Proposal: Sic-reg.org – A prospective multicenter registry study for severe immune cytopenias to harmonize diagnostic steps, stratify treatment, and observe their natural course

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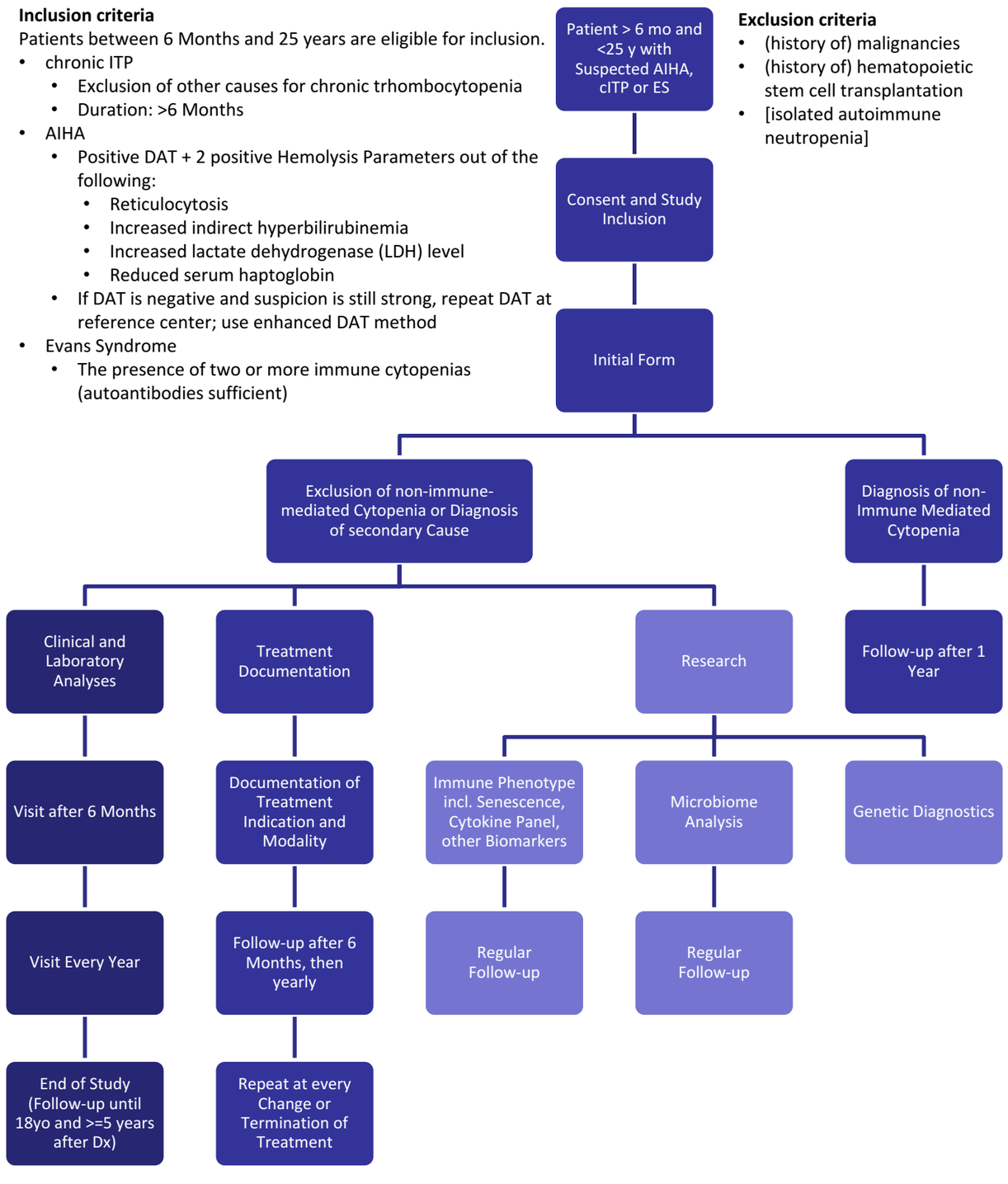
Summary

Background: Autoimmune manifestations belong to the clinical spectrum of primary immune deficiencies and dysregulation disorders (PIDDs) that may severely compromise the quality and expectancy of life. Immune cytopenias occur most frequently in B or T cell deficiencies, and patients with an underlying PID are at an at least 120-fold increased risk to develop cytopenia as compared to the general population (*Fischer et al., JACI 2017*). Among a national pediatric cohort of chronic ITP, many additional or other diagnoses (in >30% of patients, including CTLA4 haploinsufficiency, SLE, Fanconi anemia) were identified, and responses to various standard treatment approaches were highly variable (*Sipurzynski et al., 2016*), suggesting different underlying mechanisms. Thus, the awareness and the diagnostic power for underlying disorders need to be increased to improve the clinical management of patients with severe immune cytopenias.
Aims and Methods: The **proposed open science ESID level 2 registry study** should assist at the clinical level and allow translational research to identify phenotypic, functional, and epigenetic **biomarkers for prognostic and therapeutic risk stratification**. Panels for the diagnostic work-up will include hematological and immunological parameters and enable the exclusion of many differential diagnoses.
Expected Results: Biomarker analyses should allow early management stratification according to patterns reminiscent of known cytopenia-related PIDs even if a molecular diagnosis is not obtained (not needed or unavailable) or pending. Treatment guidelines will be derived from international standard recommendations and regularly complemented with data on newly available approaches. The natural course of the disease will be monitored. Data sets will be compatible with and transferrable to similar national pediatric and adult guidelines or registries.

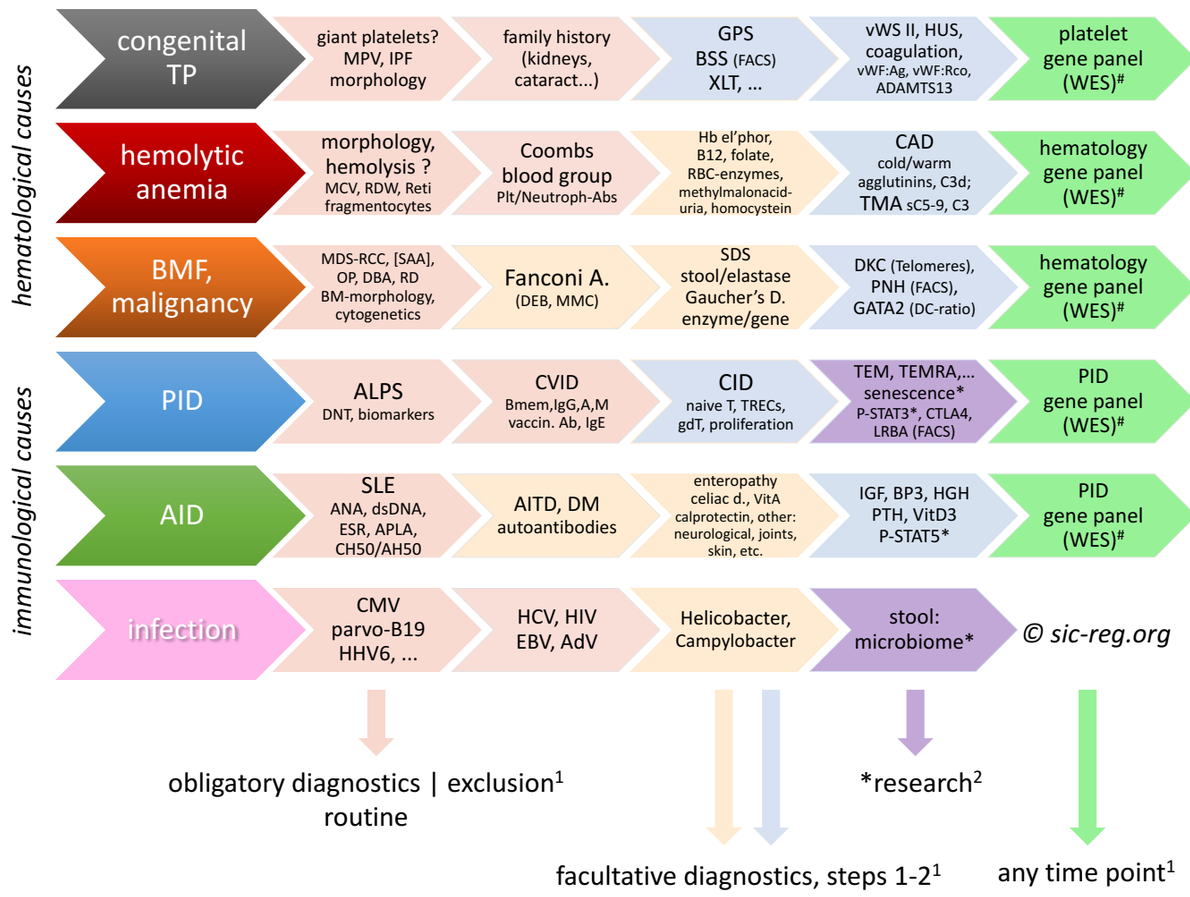
Study Algorithm

Inclusion criteria
Patients between 6 Months and 25 years are eligible for inclusion.
- chronic ITP
  - Exclusion of other causes for chronic trhombocytopenia
  - Duration: >6 Months
- AIHA
  - Positive DAT + 2 positive Hemolysis Parameters out of the following:
    - Reticulocytosis
    - Increased indirect hyperbilirubinemia
    - Increased lactate dehydrogenase (LDH) level
    - Reduced serum haptoglobin
  - If DAT is negative and suspicion is still strong, repeat DAT at reference center; use enhanced DAT method
- Evans Syndrome
  - The presence of two or more immune cytopenias (autoantibodies sufficient)

Exclusion criteria
- (history of) malignancies
- (history of) hematopoietic stem cell transplantation
- [isolated autoimmune neutropenia]

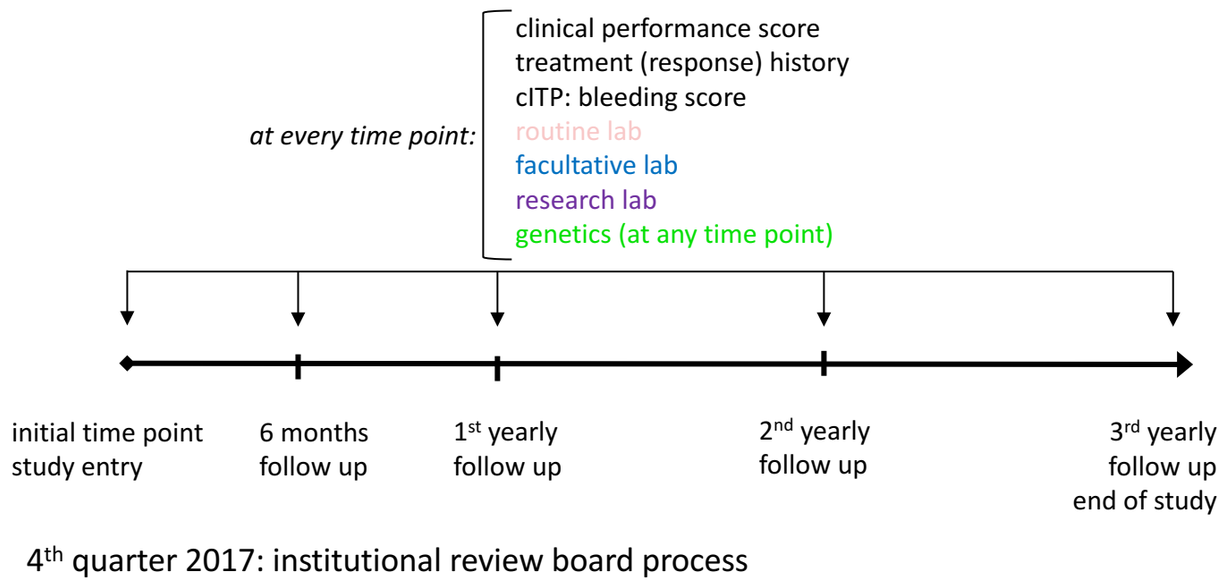


Diagnostic and accompanying research plan



[1]analyses to be done at point of care, results reported to study
[2]analyses performed either at reference centers or at study center

Time axis



4th quarter 2017: institutional review board process
11-12/2017: start as national project in Austria
4th quarter 2017-2018: additional funding acquisition
1st quarter 2018: start as ESID level 2 study
4th quarter 2023: planned study closure

Objectives and endpoints

Primary Goal
- **Rapid detection of underlying causes** of severe immune cytopenias with the aid of a structured diagnostic approach and access to a clinical care network of the participating centers, **allowing early treatment stratification**

Secondary Goals
- Collection of data about epidemiology of rare diseases
- Systemic documentation of response rates to various treatments
- Identification of biomarkers and modifiers of immune tolerance
- Collection of data about the usage of novel/experimental therapeutic agents