Management patterns of AntiThrombotics and outcomes in patients with hematological malignancy and ThrombocytopEnia: a Prospective Registry

MATTER study

Final Study Protocol: ***Update***

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Disclosure belangen spreker bijeenkomst Consortium Transfusiegeneeskundig Onderzoek 17-11-2017	
Naam: Avi Leader	
Geen (potentiële) belangenverstrengeling	I have no relevant conflicts of interests or relevant relations to declare

Antithrombotic Rx in Thrombocytopenia & Cancer

- **Common**
  - **45%** of 197 thrombocytopenic cancer patients (Plt < 80 X 10^9/L) received antithrombotic Rx in a recent cohort[1]

- **Complex and uncertain management**

Anticoagulation

- Practice guidelines (venous thromboembolism) based on expert opinion
- Variance in reported practice[2,3] (e.g. platelet tranfusion; holding/reducing dose)
- Suggestive supportive data on safety of dose reduction[4,5] and withholding Rx[6]

Antiplatelet medication

- Continuing aspirin in acute myocardial infarction and thrombocytopenia was associated with improved survival[7].

[1]Vinholt, Platelets, 2016; [2]Samuelson, Thromb Res 2016; [3] Chayaler, Transfusion 2014; [4]Khanal ; Am J Hem, 2016; [5] Mantha, J Thromb Thrombolysis, 2017; [6]Li, Blood Adv 2017; [7]Feher, Oncologist 2017

MATTER registry: Study Design

- **Changes Since 6/2017:** Protocol simplified & finalized | SOP finalized | Expansion in collaborators | REDCap eCRFs finalized

- **Current Study Status:** Initiation in Dec 2017

- **Objective:** **Evaluate management and frequency of bleeding and thrombosis**, in patients with hem malignancy, thrombocytopenia & antithrombotic Rx.

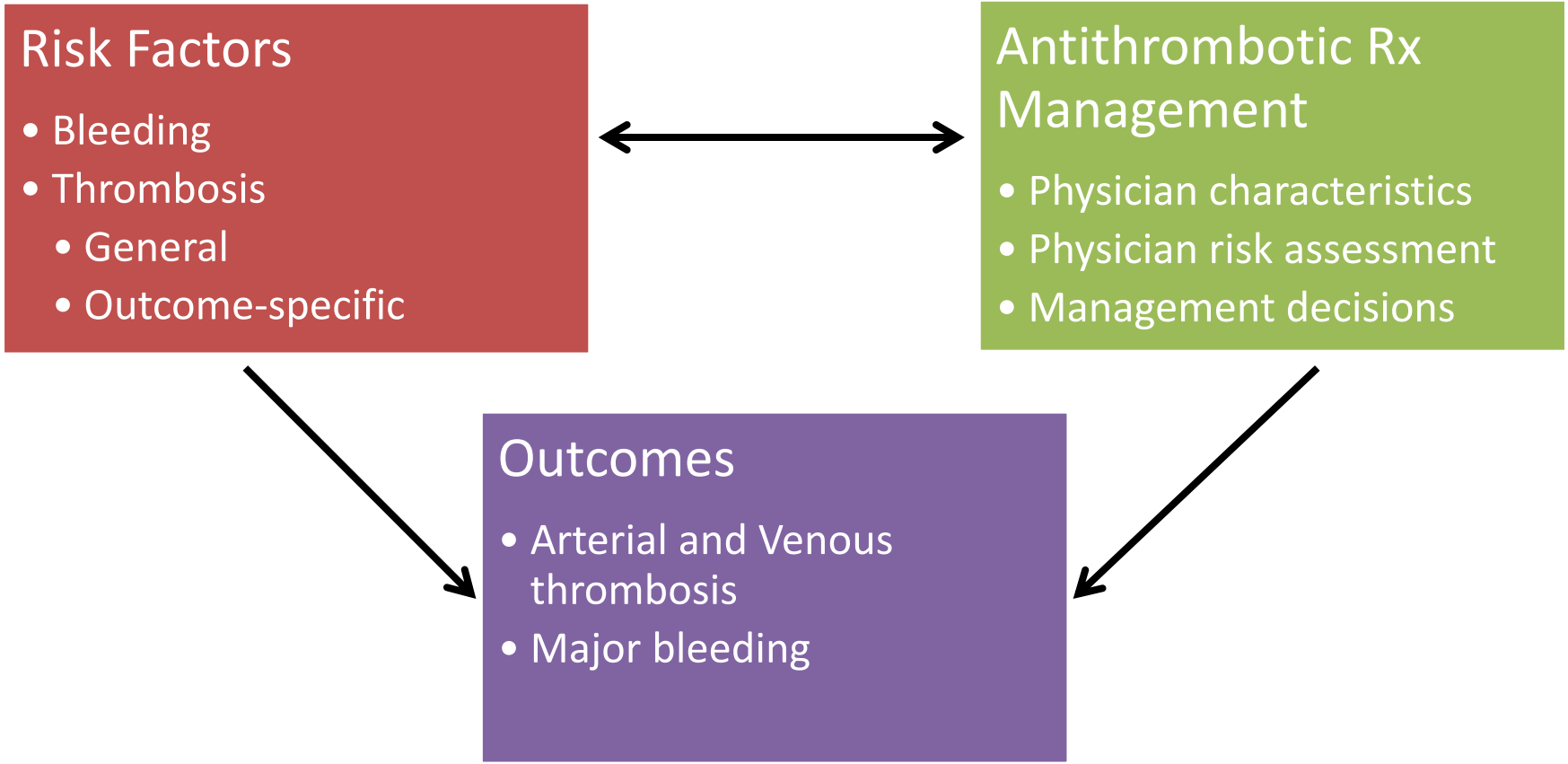
  Main Study Questions

  1. What is the **platelet threshold** at which antithrombotic Rx is **held or continued** at baseline?
  2. Calculate the **RR of bleeding or thrombosis** with **continuing** antithrombotic therapy **vs. holding** therapy

- **Design***:* Prospective multinational cohort study (clinicaltrials.gov: **NCT03288441**)

- **Study population:** Patients admitted to the inpatient hematology department or outpatient clinic

Study Concept

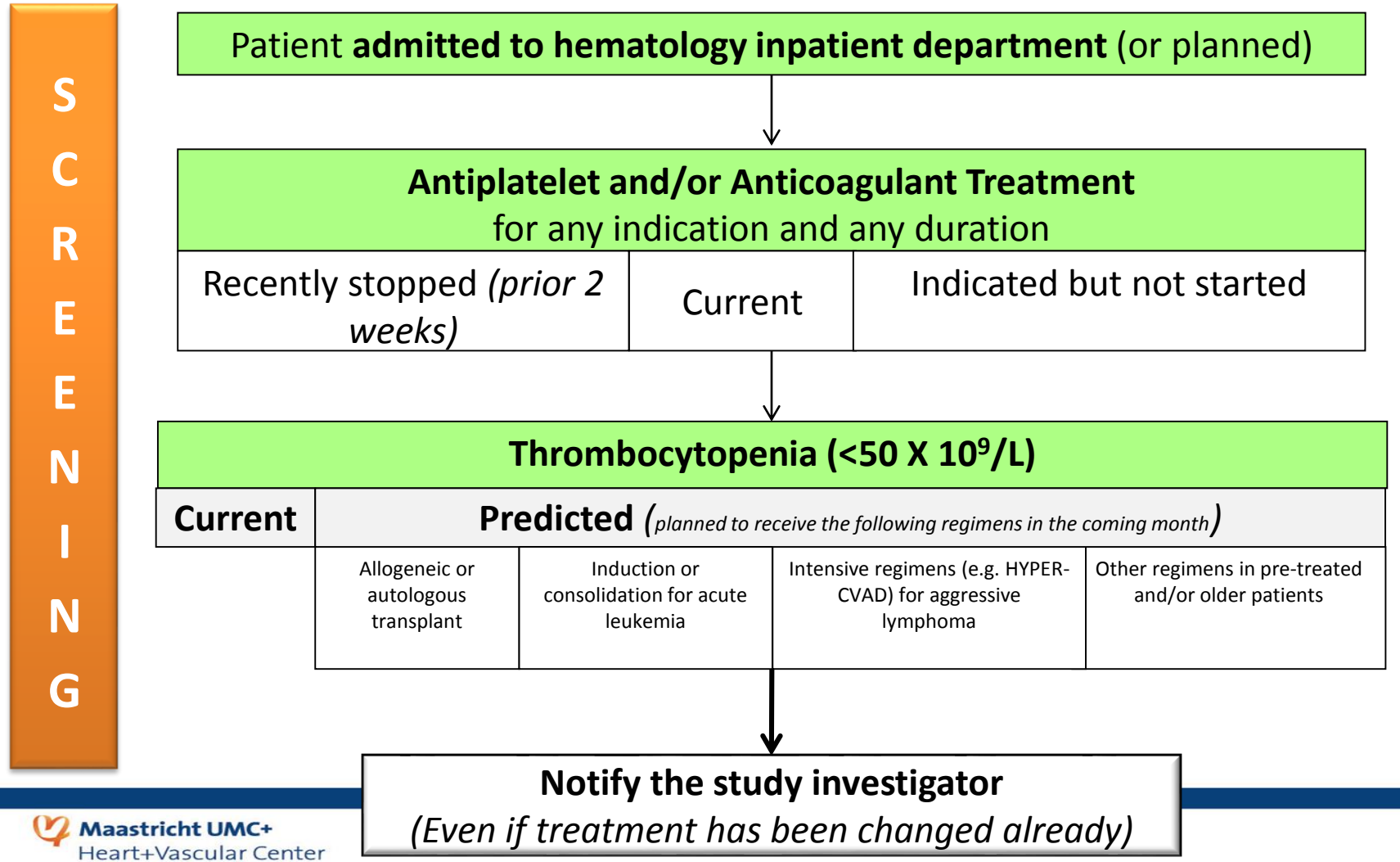


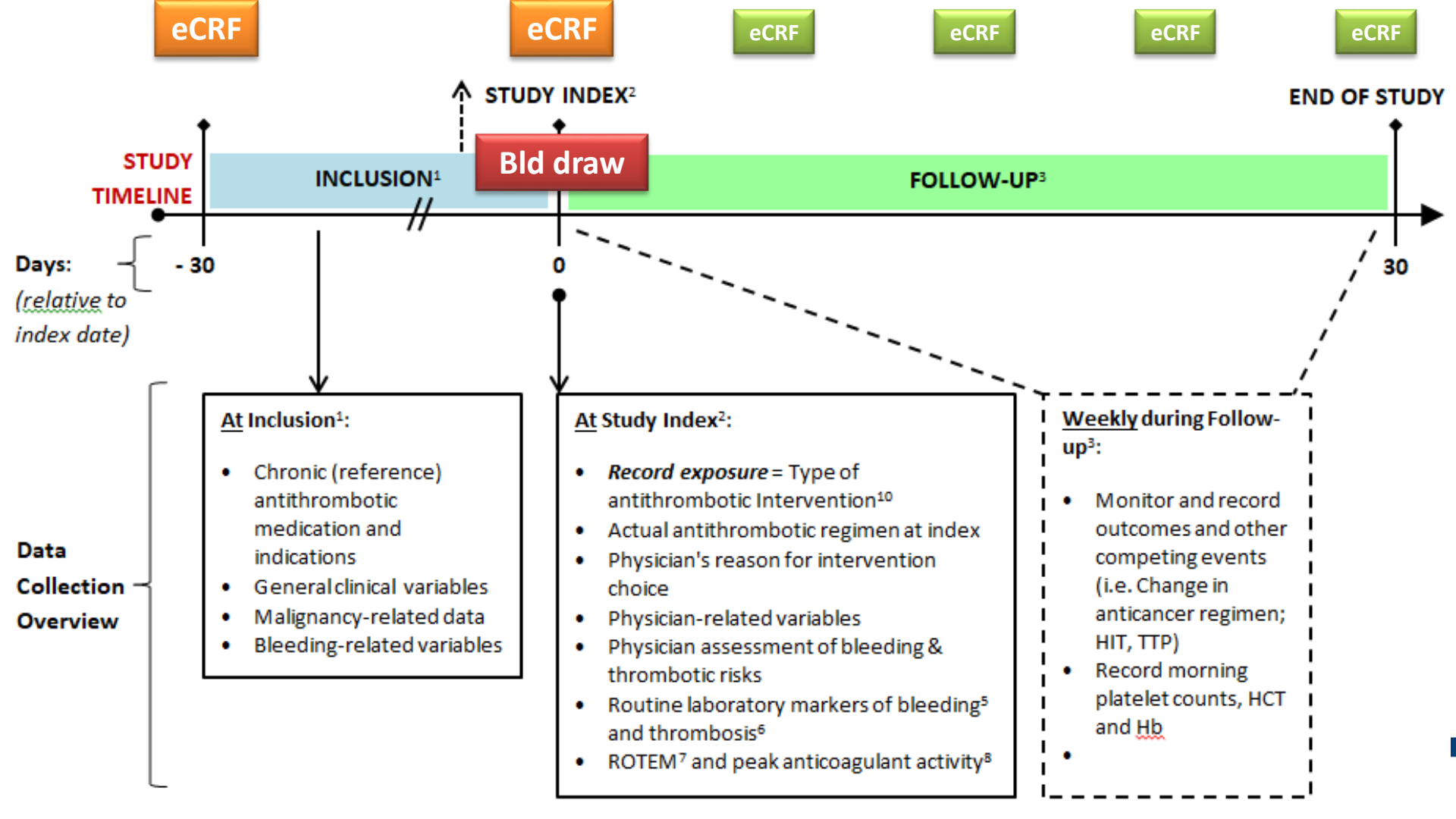
Exclusion Criteria: 1) Previous thrombocytopenia (<50 X 10^9/L) with the current antithrombotic regimen; 2) HIT/TTP/ITP

1. **Hematological malignancies (including MDS)**
   - With or without active treatment
   - Irrespective of treatment line and disease status
   - Both inpatients and outpatients

2. Current or predicted **disease or treatment-related thrombocytopenia** (<50 X 10^9/L) of any duration.

3. Current **antiplatelet and/or anticoagulant treatment**
   - Any indication. Any Duration
   - At screening (even if stopped at that stage)


SCREENING
Patient admitted to hematology inpatient department (or planned)
Antiplatelet and/or Anticoagulant Treatment
for any indication and any duration
Recently stopped (prior 2 weeks)
Current
Indicated but not started
Thrombocytopenia (<50 X 10^9/L)
Current
Predicted (planned to receive the following regimens in the coming month)
Allogeneic or autologous transplant
Induction or consolidation for acute leukemia
Intensive regimens (e.g. HYPER-CVAD) for aggressive lymphoma
Other regimens in pre-treated and/or older patients
Notify the study investigator
(Even if treatment has been changed already)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STUDY INDEX[2]
END OF STUDY
STUDY TIMELINE
INCLUSION[1]
Bld draw
FOLLOW-UP[3]
Days:
(relative to index date)
- 30
0
30
Data Collection Overview
At Inclusion[1]:
• Chronic (reference) antithrombotic medication and indications
• General clinical variables
• Malignancy-related data
• Bleeding-related variables
At Study Index[2]:
• Record exposure = Type of antithrombotic Intervention[10]
• Actual antithrombotic regimen at index
• Physician's reason for intervention choice
• Physician-related variables
• Physician assessment of bleeding & thrombotic risks
• Routine laboratory markers of bleeding[5] and thrombosis[6]
• ROTEM[7] and peak anticoagulant activity[8]
Weekly during Follow-up[3]:
• Monitor and record outcomes and other competing events (i.e. Change in anticancer regimen; HIT, TTP)
• Record morning platelet counts, HCT and Hb
•

Study Groups

- **Thrombocyte Cohorts**
  - ***Thrombocytopenic Cohort****:* morning platelet count below $50*10^9$/L at study index
    - Main study cohort
  - *Non-thrombocytopenic (reference) Cohort:* PLT >= 50

- **Treatment Cohorts**
  - *Antiplatelet Only*
  - *Anticoagulant Based*
    - Analyses performed separately on each group

Exposure/Intervention

Three Levels of Antithrombotic Management

1. **Hold vs. Continue**
   - **If CONTINUE, HOW?**: **a)** Prophylactic/intermediate dose; **b)** change drug; **c)** full dose

2. **Increase Platelet Transfusion Threshold?** (Yes / No)
   - **If YES:** What are previous and new thresholds?

3. **Use Mechanical Measures** to reduce thrombosis risk?
   - If YES, WHICH? *(remove CVC, insert IVC filter, use IPC)*

Study Outcomes

Primary Composite Outcome:

1. ISTH-defined **Major bleeding** events

OR

2. Symptomatic or incidental deep or superficial **venous thromboembolism**
   or **arterial thromboembolism**

Secondary Outcomes:

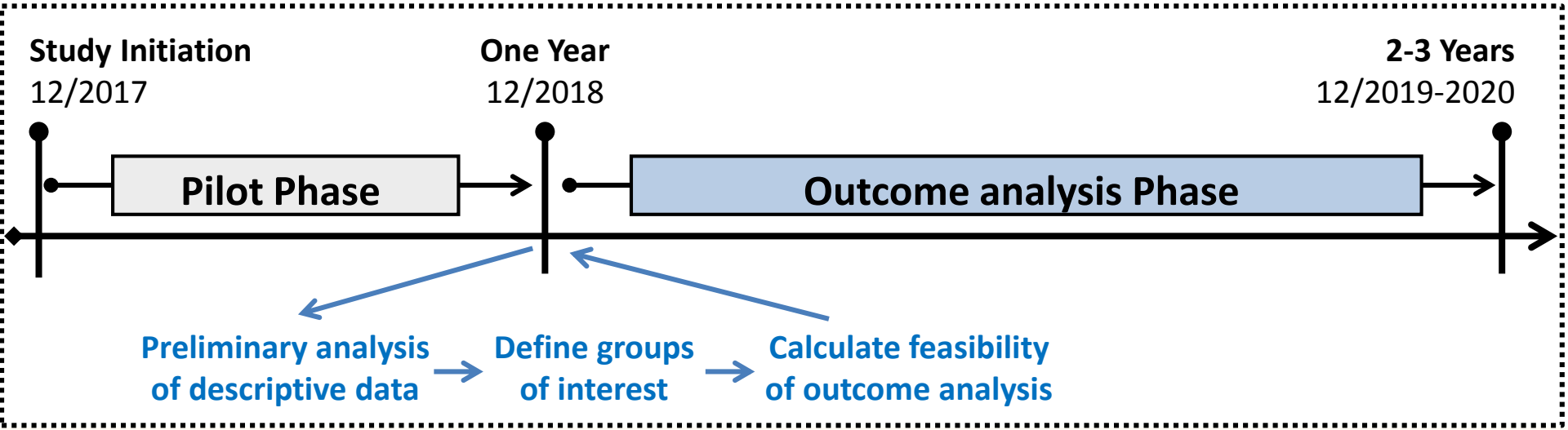
1. Next management intervention
2. ISTH- defined Clinically Relevant non-Major Bleeding[1]
3. Platelet Transfusions (number and adverse effects)
4. RBC transfusions (number)
5. Peak treatment intensity
   - Anti-Xa / Diluted thrombin time / INR / aPTT
6. Whole blood coagulation: ROTEM (Estcourt, BJH 2014)
7. Death

[1]Kaatz, JTH 2015

Pre-planned Analysis Phases

- **Sample Size Target: 300 over first full year.**
- **Pilot Phase: Descriptive analysis** of management practice and incidence of outcomes within each management group

- **Outcome Analysis Phase:** Assess the **relative risk of the outcomes** between selected **management strategy groups**



Discussion

- Additional laboratory tests?
- Additional study questions?
- Any management levels missing?
- Important methodological drawbacks?

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Study Collaborators

Maastricht University / MUMC+

- *Cardiovascular Research Institute (CARIM); Hematology Institute*
- *Thrombosis Expertise Center; Central Diagnostic Laboratory*
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  - **Anna Falanga**

Rabin Medical Center

- *Thrombosis Unit, Hematology Institute*
  - **Galia Spectre**