## Supplemental File 1.

**Study protocol summaries**

**PANE study**

**Title:** Preoperative screening for mild bleeding disorders

**Acronym**: PANE study

**Trial registry:** Nederlands Trial Register, NTR4070.

**METC (medical ethical committee):** NL38767.068.11, approved on 26 July 2013.

**Principal Investigator:** Dr. ir. Y.M.C. Henskens, Maastricht University Medical Center+, P. Debeyelaan 25, 6202 AZ, Maastricht. Email: yvonne.henskens@mumc.nl.

**Study type:** observational – diagnostic.

**Study objectives**: to assess the prevalence of haemostatic abnormalities in patients with and without reported bleeding symptoms on a preoperative questionnaire, consisting of guideline-proposed bleeding questions, and appraise the diagnostic value of several screening modalities for the identification of patients with haemostatic abnormalities

**Study design:** Patients reporting 1 or more bleeding symptoms on the preoperative questionnaire are primarily included. A random sample of patients not reporting bleeding symptoms is also included. None of these preoperative patients were referred to the haematology department for abnormal clinical bleeding. Preoperatively, all patients undergo haemostatic testing and complete the International Society of Thrombosis and Haemostasis-Bleeding Assessment Tool (ISTH-BAT).

**Study population: adults undergoing any kind of surgery**

**Inclusion criteria**: Age ≥ 18 years; undergoing elective surgery; signed informed consent.
**Exclusion criteria:** pregnancy; the use of medication which may interfere with diagnostic tests; anaemia and thrombocytopenia.

**Primary endpoint**: the prevalence of haemostatic abnormalities, defined as coagulation or fibrinolysis factor levels below the reference range and platelet function defects.

**Secondary endpoint:** diagnostic value of screening assays for haemostatic disorders, using gold standard assays as reference.

**Anesthesiology preoperative bleeding questionnaire**

| | | |
|---|---|---|
| Do you suffer from: | Prolonged bleeding after pulling teeth/molars or after an operation or after delivery? | Yes/No |
| | Spontaneous gum bleeds? | Yes/No |
| | Spontaneous large hematomas? | Yes/No |
| | Spontaneous nosebleeds? | Yes/No |
| | Bleeding after small wounds (for instance after shaving)? | Yes/No |
| | Heavy blood loss during menstruation? | Yes/No |
| Do you have any family relatives with blood clotting problems (not due to blood thinning medication)? | | Yes/No |

**ProBe-AHP study**

**Title:** Predictors of Bleeding Evaluation in Adult Haematologic Patients with Bleeding Tendencies (ProBe-AHP)

**Study Centre**: Maastricht University Medical Centre (MUMC); single center study.
**METC number:** 14-4-036, approved on 14 August 2014

**Study type:** Observational – diagnostic study.

**Study objectives**: To assess the diagnostic parameters of experimental haemostatic tests (e.g. impedance aggregometry, rotational thromboelastometry analysis) by comparing them to the standard diagnostic algorithm and laboratory tests used in MUMC for the workup of patients with a bleeding tendency.

**Study design**: Patients with (suspected) bleeding tendencies are investigated on an out-patient clinic basis, according to the standard workup of the MUMC. According to this workup, patients are assessed by a quantitative bleeding questionnaire and screening and additional blood tests are performed. In addition, extra blood will be drawn for experimental tests. Patient and treating haematologists are blinded to the results of the experimental tests. Sensitivity and specificity of the experimental tests will be estimated at various cut-off values and results will be summarized in receiver operating characteristic (ROC) curves with corresponding area under the curve (AUC).

**Patient population:** Patients referred to MUMC for evaluation of bleeding tendency.

> **Inclusion criteria**: Age ≥ 18 years; signed informed consent; patients with (suspected) bleeding tendency.
> **Exclusion criteria:** platelet count below $100 \times 10^9$/L and/or haematocrit below 0.25 L/L; pregnancy (or lactating); active bleeding due to medical interventions or surgical/obstetrical causes; the use of medication which may interfere with diagnostic tests.

**Primary endpoint**: Diagnostic value (sensitivity, specificity, negative and positive predictive value) of the experimental haemostatic tests, using gold standard assays as reference.

**BEPA study**

**Title:** Patients with established bleeding disorders: The BEPA study

**Study Centre:** Maastricht University Medical Centre (MUMC); single center study.
**METC number:** NL51315.068.14, approved on 18 May 2015

**Study type:** Observational – diagnostic study.

**Study objectives**: To assess the diagnostic accuracy of experimental haemostatic tests (e.g. impedance aggregometry, rotational thromboelastometry analysis) to detect bleeding disorders and to evaluate whether they can be used for monitoring the effects of coagulant factor replacement therapy.

**Study design:** In this diagnostic study the value of experimental tests and the bleeding assessment tool (BAT) for detection of established bleeding disorders is assessed. Sensitivity and specificity of the experimental tests will be estimated at various cut-off values and results will be summarized in receiver operating characteristic (ROC) curves with corresponding area under the curve (AUC). Values of the experimental tests in patients with a bleeding disorder before and after planned medical intervention will be evaluated to see if these tests are able to detect the differences in plasma factor levels before and after treatment.

**Patient population:** Registered patients with established bleeding disorders recruited from the haemophilia treating center ZON.

> **Inclusion criteria:** age ≥ 18 years; signed informed consent.
> **Exclusion criteria:** platelet count below $100 \times 10^9$/L and/or haematocrit below 0.25 L/L; pregnancy (or lactating); active bleeding due to medical interventions or surgical/obstetrical causes <48 hours before laboratory testing; the use of medication which may interfere with diagnostic tests.

**Primary endpoint**: Diagnostic value (sensitivity, specificity, negative and positive predictive value) of the experimental haemostatic tests, using gold standard assays as reference.