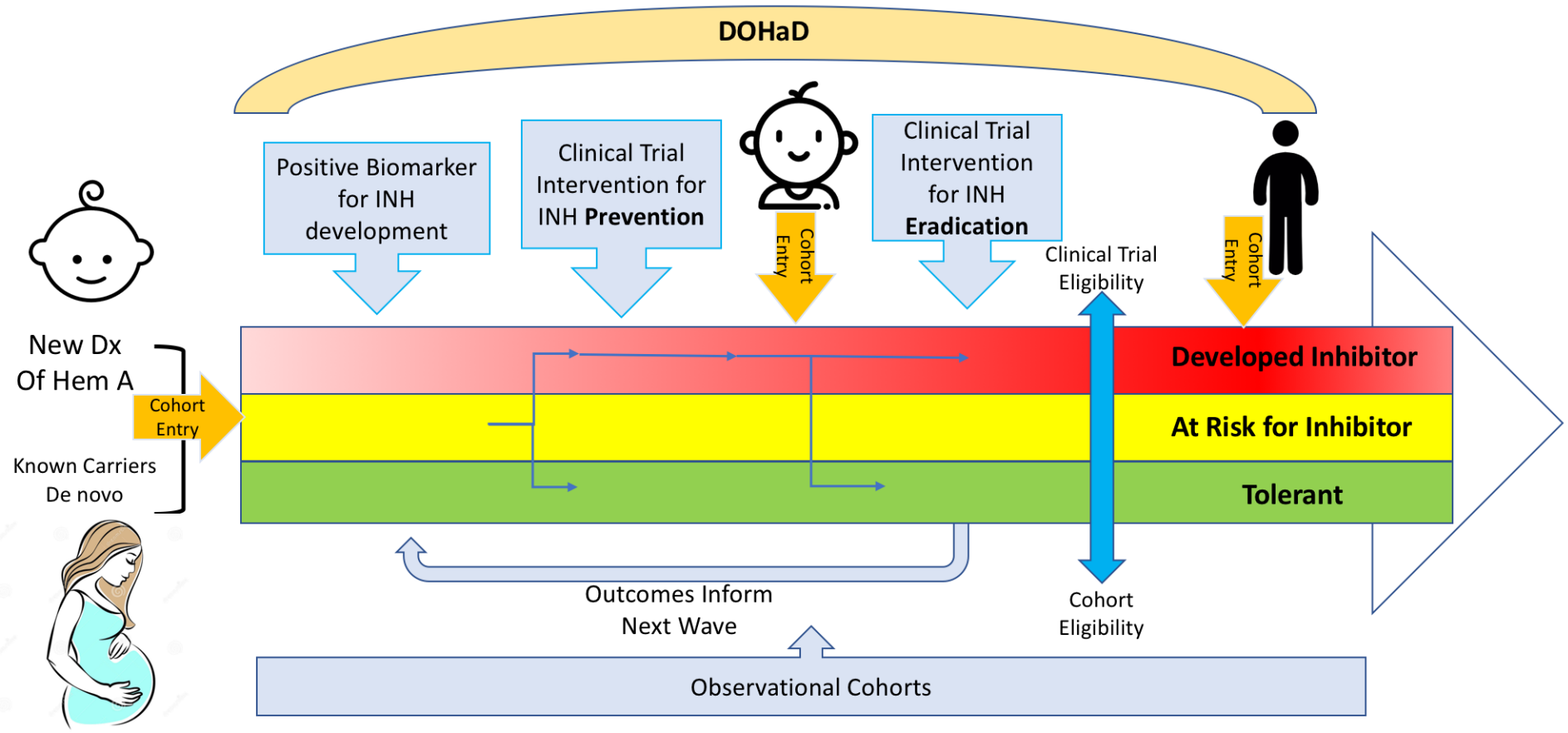


Meeks and Herzog (2019)



Johnsen and Brown (2019) *Haemophilia*. The national blueprint for pregnancy/birth longitudinal cohorts to study factor VIII immunogenicity: NHLBI State of the Science (SOS) Workshop on factor VIII inhibitors

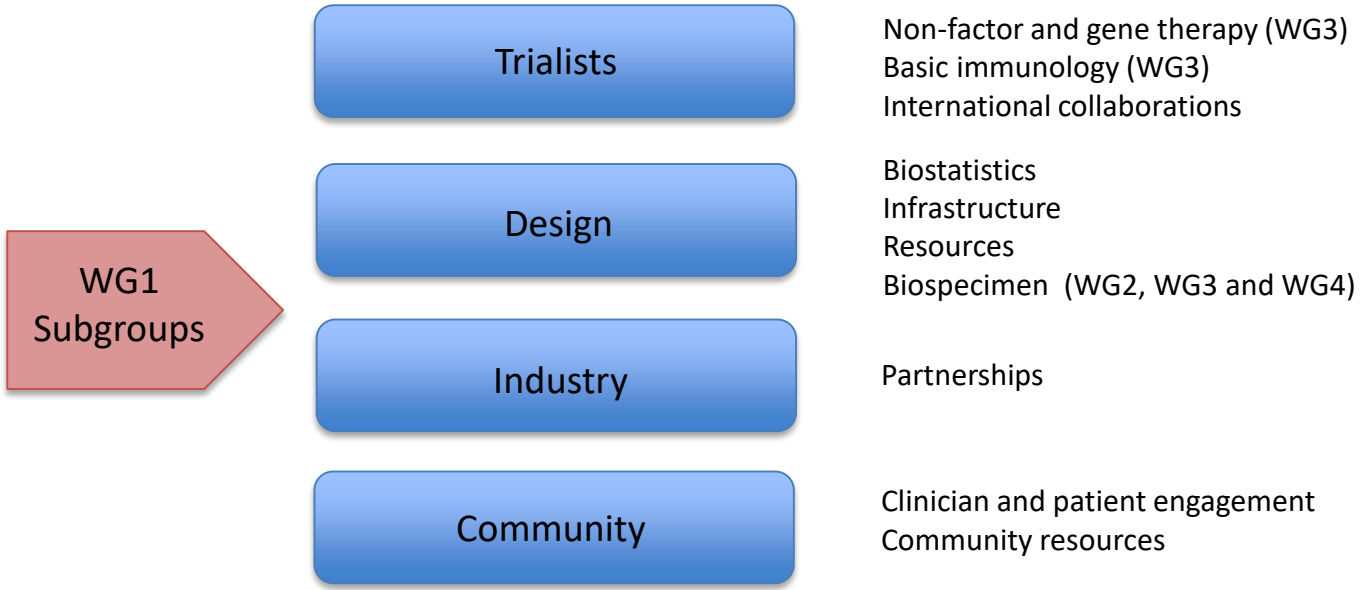
Inhibitor Investigation Over the Lifespan



Pipe et al. (2019)
Haemophilia

Scientific Priorities:

1. **Longitudinal outcomes/surveillance**
2. **Observational Cohort Discovery**
3. **Subject Discovery for Clinical Trials**
4. **Developmental Origins of Health and Disease (DOHaD)**


WG1
Subgroups
Trialists
Design
Industry
Community
Non-factor and gene therapy (WG3)
Basic immunology (WG3)
International collaborations
Biostatistics
Infrastructure
Resources
Biospecimen (WG2, WG3 and WG4)
Partnerships
Clinician and patient engagement
Community resources

SoS: General Goals for Clinical Trials

1. Define resources and partnerships to facilitate clinical trials
2. Leverage and support the HTC infrastructure
3. Embed mechanistic studies into clinical trials
4. Optimize public-private partnerships in clinical trials
5. Engage the patient community in clinical trials
6. Embed training opportunities within clinical trials

SoS: Specific Goals for Clinical Trials

1. Challenges of rare disease clinical trials
2. Statistical considerations
3. Master Protocol concept
4. Coordinated Clinical Trials Network
5. Design Prevention, Eradication Trials

1. Challenges of Rare Disease Trials

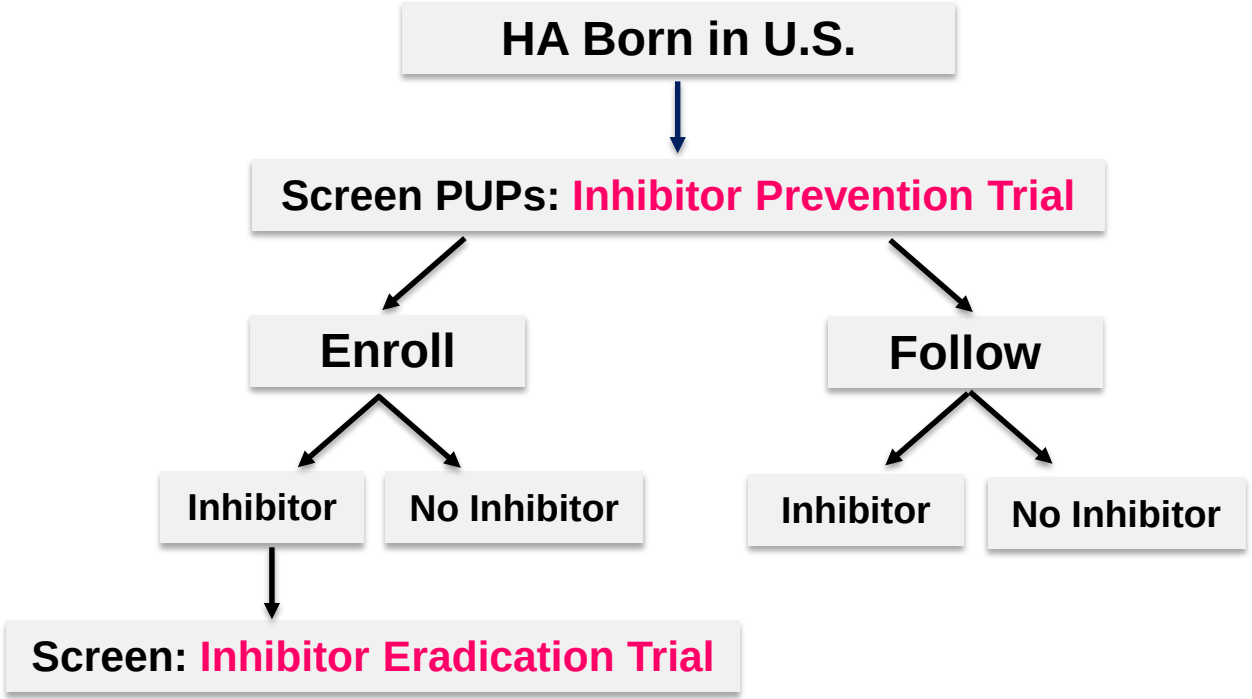
- Patients are limited: 1.82 PUP/HTC/yr
- Outcomes are rare: 30% develop inhibitors
- Competition for patients is high: pharma, non-randomized trials
- Partnerships are needed: pharma/ government/ community
- Classical RCT is not possible: too few patients, too many sites, $/time
- HTCs require resources: 40% need nurses, technicians
- RCTs requires infrastructure: 30-40 HTCs/ HCTG/ partnerships
- Optimal approach is unknown: prevent and eradicate inhibitors

2. Statistical Considerations

- **Historical controls, registries, cohorts**
  - Use historical data to reduce sample size, preferential randomization
  - Utilize CDC surveillance registry, international registries
  - Utilize databases, central labs as platform to launch clinical trials

- **Master Protocol**
  - Follow those enrolled and screened for inhibitor development
  - Establish baseline pre-inhibitor data/specimens
  - Establish inhibitor natural history among screened subject

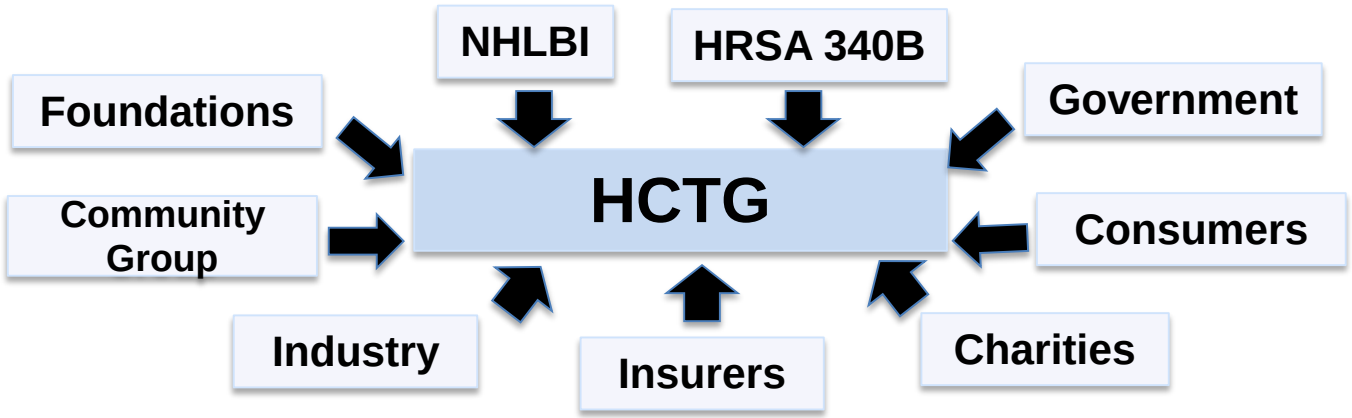
3. Master Protocol



4. Clinical Trials Network

- Provide HTCs with nurse coordinator, technician support
- Implement system for biospecimen and data collection
- Incorporate standardized outcome measures
- Incorporate mechanistic studies to study FVIII tolerance
- Engage the patient community
- Train early stage investigators
- Establish resources and partnerships to facilitate clinical trials

4. Clinical Trial Infrastructure



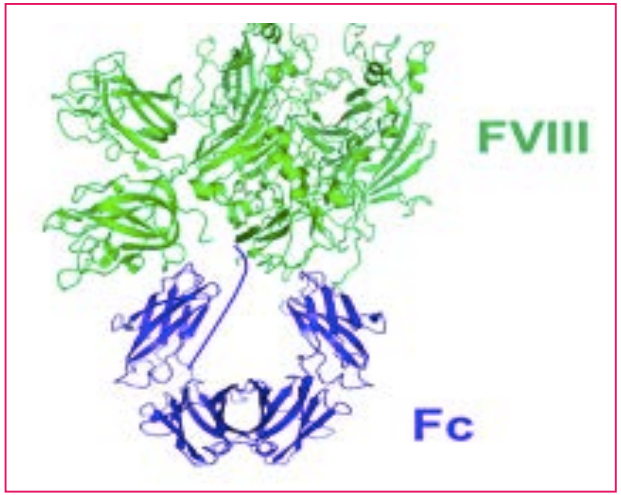
Partnerships, Resources: Leverage clinical trial infrastructure

HCTG = Hemophilia Clinical Trials Group

5. Design Trials to Prevent, Eradicate Inhibitors

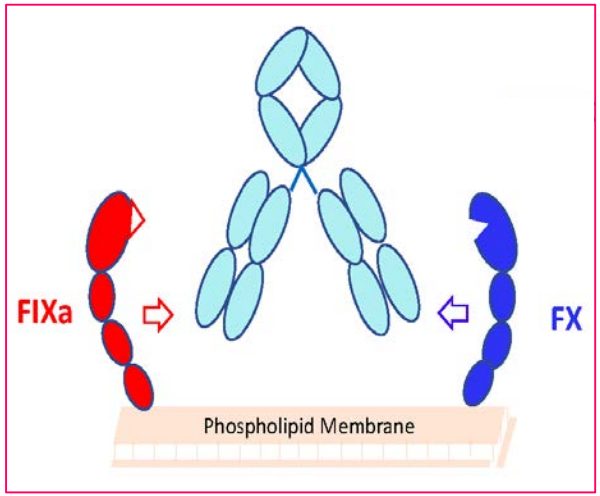
- Incorporate novel therapies into trials
- Review inhibitor prevention, eradication data
- Define state of equipoise
- Incorporate adaptive design into trials platform

Incorporate Novel Therapies into Trials



Eloctate

Fc Fusion Protein
Extends FVIII half-life, given IV
Promotes T regs, VIII tolerance

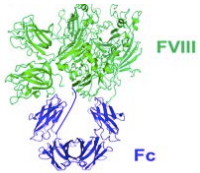


Emicizumab

Bispecific Monoclonal Antibody
Mimics FVIII, binds IXa, X, given SQ
Promotes hemostasis, avoids FVIII

Review Inhibitor Prevention, Eradication Data

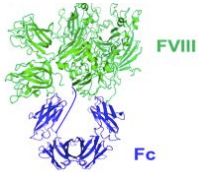
Inhibitor Prevention:



- **Eloctate reduced inhibitor incidence**
  Anti-VIII ~30%, in A-LONG Trial *(N=95, Konigs et al)*
- **Eloctate reduced inhibitor titer,** weekly
  Anti-VIII = 43.0 BU in rFVIII-rx PUP *(N=2, Ragni et al)*
  Anti-VIII = 1.4 BU in rFVIIIFc-rx cousin

Review Inhibitor Prevention, Eradication Data

Inhibitor Prevention:



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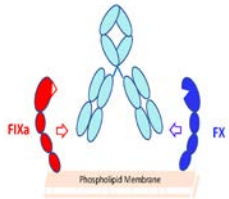
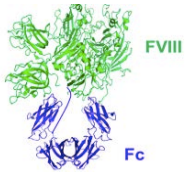
Inhibitor Eradication:

- **Eloctate reduced time to ITI** to 3-8 months
  - Time to ITI = 2.7 months *(N=3, Malec et al)*
  - Time to ITI = 6.9 months *(N=4, Carcao et al)*



- **Emicizumab + rFVIII reduced bleeds** in ITI
  - Time to ITI = NA *(N=3, Batsuli et al)*
- **Emicizumab + Eloctate reduced bleeds** in ITI
  - Time to ITI = NA *(N=1, Batsuli et al)*

Define Equipoise



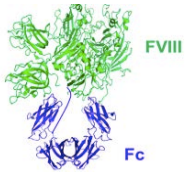
Eloctate:

- ***Prevent***: While eloctate induces Tregs and promotes tolerance, inhibitors still develop in 30% of PUPs.
  Eradicate: Eloctate shortens ITI in < 10 mos in small studies

Does eloctate sufficiently reduce inhibitors and shorten ITI to justify its use?

Define Equipoise

Eloctate:



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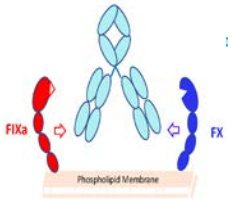
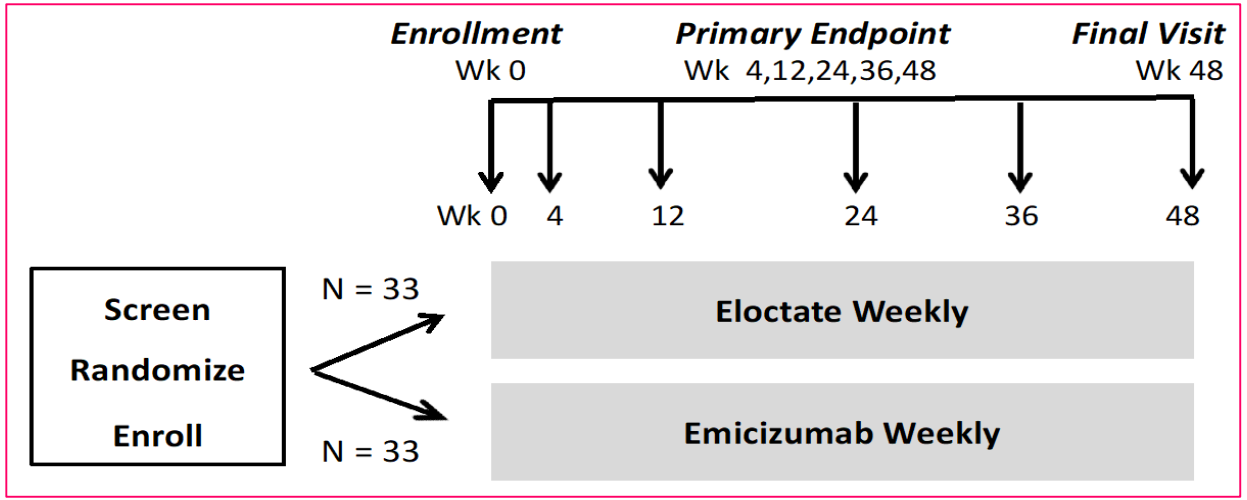
Emicizumab:



- ***Prevent & Eradicate***: While emicizumab provides hemostasis and avoids FVIII exposure, if breakthrough bleeds require FVIII, this may trigger “danger” and inhibitors and slow ITI.

Does emicizumab reduce or just delay inhibitors, or shorten ITI sufficiently to justify its use?

Clinical Trial #1: Inhibitor Prevention



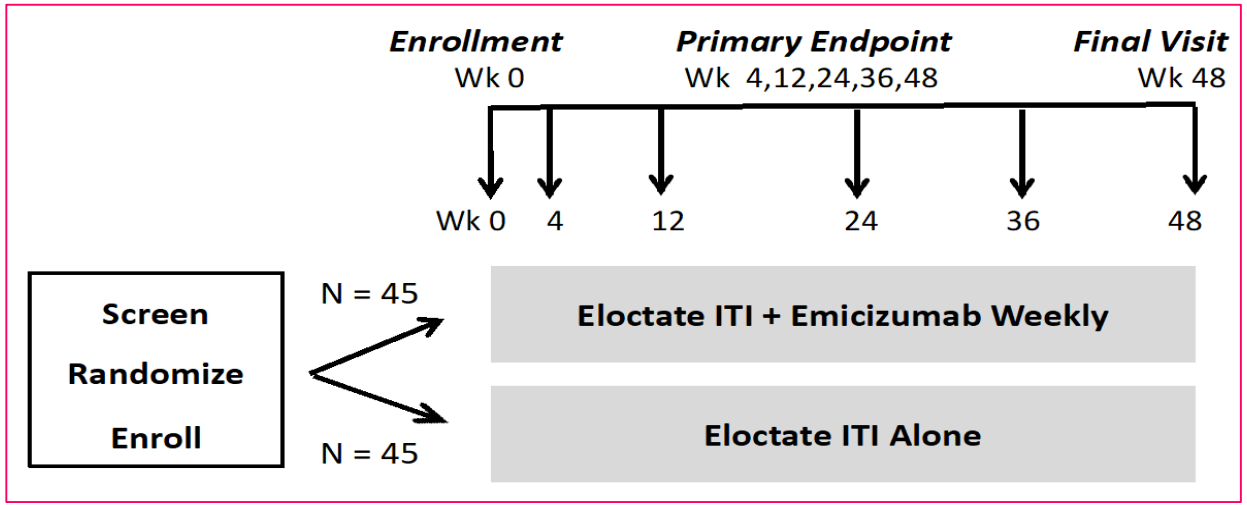
Hypothesis: EMI reduces bleeds (danger), yet less immunogenic than FVIII.

Intervention: Weekly **Eloctate** vs. **Emicizumab** before 1st bleed.

1◦ Endpoint: Inhibitor development: anti-VIII>5 NBU at 48 weeks.

2◦ Endpoints: Bleeding, mechanistic studies: ELISPOT, microbiome, precision med

Clinical Trial #2: Inhibitor Eradication



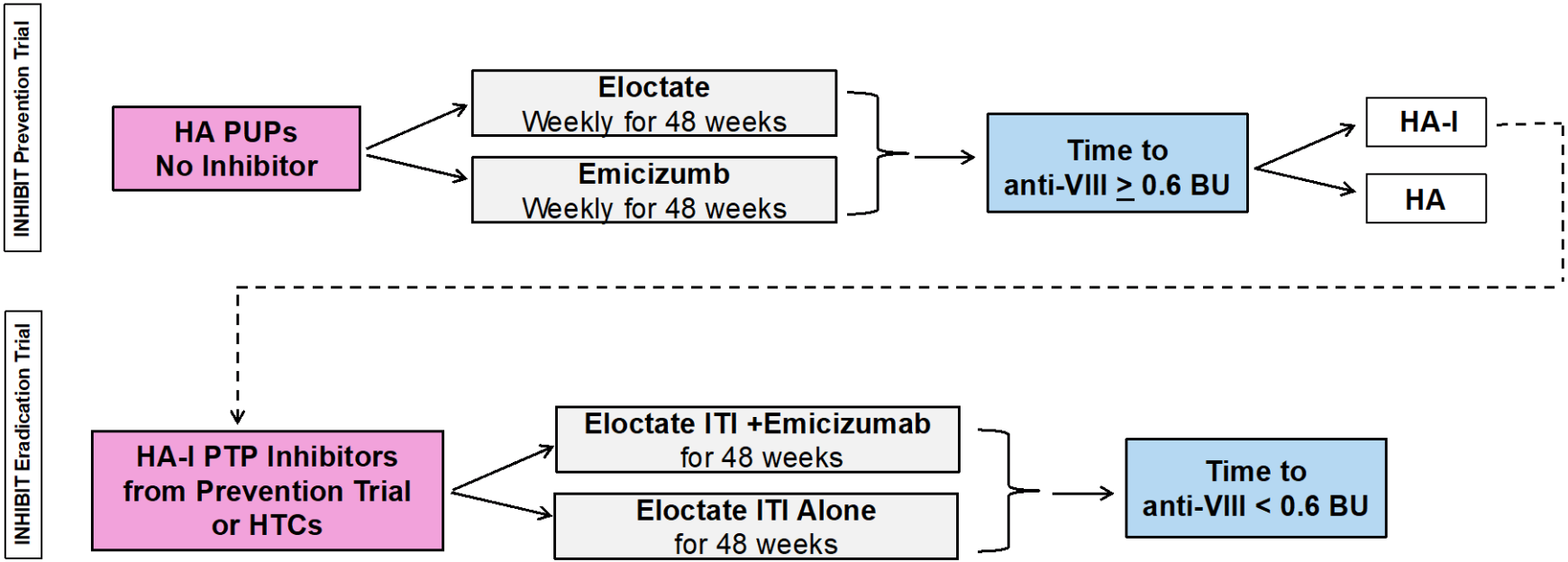
Hypothesis: EMI reduces bleeds (danger), yet less immunogenic than FVIII.

Intervention: **Eloctate ITI +/- Emicizumab** weekly in PTPs.

1◦ Endpoint: Inhibitor development: anti-VIII>5 NBU at 48 weeks.

2◦ Endpoints: Bleeding, mechanistic studies: ELISPOT, microbiome, precision med

The INHIBIT Clinical Trials Platform

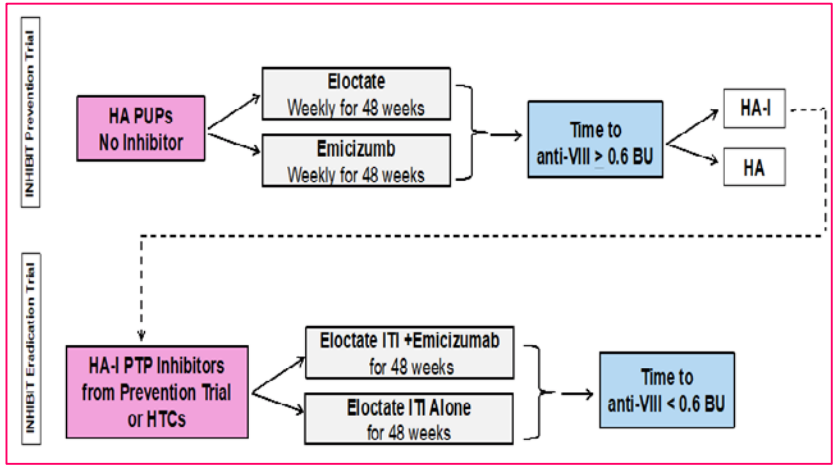


The INHIBIT Clinical Trials Platform

Advantages of Adaptive Design:

1. Efficient use of historic data
2. Preferential 1:4 randomization to novel drug
3. Two linked trials: same outcome, visits, labs
4. Validation of blood draws for small volumes
5. Mechanistic assays to study tolerance:

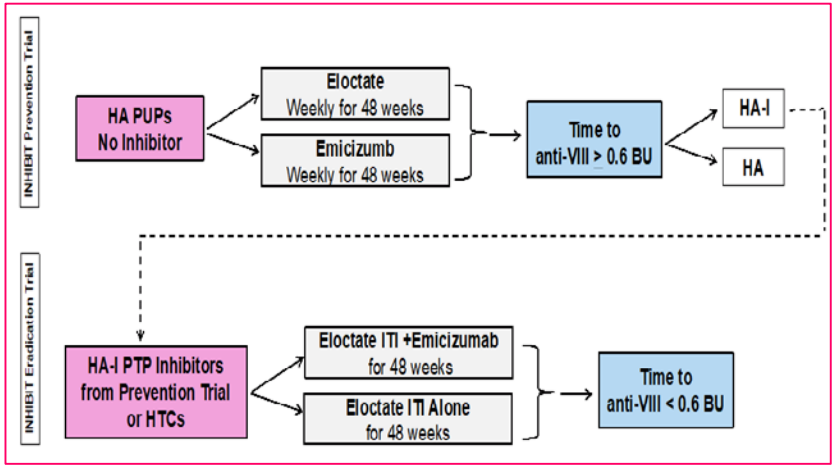
   ELISPOT/ cytokine/ omics/ registry
6. Future incorporation of novel drugs



The INHIBIT Clinical Trials Platform

Work in Progress:

1. Set up a coordinated Hemophilia Clinical Trials Network.
2. Set up Precision Medicine Registry within trial: proteomics, microbiomics.
3. Engage community: hold town meetings, engage Chapters, Regional HTCs.
4. Provide training opportunities for early stage investigators.
5. Set up single-IRB and relying agreements.



Questions & Answers

PUBLIC HEALTH WEBINAR SERIES ON BLOOD DISORDERS

BRINGING SCIENCE INTO PRACTICE

This webinar was brought to you by CDC's Division of Blood Disorders. We thank the Hemophilia Federation of America for hosting today's webinar.

Questions about this webinar series? Please contact Cynthia Sayers at CSayers@cdc.gov.

This webinar will be archived at

www.cdc.gov.ncbddd/blooddisorders/webinar.html

PUBLIC HEALTH WEBINAR SERIES ON BLOOD DISORDERS

BRINGING SCIENCE INTO PRACTICE

March 5, 2020 -- 2 to 3 pm Eastern

Selection of a Risk Assessment Model for VTE Prevention in Hospitalized Medical Patients

Holger J. Schünemann, MD, MSc, PhD, FRCPC
Professor of Clinical Epidemiology and of Medicine
Departments of Health Research Methods, Evidence, and Impact and of Medicine
Director, Cochrane Canada and McMaster GRADE Centre
McMaster University
Hamilton, Ontario, Canada

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Project Coordinator, Cochrane Canada
Department of Health Research Methods, Evidence, and Impact
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