Targeted Action for Curing Trauma Induced Coagulopathy

TACTIC

PROJECT FINAL REPORT

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1. Final publishable summary report

1.1 Executive summary

Trauma induces an inability to form clots (termed trauma induced coagulopathy, TIC), which worsens the outcome of bleeding due to trauma. Current treatment of bleeding may differ between centers but involves transfusion of blood products. Red blood cell (RBC) transfusion is needed to deliver oxygen to the tissues, and platelets and plasma are needed to treat TIC. Other products that treat TIC are fibrinogen products and tranexamic acid. It has been recognized that to treat TIC, equal amounts of RBCs, platelets and plasma is needed. This is called balanced resuscitation or ratio therapy or 1:1:1 therapy. However, with this one-size-fits-all approach, there are patients who still have or develop TIC that is not treated or prevented with a balanced approach. At the same time, there are patients who receive transfusions who do not need these particular blood products, resulting in over-transfusion. Outcome of bleeding can probably improve if we are able to apply a more personalized approach. However, the blood tests which are currently used to diagnose TIC do not allow for a personalized approach. They are too slow, as they may take up to 1 hour. Also, these tests are not a good reflection of the ability of the body to form clots. A surge of interest has evolved in the use of Visco Haemostatic Assays (VHA) which are faster and may be better to detect different forms of TIC, requiring different interventions between patients. These tests may have potential to rapidly diagnose TIC in order to initiate personalized treatment. However, there are large knowledge gaps with VHA tests. These tests have not previously been validated in the diagnosis of TIC nor in the monitoring of the treatment of bleeding, as TIC further evolves during the bleeding. Also the response of VHA test results to treatment is not known.

The TACTIC project aimed to fill in the knowledge gaps. The TACTIC programme was initiated by the consolidation of data and blood samples collected from appr. 2000 adult trauma patients at 6 major European trauma centres during the period 2008-2013 (WP2). Next, we set out to determine the current practice of treatment of traumatic bleeding by defining and comparing the diversity and health economics (costs and health outcomes) of existing treatment strategies across Europe (WP3). Then we discussed how we could optimize this treatment. We studied biomarkers and coagulation factors on legacy samples and validated cut off values of VHA that can detect the need for specific blood products. Then we determined the response of VHA tests to therapy. The final output of the project is the development of evidence-based, personalised, targeted treatment algorithms based on VHA results or conventional coagulation tests that can diagnose traumatic bleeding and monitor treatment. These treatment algorithms formed basis for a large European randomized controlled clinical trial in years 3-5 (iTACTIC) to test the efficacy of VHA targeted treatment in respect of patient outcomes, versus conventional laboratory tests of coagulopathic bleeding (WP8). An accompanying health economic model examined cost-effectiveness in the two arms. Analysis of results are ongoing. An app was developed to aid clinical personnel in using VHA and the algorithms (WP7). Implementation of results is ongoing. Throughout the project, exchange programmes have taken place in which PhD students did research in another TACTIC-associated institution.

Finally, we have and will continue to disseminate our findings to ensure these important advances in care are achieved by a coordinated European level approach that ensures discovery research is effectively transferred into clinical guidelines, translated into trauma patient care and adopted as national and global policy (WP9).

1.2. Summary description of project context and objectives

Major trauma haemorrhage is responsible for nearly half of the annual 4.6 million injury deaths worldwide. When the TACTIC project started in 2013, trauma was the world's 4th leading cause of death and the number one cause of lost life years. Most often the consequence of road traffic collisions or interpersonal violence, this health problem has an ever increasing economic and societal impact in Europe. The burden of disease is highest in children and young adults, with half of all trauma deaths the result of blood loss.

1 in 4 severely injured and shocked patients develop a clotting dysfunction (i.e. trauma-induced coagulopathy; TIC) within minutes of injury that exacerbates on-going blood loss and makes surgical repair very difficult. Ultimately, coagulopathic patients have increased blood transfusion requirements and have increased mortality (**Figure 1**).

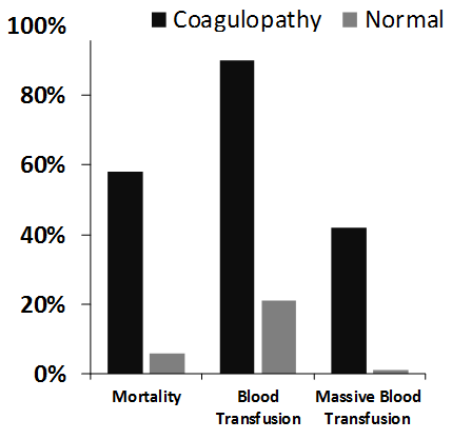


Figure 1: *Trauma patients classified as Coagulopathic (i.e. abnormal blood clotting) have a probability of mortality approaching 60% and are 20 times more likely to die than patients with normal coagulation.*

A great diversity exists in the acute clinical management of trauma haemorrhage and TIC across European hospitals. Contemporary trauma resuscitation seeks to prevent and treat TIC through the administration of various coagulation therapies following empiric treatment protocols as opposed to individualised care. A critical barrier to the enhancement of TIC management is the ability to rapidly and accurately diagnose the disease. The absence of rapid and validated tools for diagnosing TIC means that current treatment potentially incurs avoidable waste of precious resources (blood products and expensive medication), delay in time-critical treatment, longer-term complications and the inability to save life. This has led to interest in the use of point-of-care Viscoelastic Hemostatic Assays (VHAs) to diagnose and treat TIC in its many forms during the acute bleeding episode. VHA methods measure relevant coagulation properties in full blood and in real time, as opposed to conventional coagulation lab tests used as a standard of care in most hospitals.

The TACTIC collaboration built on an existing European network of clinical academic trauma experts with capacity for patient recruitment at some of the world's leading specialist trauma centres. The collaboration came about due to a need for coordinated European research for the global enhancement of trauma care, specifically bleeding coagulopathic patients, and translation into clinical practice and policy. The overall aim of TACTIC was to compare current EC practice at the local specialist centre level and deliver evidence-based clinical support for the diagnosis and delivery of personalised, targeted treatment of coagulopathic bleeding patients.

The TACTIC programme was initiated by the consolidation of data and blood samples collected from appr. 2000 adult trauma patients at 6 major European trauma centres during the period 2008-2013 (WP2). Several parallel activities delivered TACTIC's first objectives in Years 1-3, namely defining and comparing the diversity and health economics (costs and health outcomes) of existing treatment strategies across Europe (WP3); to ascertain the molecular pathophysiology of TIC (WP4) by studying patient biomarkers, and to enable the diagnosis of 'normocoagulable' patients and different patterns of TIC, based upon their molecular and functional coagulation status (WP5&6).

In Year 2 the outputs from WP3-6 enabled the development of evidence-based personalised, targeted treatment schemes (algorithms) to correct dysfunctional coagulation due to traumatic injury (WP5+6). These treatment algorithms formed basis for a large European randomized controlled clinical trial in years 3-5 (WP8) to test the efficacy of VHA targeted treatment in respect of patient outcomes, versus conventional lab tests of coagulopathic bleeding (WP8). An accompanying health economic model examined cost-effectiveness in the two arms.

We have also translated our new understanding of TIC patient patterns into a dynamic VHA visual support tool to facilitate the targeted correction of coagulopathy using VHA (WP7).

Finally, we have and will continue to disseminate our findings to ensure these important advances in care are achieved by a coordinated European level approach that ensures discovery research is effectively transferred into clinical guidelines, translated into trauma patient care and adopted as national and global policy (WP9).

1.3. Main results

The TACTIC project workflow is illustrated in **Figure 2**.

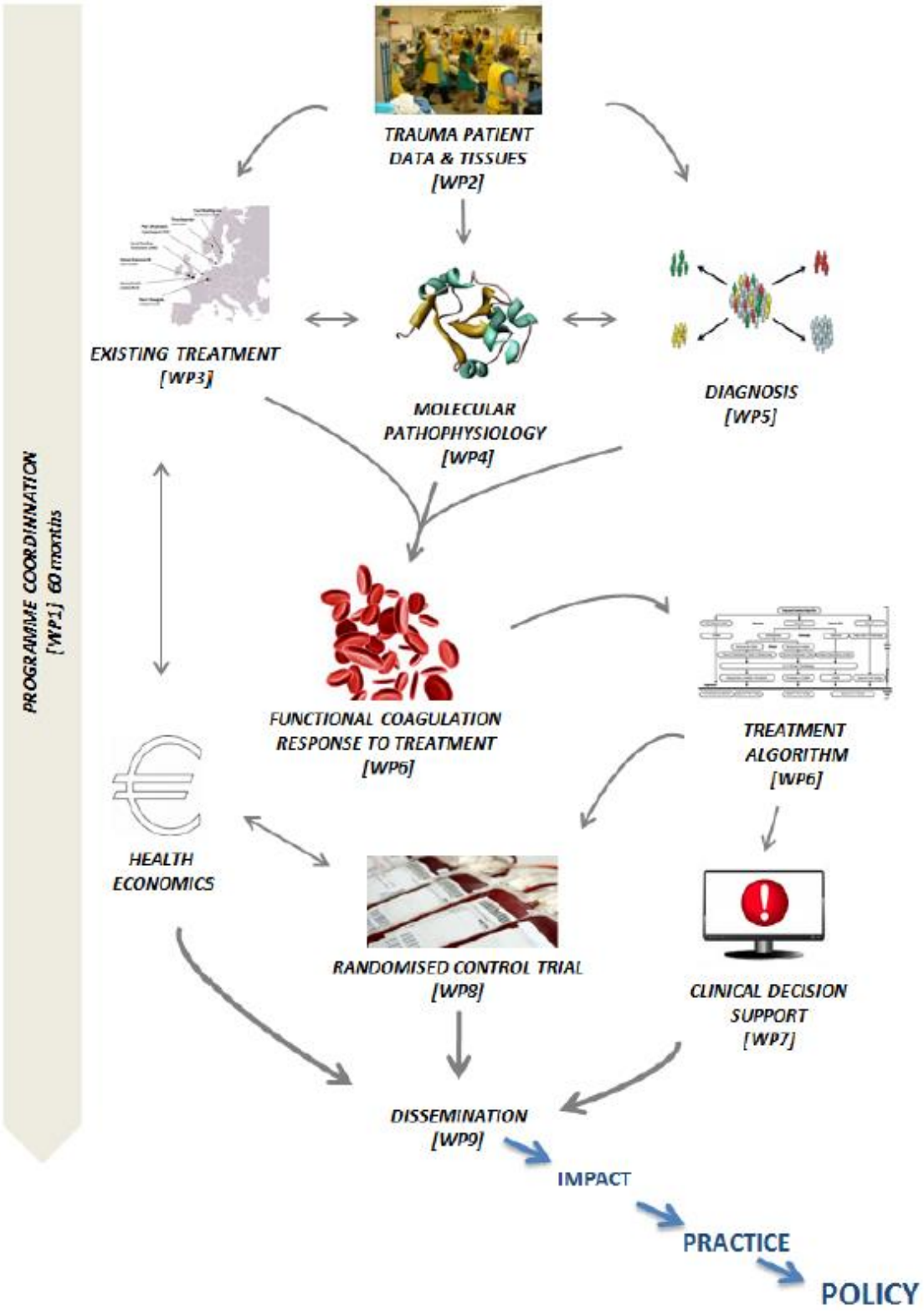


Figure 2. TACTIC workflow between and from the work packages.

The TACTIC programme was initiated by the consolidation of data and blood samples previously collected from 2000 trauma patients (WP2). The data from the 2000 trauma patients were channelled into several parallel activities to deliver TACTIC's first objectives in Years 1-2. Namely: to define and compare the diversity and health economics (costs and health outcomes) of existing treatment strategies across Europe (WP3); to ascertain the molecular pathophysiology of TIC (WP4) by studying patient biomarkers (upon admission to the Emergency Department and in response to haemostatic transfusion); and to enable the diagnosis of 'normocoagulable' patients and different patterns of TIC, based upon their molecular and functional coagulation status (WP5&6).

The outputs from WP3-6 were merged to describe the molecular and functional response to existing coagulation therapy, defined in respect of the nature, quantity and timings of products administered. This enabled the development of evidence-based, data-driven, personalised, targeted treatment algorithms to correct functional coagulation (WP6). These targeted algorithms were applied in the iTACTIC randomised control trial to test the efficacy of VHA targeted treatment in respect of patient outcomes, versus empiric management of coagulopathic bleeding (WP8). An accompanying health economic model examined cost-effectiveness.

Our new understanding of TIC patient patterns was translated into a more intuitive dynamic visual support tool that was assessed and evolve to facilitate the targeted correction of coagulopathy (WP7).

Finally, we have disseminated our findings to ensure these important advances in care are achieved by a coordinated European level approach (WP9). As the project ends we will continue the focused dissemination efforts to ensure that our research is effectively transferred into clinical guidelines, translated into trauma patient care, and adopted as national and global policy.

WP2

A sustainable infrastructure was established as the project commenced to ensure the standardised collection, consolidation, and distribution of the Consortium's clinical samples and associated trauma patient data. An international trauma research registry was established in London managed by partner 5 and a centralised repository (biobank) for tissue sample management was established in Copenhagen by partner 1.

International Trauma Registry

Throughout the project, partner 5 ensured the audited receipt and centralised reporting of all site data to the International Trauma Registry. The Registry had additional data variables added to it throughout the TACTIC project, and the final version (v4.5) was implemented on 30 October 2018.

A web-based database (Cerner Discovere) for WP8 (the iTACTIC randomised control trial) went live on 04 July 2016 and study data from the iTACTIC RCT was successfully uploaded at all sites. This database was been cleaned and locked in accordance with iTACTIC requirements after the WP8 clinical trial had ended. Discovere is now officially closed and can no longer be accessed, so the trial database is now stored securely in London with Ben.5.

Centralised Trauma Tissue Bank

Partner 1 coordinated the secure distribution of blood samples between Partner sites conducting analyses as part of TACTIC and for other ethically-approved trauma research. Prior to the TACTIC project, blood samples

from trauma patients at TACTIC participating hospitals had been collected. Samples from appr. 2000 subjects were gathered in the biobank in Copenhagen as the project commenced. Biomarker and coagulation analyses on the samples were performed by partners 1 and 5 in Copenhagen and London as part of WP4.

By the end of the project, 6,137 samples from legacy research subjects and TACTIC research subjects were stored in the centralised Biobank in Copenhagen (**table 1**). These included:

PLASMA samples (extracted from citrated whole blood): Remainders after coagulation and biomarker signature analyses by the TACTIC Consortium.

BUFFY COAT samples (i.e. the fraction of an anticoagulated blood sample that contains most of the white blood cells and platelets following centrifugation): Most buffy coat samples were used for generating purified DNA for genetic profiling. The remaining buffy coat samples are either not baseline samples (only baseline samples are used for SNP-analysis) or contain insufficient amounts of material for SNP-analysis.

PURIFIED DNA samples: DNA was purified from the samples and Single nucleotide polymorphism (SNP) analyses performed as part of WP4.

***Table 1**: Remaining biobank samples in TACTIC biobank*

Partner (site location)	Total number of plasma samples in biobank	Total number of buffy coat samples in biobank	Number of purified DNA samples in biobank (from legacy research)	Number of purified DNA samples in biobank (from iTACTIC subjects)
1 (Copenhagen)	410	233	273	102
2 (Amsterdam)	89	88	87	0
3 (Cologne)	0	0	0	0
4 (Oslo)	383	308	307	66
5 (London)	1392	1037	1034	116
JR Oxford	0	225	104	0
Total	2274	1774	1805	284

Project partners designed and implemented a centralised project Biobank (Ben.1 in Copenhagen) and a tissue-linked study patient Registry (Partner 5 in London) enabling the robust collection, transfer, storage and analysis of pre-existing locally-housed trauma patients materials and prospective TACTIC study materials throughout the project.

WP3

To assess and characterize the different existing strategies for the empiric management of trauma haemorrhage and TIC across EC sites, Ben.3 and Ben.6 collected costing and clinical patient data from clinical partner sites in Copenhagen, Amsterdam, Cologne, Oslo, London and Oxford.

All participating trauma centres have developed and implemented a local algorithm (set of rules) and protocol for the bleeding trauma patient, which employ different “Code Red”-triggered massive blood transfusion protocols (MHP), transfusion packages and “fixed-ratio” approaches. All centres work with multidisciplinary resuscitation teams (surgeons, anesthetists etc). These algorithms and protocols are uniformly activated by clinical triggers and deactivated once the bleeding stops according to clinical assessment in combination with laboratory signs of achieved haemostasis. The degree of coagulopathy and shock is mostly assessed via standard coagulation tests and extended viscoelastic testing to assess the degree of the coagulopathy. All centres have implemented the immediate use of fibrinolysis inhibitor tranexamic acid in cases of severe trauma and/or shock. All centres start their initial resuscitation by using transfusion packages with pre-fixed universal blood product combinations and ratios following the concept of “damage control resuscitation”. Transfusion packages, including applied ratios, substantially vary between centres. Two centres initially start with transfusion packages but viscoelastic testing running in parallel quickly allows a shift towards a viscoelastic test-guided therapy. A broad consensus across the six European level I trauma centres regarding their local treatment algorithms for the management of bleeding and coagulopathy was revealed, which were in accordance with the 2013 up-dated European trauma guideline. A few differences across the centres became apparent, such as pre-hospital blood product use and viscoelastic test performed routinely, which might be considered for implementation, respectively.

A web-based survey focusing on the local practice and infrastructure in treating bleeding trauma patients was conducted amongst the delegates at the 15th European Congress of Trauma and Emergency Surgery (ECTES) and the 2nd World Trauma Congress held in Frankfurt in addition to WP3. In summary, this survey confirmed substantial differences in infrastructure, logistics and clinical practice for the detection and management of trauma haemorrhage and trauma-associated coagulopathy amongst international centres.

The analysis of costs and health outcomes associated with different patient populations and existing treatment practices showed that both costs and outcomes differed between TACTIC participating hospitals. For the analysis, partner sites contributed the following numbers of patients: London n=961, Oslo n=428, Copenhagen n=273, Amsterdam n=248, Cologne n=51, and Oxford n=211.

For the full cohort in each country, total mean inpatient costs varied considerably on account of patient heterogeneity. Analyses have also been performed for sub-groups of patients for whom a massive haemorrhage protocol was activated, and for whom the risk of mortality was predicted to be greater than 50% (a RISC score <0).

Total mean inpatient costs per patient for patients where the massive transfusion protocol is activated were €41,528 (SE €2,803) in London, €40,340 (SE €3,817) in Oslo, €32,901 (SE €5,353) in Copenhagen, €38,973 (SE €9,308) in Amsterdam, and €76,700 (SE €25,759) in Cologne, and €38,620 (SE €6,526) in Oxford (numbers in parentheses refer to standard error). In the various sub-groups, the key cost drivers appear to be surgery, time in intensive care and general wards, ventilation, and blood product usage. Heterogeneity existed between the sites for a number of resource use categories including time spent in ICU and blood products transfused during the first 24 hours.

In order to analyse and compare high-risk patients across sites in a sub-analysis with respect to resource utilisation, costs, and outcome, focus was given to patients with less than 50% probability of survival according to the RISC score and to patients with activated MHP. Heterogeneity was also apparent in the risk-adjusted patient sub-group. Total mean costs were €42,925.9 (SE €7,727.2) in London, €22,922.6 (SE €4,902.8) in Oslo, €29,855.1 (SE €8,087.3) in Copenhagen, €25,973.2 (SE €9,576.7) in Amsterdam, €30,713.2

(SE €13,132.8) in Cologne, and €33,125.3 (SE €13,406.7) in Oxford. Due to higher injury severity, and thus, higher expected and observed mortalities, the risk-adjusted patients cause lower costs in most centres than the sub-group of patients with activated MHP.

Outcome in terms of survival at 24 hours and at 28 days also varied across centres. The percentage of patients who had died at 24 hours ranged from 0-21.6% (patients with activated MHP protocol) and from 0-42.5% (risk-adjusted patients), and at 28 days ranged from 15.8-40.5% (patients with activated MHP protocol) and 62.5-100% (risk-adjusted patients).

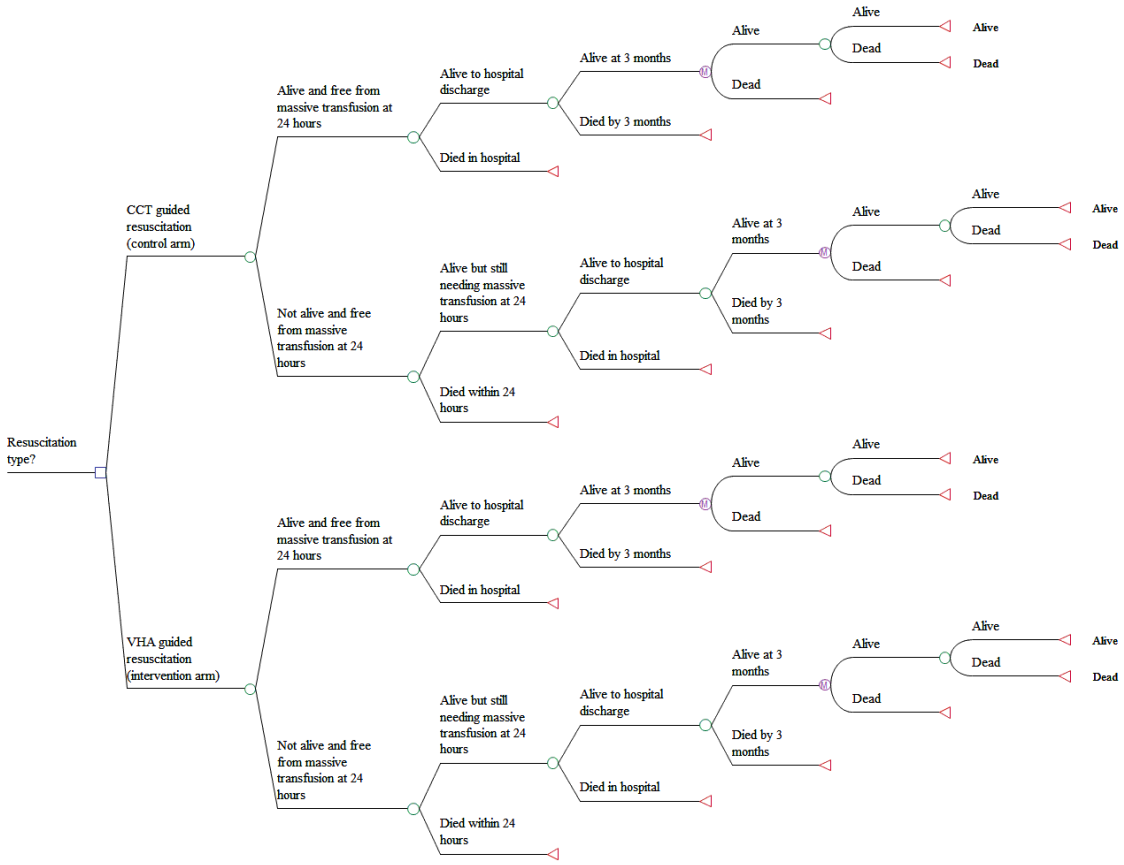


***Figure 3**. Health economic model which was used as part of WP8 to model the cost-effectiveness of VHA-led resuscitation versus conventional resuscitation in haemorrhaging trauma patients.*

The final output from WP3 was a health economic model centred on the correction of coagulopathy during patient management for estimating the cost-effectiveness of personalised treatment in the WP8 clinical trial (**Figure 3**).

WP4

To increase our understanding of the blood clotting defects/coagulopathy that some trauma patients develop, 1.796 plasma samples from 1.571 trauma patients were analyzed at Rigshospitalet, Copenhagen (RH), Denmark and Queen Mary, University of London (QMUL), UK (**Table 2**). Each of the plasma samples were more specifically analyzed for the following plasma biomarkers: *Coagulation factors:* Fibrinogen, FVII,

FVII, FXII, FXI, FIX, FV, FII, FX, PF1+2, *Anticoagulation factors:* Protein S, Protein C, aPC, EPCR, AT, antiplasmin; *Fibrinolytic factors:* PAI-1, tPA, FMC, D-dimer, PAP, TAFI; *Endothelial markers:* vW, Syndecan-1, VE-cadherin, VEGFR1, HcDNA, E-selectin; *Catecholamines:* adrenaline, noradrenaline.

***Table 2**. Number of plasma samples analyzed for vasculopathic and endothelial marker levels at Admission, during resuscitation and at 24 and 72 hours from each Partner.*

Plasma samples	RegionH n=438	QMUL n=1460	AMC n=93	NAKMI n=394	OXFU n=42	Total n=2,485
0 h	276	663	60	217	42	**1,258 (100%)**
4 RBC	8	56	2	20	0	**86 (7%)**
8 RBC	3	24	0	11	0	**38 (3%)**
12 RBC	4	16	0	10	0	**30 (2%)**
24 h	92	374	18	94	33	**611 (49%)**
72 h	55	327	13	42	25	**462 (37%)**

Furthermore, DNA from 1.812 patients was extracted and after quality control 1.761 DNA samples were available to investigate gene variants related to the coagulation, anticoagulation, fibrinolytic and endothelial cell systems by single nucleotide polymorphism (SNP) analysis of the following: β1-adrenergic receptor Rs1801253, Rs2801252; β2-adrenergic receptor Rs1042713, Rs1042714, Rs1800888, Rs1042717; Syndecan-1 Rs11544860; Heparan sulphate Rs4693608, Rs4364254; E-selectin Rs5361, Rs1805193; TM Rs1042579, Rs3176123, Rs1962, Rs1042580; Protein C Rs121918149; EPCR Rs867186; IP receptor Rs2229131, Rs201475182; tPA Rs2020918 (**Table 3**).

***Table 3.** SNP´s selected for analysis.*

Molecule	Gene	Reference SNPs ID (rs) no
β1-adrenergic receptor	*ADRB1*	Rs1801253, Rs2801252,
β2-adrenergic receptor	*ADRB2*	Rs1042713, Rs1042714, Rs1800888, Rs1042717
Syndecan-1	*SDC-1*	Rs11544860
Heparan sulphate	*HPSE*	Rs4693608, Rs4364254
sE-selectin	*SELE*	Rs5361, Rs1805193
Thrombomodulin	*THBD*	Rs1042579, Rs3176123, Rs1962, Rs1042580
Protein C	*PROC*	Rs121918149
Endothelial protein C receptor	*PROCR*	Rs867186
Prostacyclin receptors	*hIP*	Rs2229131, Rs201475182
tPA	*PLAT*	Rs2020918

The analysis of 25 targeted biomarkers of coagulation and fibrinolysis for 1,571 individual trauma patients, using advanced statistical analysis revealed a limited number of different phenotypes of TIC and a detailed

description of this will be published. An important finding was the identification of a novel hyperfibrinolytic TIC phenotype published by *Gall et al, Annals of Surgery (2018)* https://www.ncbi.nlm.nih.gov/pubmed/29557885. This is of profound importance in diagnosis, management and outcomes of trauma patients. For diagnosis, it supports the empiric use of antifibrinolytic therapy in these patients and drives the development of new diagnostic modalities. For management, it suggests antifibrinolytics such as tranexamic acid may have a role in the management of traumatic brain injury and supports on-going and future clinical trials in this area.

Pivotally, the biomarker data of coagulation and fibrinolysis were combined with clinical data from the respective patients and this was used for development of data driven haemostatic resuscitation protocols (set of rules for treatment) that were tested in the randomized clinical trial iTACTIC.

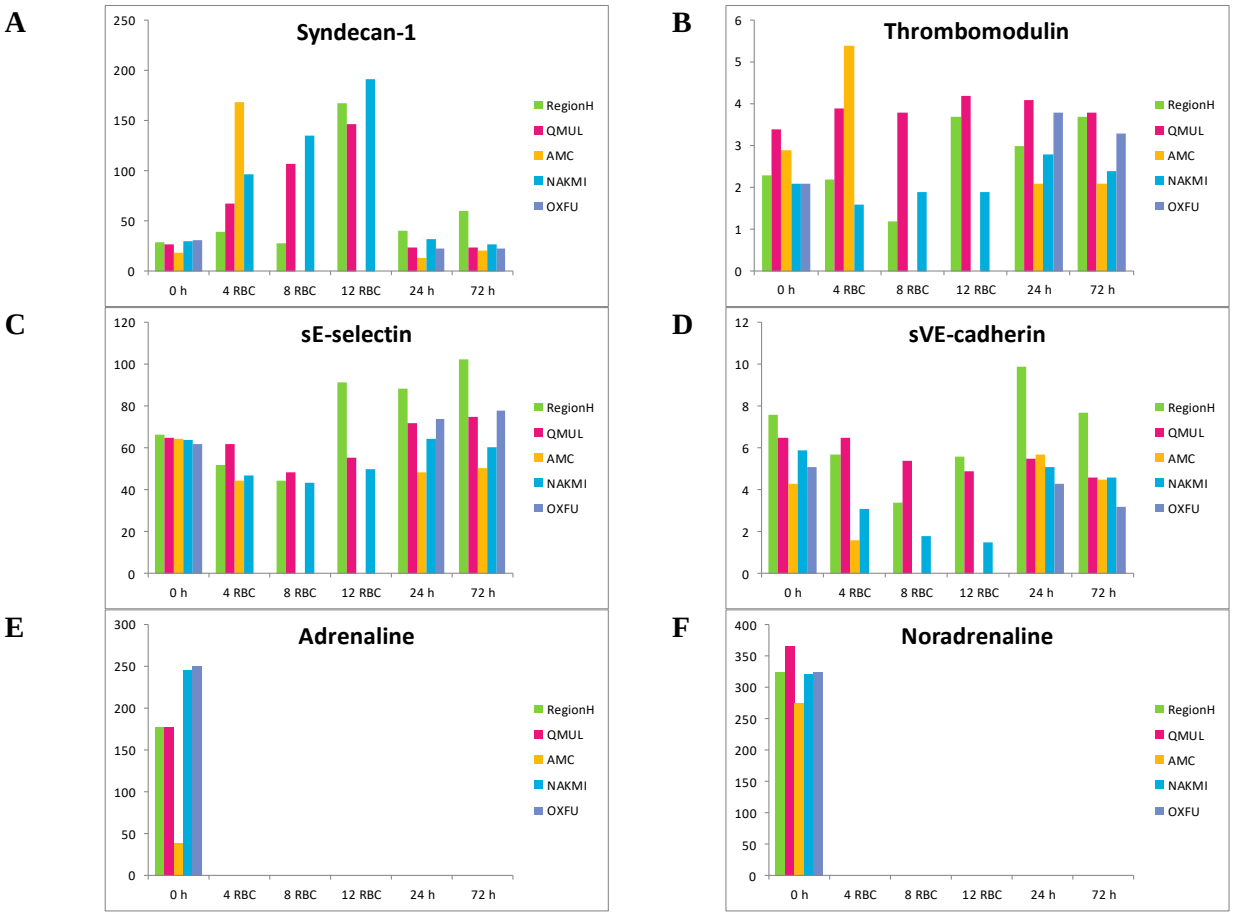


Figure 4. *Median values of plasma biomarkers of endothelial damage, sympathoadrenal activation and shock at admission and for up to 72 hours*

With regard to the biomarkers reflecting endothelial damage, and in accordance with previous findings, we found positive correlations between tissue/endothelial damage biomarkers (Syndecan-1, TM, VE-cadherin, E-selectin) and sympathoadrenal activation/shock biomarkers (Adrenaline, Noradrenalin) at trauma admission (baseline) as adrenaline and noradrenaline both correlated with syndecan-1 ($r=0.18$, $p<0.0001$ and $rho=0.11$, $p=0.0032$, respectively) and TM ($r=0.11$, $p=0.0020$ and $r=0.14$, $p<0.0001$, respectively). Most of the endothelial damage biomarkers were highly positively inter-correlated at baseline and to a varying degree

during resuscitation after transfusion of 4-8-12 red blood cell (RBC) units as well at 24 hours and 72 hours (**Figure 4**).

With regard to SNP analysis, out of the 20 SNP´s we were able to find probes that could give a relevant signal for 13 SNP´s (highlighted in the table below) in 1.761 patients, whereas the remaining 7 SNP´s were not possible to analyze. The respective SNP´s potential influence on clinical outcome data in trauma patients with haemorrhagic shock was ascertained in 774 trauma patients of whom 110 did not survive. The results will be presented in a peer-review international medical journal.

WP5

There are currently two market-leading VHA systems using slightly different test modes, namely Thrombelastography (TEG; Partner 7) and Rotational Thrombelastometry (ROTEM; Partner 8). Each assesses the viscoelastic properties of blood samples under low shear conditions, to provide a more comprehensive visual profile of blood clot formation and fibrinolysis. In practice, whole blood is incubated at 37°C in a series of heated cups with activators of coagulation. The relative contribution of components such as fibrinogen and platelets to clot strength can be evaluated through the addition of specific compounds.

Clinical data from patients upon admission to the hospital from conventional coagulation tests (CCT), rotational thrombelastometry (ROTEM) and thrombelastography (TEG), were collected prospectively for 2287 adult trauma patients at 6 major European trauma centres (ROTEM in 2019 patients; TEG in 968 patients) during the period 2008-2013.

To identify significant VHA parameters capable of detecting TIC (defined as INR above 1.2), low fibrinogen (< 2.0g/L) and low levels of platelets (thrombocytopenia) (< 100 x10^9/L) univariate regression models were constructed for these outcomes and area under the curves (AUCs) were calculated. Based on these analyses we constructed algorithms for ROTEM, TEG and CCTs for correcting coagulopathy (blood clotting disorder) in addition to baseline ratio driven blood transfusions and tranexamic acid (TXA).

A paper describing the performance of both devices (ROTEM® and TEG®) and including the resulting algorithms was published by Baksaas-Aasen et al. in Annals of Surgery - *Data-driven Development of ROTEM and TEG Algorithms for the Management of Trauma Hemorrhage: A Prospective Observational Multicenter Study. Ann Surg. 2018 May 23*. (https://www.ncbi.nlm.nih.gov/pubmed/29794847). The algorithms are presented below (**Figure 5**). The algorithms were taken forward and utilized in the completed RCT (WP8), iTACTIC, from which the results are currently being processed.

a) ROTEM **b) TEG** **c) CCT**

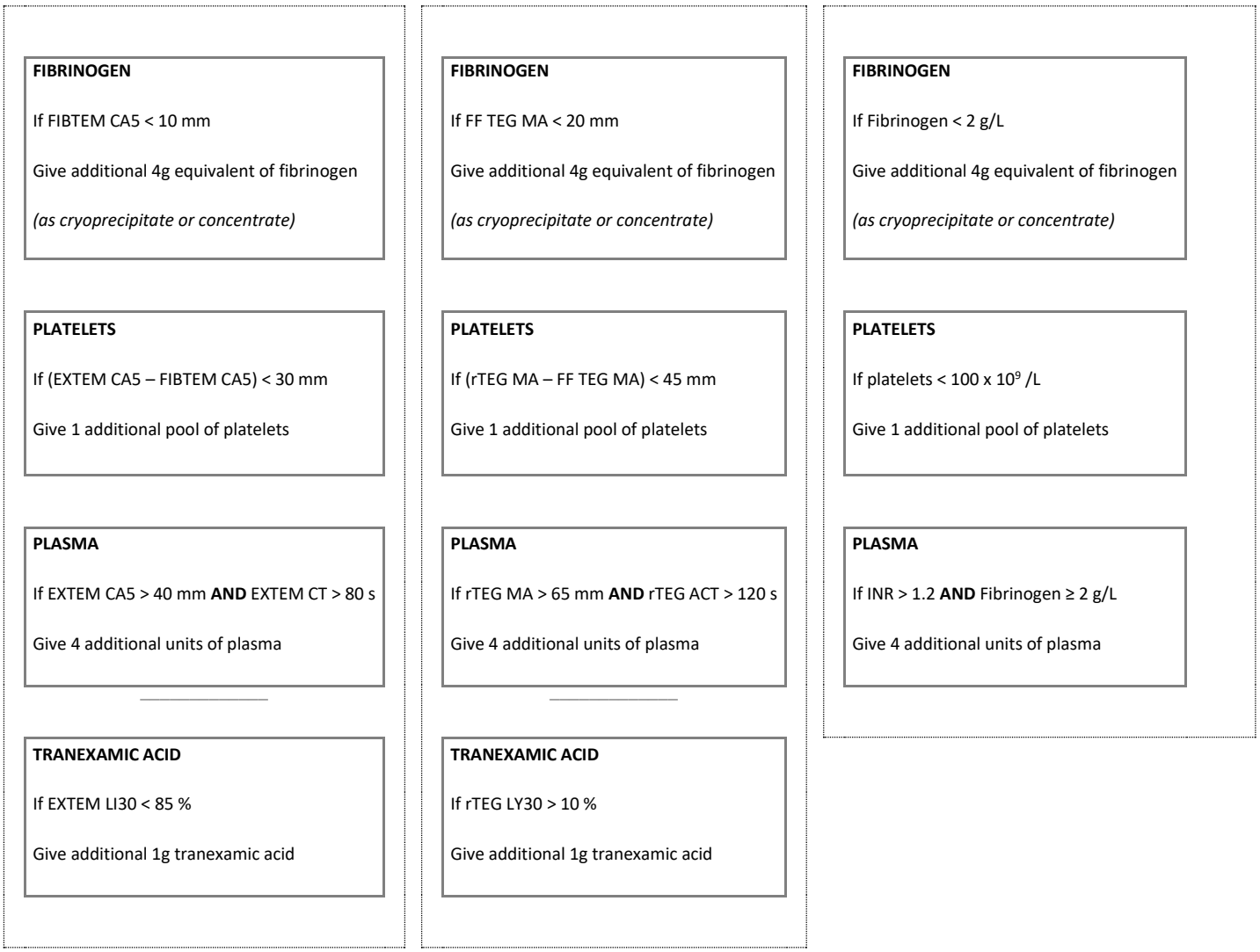


Figure 5: Algorithms for correcting coagulopathy. *CA5 = clot amplitude at 5 minutes, CT = clotting time, LI30 = Lysis Index at 30 minutes, FF TEG = Functional Fibrinogen TEG, rTEG = rapid TEG, MA = maximum amplitude, ACT = activated clotting time, LY30 = clot lysis at 30 minutes.*

Additionally, we identified a large cohort of patients whose hyperfibrinolytic coagulopathy is not identified by viscoelastic assays (or other assays). This is a vitally important group to recognize, as many clinicians withhold antifibrinolytic therapy without diagnostic evidence of hyperfibrinolysis. We identified a new mechanism for this fibrinolysis and explained why this group is occult to the diagnostic tests. This has been published and will lead to new management approaches and to new diagnostic approaches to this group (https://www.ncbi.nlm.nih.gov/pubmed/29557885)

We have focused on a single phenotype identified within WP4 as an occult hyperfibrinolytic phenotype as this constitutes the largest number of patients and failure to identify and treat this group is potentially the largest gap in trauma coagulopathy management. Full details are in our paper published in Annals of Surge (https://www.ncbi.nlm.nih.gov/pubmed/29557885). In brief, we identified a group of patients with low VHA levels of lysis (maximum lysis measure – ML) who had increased mortality (Fig 2-A). We then showed that this group was heterogenous and clinical outcomes defined by D-Dimer level and ML was non-discriminatory for patients with good and bad outcomes (**Figure 6-A**).

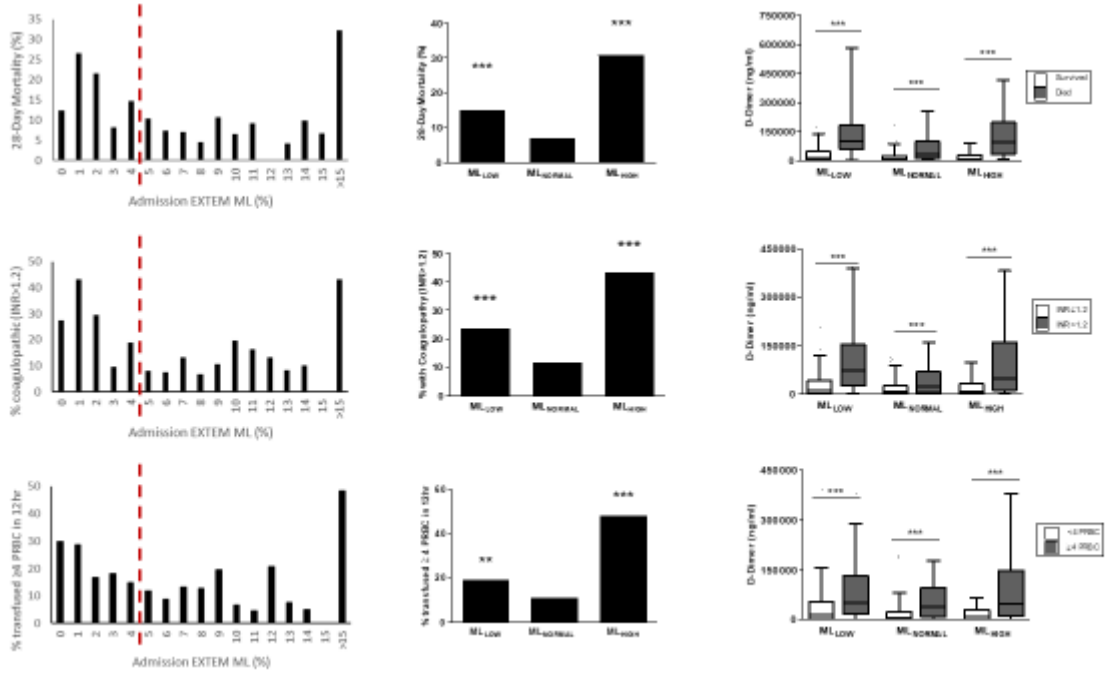


Figure 6-A.

We showed that a group of patients with low ML and high D-Dimer had high mortality while low ML but normal D-Dimer levels had normal outcomes (Figure 2-B). This group of patients had a much higher incidence of traumatic brain injury, suggesting a novel mechanism for the hyperfibrinolysis which we explored further in WP4.

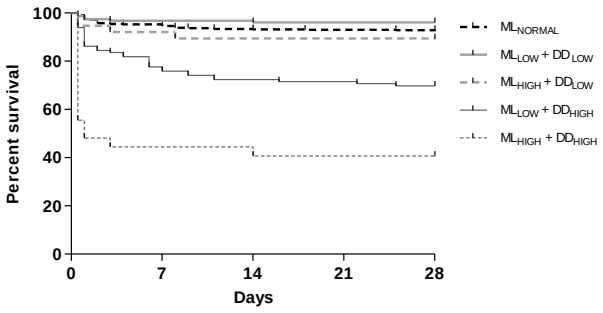


Figure 6-B.

This provides strong evidence against the "early fibrinolytic shutdown" hypothesis which actively advocated against giving empiric antifibrinolytic therapy to patients. We believe our work supports the findings of the international CRASH-2 trial and shows the potential for antifibrinolytics to also show benefit in traumatic

brain injury. These findings were presented to the international Chicheley Hall group (see WP9) and will be taken forward in future dissemination plans.

WP6

Large variation in transfusion strategies exists across the globe, including treatment of coagulation disorders induced by trauma (termed trauma induced coagulation, TIC). In the United States, blood products including red blood cells (RBCs), plasma and platelets are transfused in a balanced approach, using a fixed ratio. Tranexamic acid (TXA) and fibrinogen products are given to a minority of patients. In contrast, in Europe, TXA and fibrinogen products are widely used. The effect of a combined approach of a balanced transfusion ratio together with the administration of TXA and fibrinogen products on outcome of trauma patients is not known and was investigated in a prospective study involving 6 European trauma centres. From the trauma cohort of 2000 patients, there were 385 patients requiring massive transfusions (defined as needing ≥10 units of red blood cells within 24 hours). In this group, logistic regression models were performed to assess the effect of transfusion strategies on outcome. It was found that a high platelet to RBC ratio (OR 2.67, 95% CI 1.24-5.77, p=0.01), a high plasma to RBC ratio (OR 2.2, 95% CI 1.03-4.13, p=0.04) and use of TXA (OR 2.71, 95% CI 1.29-5.71) are associated with a decreased need for massive transfusion and with an increased survival (**Table 4**).

Table 4. Multivariate analysis for correction of TIC within 24 hours (values are 95% CI).

	Odds ratio	*P*
Age	1·03 (1·01, 1·05)	0·001
Fluids per 100 ml in 24 h	0·98 (0·97, 0·99)	0·001
High ratio of plasma to RBCs	0·89 (0·45, 1·78)	0·747
High ratio of platelets to RBCs	0·63 (0·32, 1·26)	0·194
Use of tranexamic acid	1·64 (0·82, 3·29)	0·165
Use of fibrinogen products	1·61 (0·74, 3·54)	0·233

Further research focused on the utility of the point-of-care test Rotational Thromboelastometry (ROTEM) to guide therapy in bleeding trauma patients receiving resuscitation therapy. ROTEM can rapidly detect TIC and, therefore, this test is currently used in transfusion algorithms. However, the response of ROTEM to transfusion therapy is unknown. This response to treatment may vary, yielding specific subtypes of coagulation disorders that react differently to therapy. Also, specific patient characteristics may determine the response to therapy.

From 2000 included trauma patients, there were 309 bleeding patients for whom ROTEM values were available for analysis. Blood samples were drawn on arrival at the emergency department, and after administration of 4, 8 and 12 RBCs. The response of ROTEM to plasma, platelets, TXA and fibrinogen products was evaluated in the whole cohort as well as in the subgroup of patients with ROTEM values indicative of TIC. A mean dose of 3.8 grams of fibrinogen increased FIBTEMCA5 with 5.2 mm (4.1–6.3). TXA administration decreased lysis by 5.4 % (4.3–6.5). Platelet transfusion prevented further derangement of parameters of clot formation. The effect of platelets on EXTEMCA5 values was more pronounced in patients with a ROTEM value indicative of a coagulation disorder, as compared to the whole cohort (**Table 5**).

Table 5. ROTEM response to platelets

	All patients receiving platelets $N = 137$ intervals	Patients with EXTEM ca5 – FIBTEM CA5 < 30 receiving platelets $N = 25$ intervals	Patients not receiving platelets $N = 103$ intervals
EXTEM ca5 (mm)	− 1.55 (− 4.48 to 1.37)	0.74 (− 4.77 to 6.25)*	− 4.39 (− 6.06 to − 2.72)
EXTEM CA10 (mm)	− 1.14 (− 4.24 to 1.95)	0.53 (− 5.6 to 6.66)	− 4.13 (− 5.96 to − 2.3)
EXTEM MCF (mm)	− 0.11 (− 2.77 to 2.55)	1.45 (− 3.92 to 6.81)	− 2.67 (− 4.58 to − 0.75)
EXTEM α angle (°)	0.43 (− 2.96 to 3.82)	1.18 (− 5.8 to 8.16)	− 3.34 (− 5.07 to − 1.62)

CA5, clot amplitude after 5 min; CA10, clot amplitude after 10 min; Data are median and interquartile range (IQR); MCF, maximum clot firmness. *$P < 0.05$ versus not receiving platelets. ROTEM response was determined in intervals during resuscitation therapy.

Plasma transfusion decreased EXTEM CT with 3.1 sec (-10–3.9) in the whole cohort and with 10.6 sec (-45–24) in the subgroup of patients with a ROTEM value indicative of coagulopathy (**Table 6**).

Table 6. ROTEM response to plasma

	All patients receiving plasma $N = 117$ intervals	Patients with EXTEM CT > 80 and CA5 > 40 receiving plasma $N = 17$ intervals	Patients not receiving plasma $N = 42$ intervals
EXTEM CT (s)	− 3.1 (− 10.0 to 3.9)*	− 10.6 (− 45.7 to 24.2)	10.8 (− 0.8 to 22.3)
EXTEM MCF (mm)	− 1.7 (− 3.3 to − 0.1)	− 5.2 (− 12.1 to 1.7)	− 4.1 (− 7.9 to − 0.4)
EXTEM CFT (s)	19.5 (4.7–34.3)	30.31 (1.2–59.4)	37.4 (5.4–69.4)

CT, clotting time; CFT, clot formation time; Data are median and interquartile range (IQR); MCF, maximum clot firmness. *$P < 0.05$ versus not receiving plasma. ROTEM response was determined in intervals during resuscitation therapy.

Therefore, ROTEM can be used for monitoring of treatment during ongoing traumatic haemorrhage. In patients with ROTEM threshold values known to correspond to coagulopathy, the efficacy of plasma and platelets to correct deranged ROTEM values was possibly clearer compared to the whole bleeding population, suggesting that ROTEM-based algorithms can be used to treat and monitor TIC.

Further analyses compared the coagulation profile of specific patient subgroups at baseline. This would enable personalization of treatment even prior to guidance by VHA results. In 564 patients who had received at least 1 blood product due to traumatic bleeding, comparisons of ROTEM profiles at admission were made based on gender, age and the presence of traumatic brain injury.

We found that on admission to the emergency department, bleeding female trauma patients consistently show slightly more deranged ROTEM parameters compared to males, whereas they are less shocked, associated with increased mortality. Patients with TBI presented with more severely deranged ROTEM parameters compared to non-TBI patients, associated with more shock and increased mortality. There was no clear impact of age on ROTEM profiles.

Taken together, point of care tests can be used to guide therapy in actively bleeding patients, enabling a patient- specific approach.

WP7

A key premise of TACTIC is that the ability to predict which interventions in massive bleed traumas can save life is enhanced by using devices that accelerate the clotting behaviour of blood samples. Specifically, these interventions can reduce the risk of Trauma Induced Coagulopathy (TIC) by enabling more targeted or personalised use of appropriate blood products. Devices developed by TACTIC partner 7 (Haemonetics Corporation; Thromboelastography (TEG) device) and partner 8 (TEM Innovations GMBH; rotational thromboelastometry (ROTEM) device) are used for this purpose. These devices analyse viscoelastic haemostatic assays (VHA) and provide information that can help the clinical team decide which blood products should be used to reduce the risk of TIC. A number of quick reference sets of rules (treatment algorithms) have been developed to help the anaesthetist decide when and how to intervene. Hospitals sometimes use descriptions of these treatment algorithms, either presented on pocket-sized cards or posted on convenient walls within the Emergency Department, to help the anaesthetist make appropriate decisions.

The design problem that was the focus of this work package was to engineer a simple computer-based application to implement new knowledge from the TACTIC project and enable clinicians to use VHA analyses to aid the prompt and effective transfusion of blood products, thereby saving lives as well as reducing blood product wastage. Because the situations in which VHA analyses are used in massive bleed traumas are rare (~20 per month even in a Major Trauma Centre such at the Royal London Hospital, for example), additional support is required to enable the clinical team to use the analysis results appropriately.

TACTIC partners 5, 7 and 8 therefore developed an application implemented for an Apple iPad. The software can be linked to the ROTEM and TEG VHA devices, and was actually connected to the ROTEM simulator for the purpose of this work package. The application is also designed to be configurable to alternative algorithms. The application was developed using user-centred design principles, and involved interviews and preliminary evaluations with clinicians in hospitals in the TACTIC network and beyond.

The next step would normally have been to evaluate the application in the clinical context. However, this was not possible given the time constraints of the TACTIC project. In addition, further analysis of data from the iTACTIC RCT (WP8) led to concern that the preliminary interviews with clinicians had not provided sufficient information about the context in which the application was to be used. It was decided therefore to simulate the clinical context and to use the simulation for two purposes: (i) to evaluate whether the application helped the anaesthetist to follow the algorithm in a clinical situation; (ii) to provide the basis for a training game.

The TACTIC training game

The training game is designed to be organised as a set of scenarios each of which involves a discrete sequence of scenes. The scenarios and the data are derived from clinical data but include additional information. Each scene represents a step in an evolving scenario. Information is provided to participants on the display in a format that approximates to the information environment in three situations: pre-hospital, resuscitation and theatre. The aim is that the scenario situation is presented realistically and therefore participants will intervene, for example ordering blood products, transfusing blood products, or undertaking many other interventions not related to blood products as the scenario unfolds.

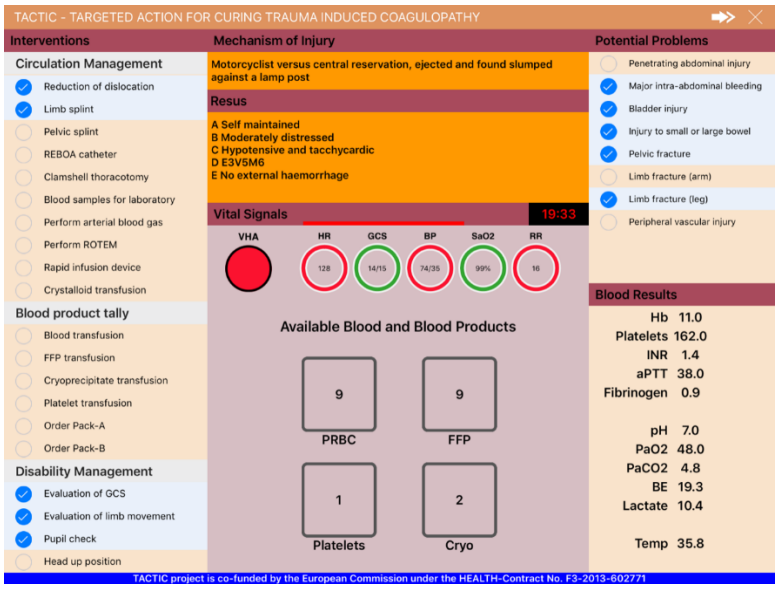


Figure 7: The game layout

The main display of the game (see **Figure 7**) is a dashboard that provides information about the patient's current situation. Further displays can be invoked as required, providing information, for example, about currently available blood products and the current state of VHA analysis. In **Figure 7**, the contents of the local blood store are shown. The main dashboard display shows five panels, namely mechanism of injury (MOI), vital signs (VS), potential problems (PB), interventions (I) and notifications (N).

A summary description of the situation relevant to the current scene is shown in the MOI panel. It describes the circumstances of the injury and information that is relevant to the participant's ability to manage the currently unfolding scenario. Further quantitative information is provided by the VS panel (Heart Rate, Glasgow Criticality Score, Blood Pressure, Oxygen Saturation and Risk Rate). The I panel is designed to allow the participant to intervene in response to the on-going situation as represented by the dashboard display. Interventions include requests for tests, requests for, and transfusions of, blood products, the use of medications such as analgesics and physical interventions (for example, “Removal of Clothing”). The availability of interventions depends on situations depicted by the scenes. For example, only limited interventions may be possible when the patient is pre-hospital. N shows test results when ready. Other information relating to tests appear in a pop-up box. The PB panel shows potential problems that could be relevant to the situation. This list, presented as a tick list, invites the participant to assess what conditions are relevant to this scene given the information provided by the scenario.

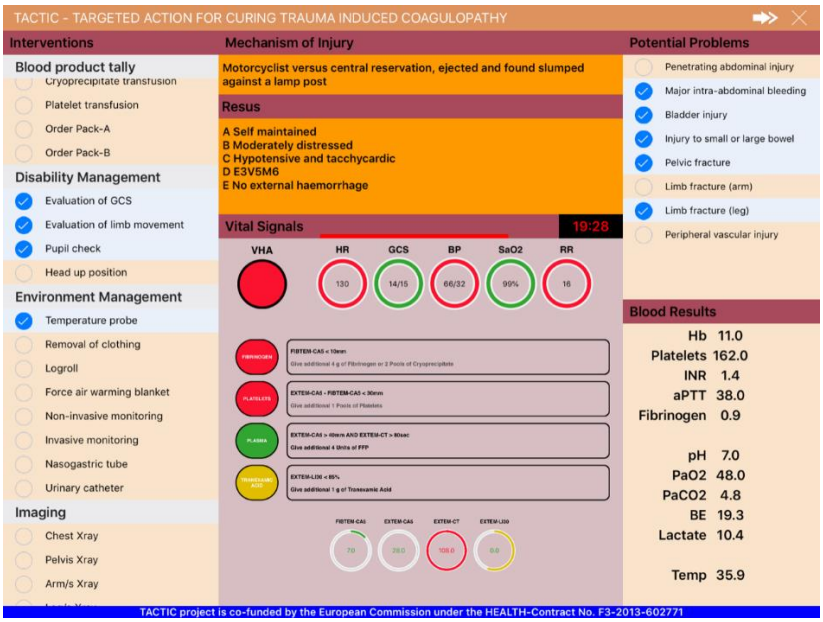


Figure 8: The "application" version of the game

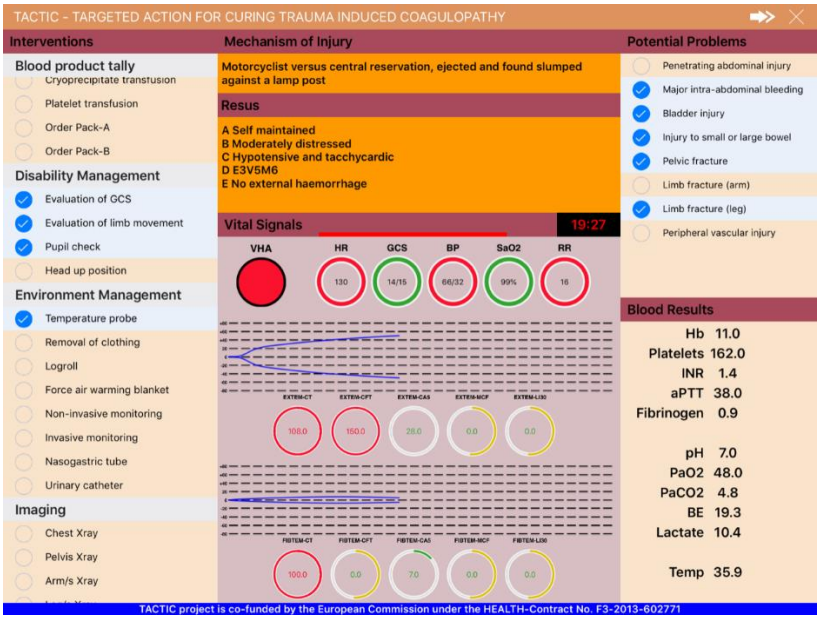


Figure 9: The "non app" version of the game

The standard dashboard is made available to the participant irrespective of whether the application is available to them or not. Swiping the middle screen at the bottom of the dashboard enables the user to see the blood store, the application (if appropriate) and the VHA device display (TEG or ROTEM, see **Figure 9**). In the form that represents only the VHA device display of results it is assumed that the participant also has a card that describes the algorithm that they can use to interpret the results. The screen layouts shown in **Figures 8** and **9** show situations in which several interventions have been made and notifications are indicating their effects.

Results

This work package successfully delivered:

- a VHA software application designed to mediate between a VHA device and an anaesthetist during a big-bleed trauma situation. This application can be configured to support a desired treatment algorithm and provides the potential for interface to ROTEM and TEG devices.
- Software that enabled the evaluation of the application in a simulated context.
- A qualitative evaluation that enabled a refined description of the contexts in which these trauma cases occur.
- A quantitative evaluation that indicated that the VHA software application improved the likelihood of following the algorithm compared with the standard device interface and a paper description of the algorithm.
- A prototype training game based on the simulation that was used as the basis for wider TACTIC dissemination work
- A journal paper describing the research entitled "Simulating context as part of the process of engineering of a medical application" that was submitted to the Journal of Biomedical Informatics and is currently in revision.

In addition, a PhD student co-supervised by Prof. Harrison (at Newcastle University) is currently working on process models to describe anaesthetists' activities relevant to big bleed trauma care. The aim is to produce simulations that will enable more effective analysis of the anaesthetic process based on the simulations produced as part of WP7.

WP8

Based on the preparations made in WP3-6, the consortium has performed a prospective randomized controlled trial comparing the effect of patient-matched haemostatic resuscitation, using a Viscoelastic Haemostatic Assay (VHA) treatment algorithm (WP5-6) versus an optimized treatment-algorithm based on conventional coagulation tests (CCTs). Adult trauma patients (according to local definitions) were enrolled if they presented with clinical signs of haemorrhagic shock, the local massive haemorrhage protocol was activated and transfusion of blood products was initiated. Participants had to be randomised within three hours of injury and maximum one hour after admission to the Emergency Department (ED). The study was approved by the respective ethics committees of all the participating centres and performed in accordance with local ethical regulations and the Declaration of Helsinki. The study protocol was published in Trials: *Baksaas-Aasen et al, Trials (2017) 18(1): pp 486* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5648415/

Corresponding and optimised algorithms based on VHA trigger parameters for the VHA group and CCT results for the CCT group have been developed and published (WP5). These algorithms are based on an empiric Massive Transfusion Protocol (MTP) with an initial 1:1:1 ratio of blood products (red blood cells (RBC) 1: plasma 1: platelets 1) and Tranexamic Acid (TXA). Additional haemostatic therapy, namely

fibrinogen concentrate or cryoprecipitate, as well as additional plasma or platelets, were administered in both the VHA and the CCT groups as soon as test results were available. Additional TXA could only be prescribed in the VHA group, because only VHA can provide specific threshold values for hyperfibrinolysis.

The primary outcome of this study was the proportion of subjects alive and free of massive transfusion (defined as ≥10 units of RBCs) at 24 hours post admission. Secondary endpoints were analysed in order to provide a sensitive and comprehensive description of outcomes and healthcare resource demands for patients in both arms.

The RCT started on 1st June 2016, seven months later than intended due to delays in obtaining the necessary ethical approval at partner 5 (QMUL). To mitigate the delay, a new beneficiary, Ben.10 (Nottingham University Hospital) was invited to participate in the RCT. In addition, an application for a 6 month extension was approved and we were able to finalize enrolment in June 2018 and complete data collection within this new timeframe.

Patients were recruited at 7 major trauma centres in Europe. Royal London Hospital in London enrolled most patients, followed by Copenhagen and Oslo. The study centres were pre-designated to conduct either Thromboelastography (TEG®) or Rotational Thromboelastometry (ROTEM®) in the VHA arm.

The ITACTIC trial successfully enrolled the required critically bleeding patients into a complex clinical trial. The main manuscript is in progress and will be submitted to a peer-reviewed medical journal.

1.4 The potential impact

(including the socio-economic impact and the wider societal implications of the project so far) and the main dissemination activities and exploitation of results (not exceeding 10 pages).

The TACTIC project has delivered data driven haemostatic resuscitation algorithms that can be applied by every European hospital that manages severely bleeding trauma patients. Of particular importance is that these algorithms not only concern the use of viscoelastic haemostatic assays such as Thrombelastography (TEG) and Rotational Thrombelastometry (ROTEM) but also conventional coagulation assays encompassing Fibrinogen, platelet count and INR. Thereby, optimized haemostatic resuscitation can be performed both at large highly specialized trauma centres at university hospitals, similar to the TACTIC clinical partners, and at less specialized or smaller hospitals. Clinical data indicate that trauma mortality can be significantly reduced when optimized and goal-directed haemostatic resuscitation is employed, and the published algorithms developed by the TACTIC project support this notion.

Importantly, although the resuscitation algorithms were developed for traumatic bleeding, they are applicable to all patients experiencing massive bleeding, since coagulopathies secondary to massive transfusion exemplified by heart-and liver transplantation, major vascular surgery, and obstetric calamities can also be mitigated using the TACTIC algorithms. Therefore, the societal benefit of these algorithms cannot be overstated.

Specifically, for trauma, the TACTIC project has identified a novel hyperfibrinolytic phenotype which is associated with the highest risk of death in bleeding trauma patients. Furthermore, a novel patho-physiological mechanism has been revealed that refutes the current paradigm of a state of fibrinolytic shutdown. This is extremely important since this mechanism can be therapeutically modulated by tranexamic acid, which reduces both bleeding and mortality risk.

Overall, the TACTIC project results have the potential to be implemented in international guidelines not only in the EU but worldwide, underscoring the great value created for the individual patient as well as for society as a whole. From a European perspective, the TACTIC project has enabled a sustainable infrastructure encompassing both a trauma registry and a biobank for the partners that will provide the basis for continued cutting-edge research in trauma.

1.4.1 The TACTIC WP9

The TACTIC WP9 focused on the dissemination of information and results generated within the project to clinical scientific colleagues, to the media (e.g. popular scientific and lay press, TV, radio), to the key stakeholders on health policy and decision making levels and to other interested parties.

Publications

Seven scientific articles were published during the period of the TACTIC project – please see Template A1 in section 3.

A further three articles are in preparation/press (see below), with more being planned:

1. D Kleinveld, NP Juffermans, K Brohi, others. *Point of care coagulation profiles in trauma: a step towards precision medicine*.
2. Mathijs R Wirtz, Marcella CA Müller, Pär I Johanssen, Karim Brohi, Simon J Stanworth, Marc Meagele, Christine Gaarder, J Carel Goslings, Nicole P Juffermans. *Hypercoagulability as measured by viscoelastic haemostatic assays and outcome of trauma*.
3. M.R. Wirtz, R. Nieuwland, C. Goslings, N.P. Juffermans, others. *The contribution of microparticles to coagulation and inflammation following trauma: the role of blood products*.

Presentations

There were also multiple conference presentations, including:

Visco-elastic test guided treatment of bleeding presented on the 39th International Symposium on Intensive Care and Emergency Medicine in Brussels on 22 of April 2019 by NP Juffermans

Incidence, risk factors and outcome of hypercoagulability in trauma as measured by viscoelastic haemostatic assays presented on the 30th annual congress of the European Society of Intensive Care Medicine in Paris on 22 October 2018 by MR Wirtz

Presentation Session on Fibrinolysis: *Modeling of TEG, ROTEM and CCT algorithms for Trauma Resuscitation* on 18 July 2018 at ISTH 2018 by Kjersti Baksaas-Aasen

Oral presentation of Abstract: *Data-driven ROTEM and THE algorithms for the Management of Trauma Hemorrhage* on 11 July 2017 at ISTH 2017 in Berlin by Kjersti Baksaas-Aasen

Oral presentation: *Data-driven ROTEM and TEG algorithms for the Management of Trauma Hemorrhage* at Annual Meeting Norwegian Society for Anesthesiologists 2017 on 24 October 2017 by Kjersti Baksaas-Aasen

International Society on Thrombosis and Haemostasis; Berlin, July 2017, "Data-driven ROTEM and TEG Algorithms for the Management of Trauma Haemorrhage", K. Baksaas-Aasen (Partner 4) http://www.professionalabstracts.com/isth2017/iplanner/#/grid

DKOU 2017: German Congress of Orthopedic and Trauma Surgery, Berlin, 25th October 2017, “Data-driven development og ROTEM and TEG algorithms for the management of trauma hemorrhage – a prospective observational multicenter study “ P. Johansson (Partner 1) http://2017.dkou.org/wp-content/uploads/2017/07/DKOU17_International_Program.pdf

Professor Brohi (partner 5; London) presented parts of the WP5.2 work at the 30th Annual Meeting of the Japanese Association for the Surgery of Trauma (30th – 31st May 2016, Yasuhiro Otomo, Tokyo), in a talk entitled 'Trauma Induced Coagulopathy is not Disseminated Intravascular Coagulation'.

Professor Gaarder (partner 4; Oslo) gave several presentations related to TACTIC in 5 different countries at meetings and course relevant to the international trauma society, including Definitive Surgical Trauma Course (DSTC®; owned by the International Association for Trauma Surgery and Intensive Care – IATSIC) and the International Society of Surgery (ISS).

Dr. Jakob Stensballe (partner 1; Copenhagen) presented the TACTIC view on management of major bleeding in trauma at the 17th Annual NATA Symposium (Network for the Advancement of Patient Blood Management, Haemostasis and Thrombosis) in Dublin on 15th April 2016: http://www.nataonline.com/content/17th-annual-nata-symposium-scientific-programme

Professor Juffermans (partner 2; Amsterdam) presented TACTIC WP6 results at the ROTEM User Meeting in Leuven 9th November 2015 and at the Sanquin Blood Bank national conference in the Netherlands in May 2016.

15th Annual NATA Symposium Scientific Program; Porto, April 2014, "Targeted Action for Curing Trauma Induced Coagulopathy (TACTIC) - A 5-year Research Program to Investigate Abnormal Bleeding in Trauma Patients", P. Johansson (Partner 1) http://www.nataonline.com/content/15th-annual-nata-symposium-scientific-program

Traumatic Hemostasis and Oxygenation Research (THOR) Network Symposium; Bergen, June 2014, "Pre-Hospital POC Monitory/ Goal Directed Therapy-Debate: Does it Make a Difference?" T.Gaarder (Partner 4) http://rdcr.org/symposium-2/2014-symposium/

European Congress Trauma and Emergency Surgery (ECTES); Amsterdam, May 2015, "O078 - Infrastructure and clinical practice for the detection and management of trauma associated haemorrhage and coagulopathy" A. Driessen et al (Partner 3) http://www.estesonline.org/wordpress/wp-content/uploads/ECTES-2015_A5-Final-Programme-WEB.pdf

Exchange placements

The TACTIC exchange program was intended to facilitate the clinical, scientific and personal development of partners' researchers. During the exchange placements, staff and students were able to conduct standardised patient recruitment (incl. VHA assays) and specific TACTIC tasks (e.g. database analysis) in different EC-regions, thereby promoting wider experience for clinical researchers themselves and promoting the exchange of knowledge and ideas between EC centres. The TACTIC exchange placement programme was completed as planned, with five successful exchange placements:

1. Julian-Dario Rembe visited Partner 5 (QMUL) from Partner 3 (Cologne) in March and April 2015
2. Kirsten Balvers visited Partner 5 (QMUL) from partner 2 (AMC) in December 2015
3. Mathijs Wirtz visited Copenhagen (partner 1) from (partner 2 AMC) in October and November 2016
4. Kjersti Baksaas-Aasen visited Partner 5 (QMUL) from Partner 4 (NAKMI) in October and November 2018
5. Derek Kleinveld visited Partner 5 (QMUL) from Partner 2 (AMC) in March 2019

Website

The TACTIC website (http://www.tacticgroup.dk/) was regularly updated to include new partners, publications and other information. Information about TACTIC and iTACTIC has also disseminated in relevant talks and teaching programmes run by all of the TACTIC Partners, and via Partner websites:

http://www.c4ts.qmul.ac.uk/intrn-projects/tactic

http://www.c4ts.qmul.ac.uk/intrn-projects/itactic

and Partner publications:

https://issuu.com/centrefortraumasciences/docs/barts_c4ts_autumn_2017_newsletter

Training app

As part of WP7 an app was produced that simulates the environment of a big bleed trauma, including scenes that involve, for example, pre-hospital, resus and theatre activities. The simulation is configurable, enabling alternative scenarios to be simulated, and evaluation of the simulation is complete. See WP7 report for further details.

As part of the TACTIC Dissemination programme it was proposed that this app be transformed into a serious game designed to train anaesthetists in this aspect of trauma care. The proposed transformation involved: (1) modifying the web version of the app to take account of the evaluations of the iPad version; (2) refining the web version of the app to include a facility for module leaders to configure the game with additional scenarios so that the game can be used in medical courses and by appropriate professional bodies; (3) recruiting appropriate bodies, medical courses and professional societies to test and evaluate the game as a tool for training anaesthetists.

The training game has been further developed, as a result of feedback, with improved scenarios and training details. The iPad version has also been extended to enable easy tuning of the key parameters relevant to a particular scenario. The web version has been completed with the same functionality as the iPad version and this has been evaluated with appropriate anaesthetists at the Royal London Hospital.

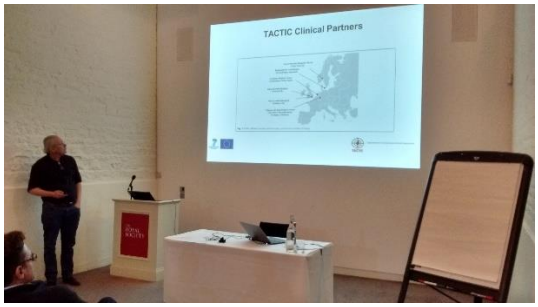
An appropriate location to host the web version of the game is being arranged to improve access and therefore enable distribution to students on the QMUL Trauma Sciences MSc Programmes and other similar educational programmes.

Best practice symposia

At the International Symposium for Critical Bleeding in Copenhagen on 31st August – 1st Sept 2015, a TACTIC session was organized to present TACTIC results obtained so far: http://iscb2015.dk/ . TACTIC coordinator Prof. Pär Johansson was chairing the session that had contributions from 5 different partner-sites (1-5). Please also see attached program for ISCB 2015. There was significant interest from the international audience that had many questions both during the session and at the following panel discussion.

ISCB programme 2015

Consensus meetings



A meeting to develop the 'TACTIC International position statements on diagnosis, detection and management of trauma induced coagulopathy and trauma haemorrhage' was held at the Kavli Royal Society International Centre, Chicheley Hall, Newport Pagnell, MK16 9JJ, UK, on 30 November and 01 December 2017. More than 60 international experts in trauma induced coagulopathy and trauma haemorrhage attended the invitation-only event, laying the groundwork for international position statements in three areas. Proposals for the content of each area based on the results from the meeting were circulated to specific authors in early 2018. Results are being complied into three position statement papers for publication in an appropriate open access journal.:

1. Definitions and mechanisms of trauma-induced coagulopathy (TIC)

   TACTIC leads: K Brohi, P Johansson
2. Diagnostic tests and precision in monitoring TIC

   TACTIC leads: M Maegele, S Stanworth, R Davenport
3. Management of TIC and trauma haemorrhage

   TACTIC leads J Stensballe, T Gaarder, N Juffermans.

Paper 3 has been written. Abstract: This review describes consensus on current management of traumatic bleeding, as well as describing knowledge gaps. It was felt that in the care for bleeding trauma patients, massive transfusion protocols (MTPs) take a central place. This review describes what an MTP should cover, including when to initiate, what to give, how to monitor effect and when to stop. Also, shortcomings of 'best practice' are discussed, as well areas to be explored in future research.

Best practice Guidelines

This has been delivered as a scientific deliverables report D9.1.

1.5. Public website and contact details of consortium

TACTIC public website: www.tacticgroup.dk

TACTIC consortium participants:

Partner 1: Region Hovedstaden, Copenhagen; Pär Johansson: per.johansson@regionh.dk
Partner 2: AMC, Amsterdam; Nicole Juffermans: n.p.juffermans@amc.uva.nl
Partner 3: Universität Witten-Herdecke, Cologne; Marc Maegele: marc.maegele@t-online.de
Partner 4: Oslo University Hospital, Oslo; Christine Gaarder: tinagaar@online.no
Partner 5: Queen Mary University of London, London; Karim Brohi: k.brohi@qmul.ac.uk
Partner 6: University of Oxford, Oxford
Partner 7: Haemonetics; Joao Dias: Joao.Dias@haemonetics.com
Partner 8: TEM; Klaus Göerlinger: klaus.goerlinger@ilww.com
Partner 9: University of Copenhagen, Copenhagen; Karsten Vrangbæk: kavr@sund.ku.dk
Partner 10: Nottingham University Hospital, Nottingham; Adam Brooks: adam.brooks@nuh.nhs.uk
Third party: John Radcliffe Hospital, Oxford; Simon Stanworth: simon.stanworth@nhsbt.nhs.uk

2. Use and dissemination of foreground

A plan for use and dissemination of foreground (including socio-economic impact and target groups for the results of the research) shall be established at the end of the project. It should, where appropriate, be an update of the initial plan in Annex I for use and dissemination of foreground and be consistent with the report on societal implications on the use and dissemination of foreground (section 4.3 – H).

The plan should consist of:

- Section A

  This section should describe the dissemination measures, including any scientific publications relating to foreground. **Its content will be made available in the public domain** thus demonstrating the added-value and positive impact of the project on the European Union.

- Section B

  This section should specify the exploitable foreground and provide the plans for exploitation. All these data can be public or confidential; the report must clearly mark non-publishable (confidential) parts that will be treated as such by the Commission. Information under Section B that is not marked as confidential **will be made available in the public domain** thus demonstrating the added-value and positive impact of the project on the European Union.

Section A (public)

This section includes two templates

- Template A1: List of all scientific (peer reviewed) publications relating to the foreground of the project.
- Template A2: List of all dissemination activities (publications, conferences, workshops, web sites/applications, press releases, flyers, articles published in the popular press, videos, media briefings, presentations, exhibitions, thesis, interviews, films, TV clips, posters).

These tables are cumulative, which means that they should always show all publications and activities from the beginning until after the end of the project. Updates are possible at any time.

TEMPLATE A1: LIST OF SCIENTIFIC (PEER REVIEWED) PUBLICATIONS, STARTING WITH THE MOST IMPORTANT ONES

NO.	Title	Main author	Title of the periodical or the series	Number, date or frequency	Publisher	Place of publication	Year of publication	Relevant pages	Permanent identifiers[2] (if available)	Is/Will open access[3] provided to this publication?
1	Data-driven Development of ROTEM and TEG Algorithms for the Management of Trauma Hemorrhage	*Baksaas-Aasen et al*	Annals of Surgery	23/05/2018	Lippincott Williams and Wilkins	United States	*2018*		10.1097/SLA.0000000000002825 https://qmro.qmul.ac.uk/xmlui/	Yes
2	The S100A10 Pathway Mediates an Occult Hyperfibrinolytic Subtype in Trauma Patients	Gall et al	Annals of Surgery	Vol. 269/Issue 6	Lippincott Williams and Wilkins	United States	*2019*	1184-1191	10.1097/SLA.0000000000002733	Yes

[2] A permanent identifier should be a persistent link to the published version full text if open access or abstract if article is pay per view) or to the final manuscript accepted for publication (link to article in repository).

[3] Open Access is defined as free of charge access for anyone via Internet. Please answer "yes" if the open access to the publication is already established and also if the embargo period for open access is not yet over but you intend to establish open access afterwards.

3	iTACTIC – implementing Treatment Algorithms for the Correction of Trauma-Induced Coagulopathy: study protocol for a multicentre, randomised controlled trial	Baksaas-Aasen et al	Trials	Vol. 18/Issue 1	BioMed Central	United Kingdom	2017	1-13	1186/s13063-017-2224-9	Yes
4	Towards patient-specific management of trauma hemorrhage: the effect of resuscitation therapy on parameters of thromboelastometry	Juffermans et al	Journal of Thrombosis and Haemostasis	Vol. 17/Issue 3	Blackwell Publishing	United Kingdom	2019	441-448	10.1111/jth.14378	Yes
5	Diversity in clinical management and protocols for the treatment of major bleeding trauma patients across European level I Trauma Centres	Schäfer et al	Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine	Vol. 23/Issue 1	BioMed Central	United Kingdom	2015	1-13	10.1186/s13049-015-0147-6	Yes
6	Combined effect of therapeutic strategies for bleeding injury on early survival, transfusion needs and correction of coagulopathy	Balvers et al	British Journal of Surgery	Vol. 104/Issue 3	John Wiley and Sons Ltd	United Kingdom	2017	222-229	10.1002/bjs.10330	
7	Infrastructure and clinical practice for the detection and management of trauma-associated haemorrhage and coagulopathy	Driessen et al	European Journal of Trauma and Emergency Surgery	Vol. 41/Issue 4	Urban und Vogel	Germany	01/08/2015	413-420	10.1007/s00068-014-0455-y	

TEMPLATE A2: LIST OF DISSEMINATION ACTIVITIES								
NO.	Type of activities[4]	Main leader	Title	Date/Period	Place	Type of audience[5]	Size of audience	Countries addressed
1	Please see list of dissemination activities on Participants Portal							
2								
3								

[4] A drop down list allows choosing the dissemination activity: publications, conferences, workshops, web, press releases, flyers, articles published in the popular press, videos, media briefings, presentations, exhibitions, thesis, interviews, films, TV clips, posters, Other.

[5] A drop down list allows choosing the type of public: Scientific Community (higher education, Research), Industry, Civil Society, Policy makers, Medias, Other ('multiple choices' is possible).

Section B (Confidential[6] or public: confidential information to be marked clearly)
Part B1

The applications for patents, trademarks, registered designs, etc. shall be listed according to the template B1 provided hereafter.

The list should, specify at least one unique identifier e.g. European Patent application reference. For patent applications, only if applicable, contributions to standards should be specified. This table is cumulative, which means that it should always show all applications from the beginning until after the end of the project.

TEMPLATE B1: LIST OF APPLICATIONS FOR PATENTS, TRADEMARKS, REGISTERED DESIGNS, ETC.					
Type of IP Rights[7]:	Confidential Click on YES/NO	Foreseen embargo date dd/mm/yyyy	Application reference(s) (e.g. EP123456)	Subject or title of application	Applicant (s) (as on the application)

[6] Note to be confused with the "EU CONFIDENTIAL" classification for some security research projects.

[7] A drop down list allows choosing the type of IP rights: Patents, Trademarks, Registered designs, Utility models, Others.

Part B2

Please complete the table hereafter:

Type of Exploitable Foreground[8]	Description of exploitable foreground	Confidential Click on YES/NO	Foreseen embargo date dd/mm/yyyy	Exploitable product(s) or measure(s)	Sector(s) of application[9]	Timetable, commercial or any other use	Patents or other IPR exploitation (licences)	Owner & Other Beneficiary(s) involved
	Ex: New supercond uctive Nb-Ti alloy			*MRI equipment*	*1. Medical 2. Industrial inspection*	*2008 2010*	*A materials patent is planned for 2006*	*Beneficiary X (owner) Beneficiary Y, Beneficiary Z, Poss. licensing to equipment manuf. ABC*

In addition to the table, please provide a text to explain the exploitable foreground, in particular:

- Its purpose
- How the foreground might be exploited, when and by whom
- IPR exploitable measures taken or intended
- Further research necessary, if any
- Potential/expected impact (quantify where possible)

[19] A drop down list allows choosing the type of foreground: General advancement of knowledge, Commercial exploitation of R&D results, Exploitation of R&D results via standards, exploitation of results through EU policies, exploitation of results through (social) innovation.

[9] A drop down list allows choosing the type sector (NACE nomenclature) : http://ec.europa.eu/competition/mergers/cases/index/nace_all.html

3. Report on societal implications

Replies to the following questions will assist the Commission to obtain statistics and indicators on societal and socio-economic issues addressed by projects. The questions are arranged in a number of key themes. As well as producing certain statistics, the replies will also help identify those projects that have shown a real engagement with wider societal issues, and thereby identify interesting approaches to these issues and best practices. The replies for individual projects will not be made public.

A General Information *(completed automatically when **Grant Agreement number** is entered.*

Grant Agreement Number:	**602771**
Title of Project:	**TACTIC**
Name and Title of Coordinator:	Pär Johansson, Prof, DMSc, MPA

B Ethics

1. Did your project undergo an Ethics Review (and/or Screening)? • If Yes: have you described the progress of compliance with the relevant Ethics Review/Screening Requirements in the frame of the periodic/final project reports? Special Reminder: the progress of compliance with the Ethics Review/Screening Requirements should be described in the Period/Final Project Reports under the Section 3.2.2 *'Work Progress and Achievements'*	***No***
2. Please indicate whether your project involved any of the following issues (tick box) :	***YES***
RESEARCH ON HUMANS	
• Did the project involve children?	
• Did the project involve patients?	X
• Did the project involve persons not able to give consent?	X
• Did the project involve adult healthy volunteers?	
• Did the project involve Human genetic material?	X
• Did the project involve Human biological samples?	X
• Did the project involve Human data collection?	X
RESEARCH ON HUMAN EMBRYO/FOETUS	
• Did the project involve Human Embryos?	
• Did the project involve Human Foetal Tissue / Cells?	
• Did the project involve Human Embryonic Stem Cells (hESCs)?	
• Did the project on human Embryonic Stem Cells involve cells in culture?	
• Did the project on human Embryonic Stem Cells involve the derivation of cells from Embryos?	
PRIVACY	
• Did the project involve processing of genetic information or personal data (eg. health, sexual lifestyle, ethnicity, political opinion, religious or philosophical conviction)?	X
• Did the project involve tracking the location or observation of people?	
RESEARCH ON ANIMALS	
• Did the project involve research on animals?	
• Were those animals transgenic small laboratory animals?	
• Were those animals transgenic farm animals?	

• Were those animals cloned farm animals?	
• Were those animals non-human primates?	
RESEARCH INVOLVING DEVELOPING COUNTRIES	
• Did the project involve the use of local resources (genetic, animal, plant etc)?	
• Was the project of benefit to local community (capacity building, access to healthcare, education etc)?	
DUAL USE	
• Research having direct military use	No
• Research having the potential for terrorist abuse	No

C Workforce Statistics

3. Workforce statistics for the project: Please indicate in the table below the number of people who worked on the project (on a headcount basis).

Type of Position	Number of Women	Number of Men
Scientific Coordinator		1
Work package leaders	3	6
Experienced researchers (i.e. PhD holders)	10	20
PhD Students	7	9
Other	13	4

4. How many additional researchers (in companies and universities) were recruited specifically for this project?	**1**
Of which, indicate the number of men:	1

D Gender Aspects

5.	**Did you carry out specific Gender Equality Actions under the project**?	○ x	Yes No

6. Which of the following actions did you carry out and how effective were they?

		Not at all effective				Very effective
❑	Design and implement an equal opportunity policy	○	○	○	○	○
☒	Set targets to achieve a gender balance in the workforce	○	○	○	○	X
❑	Organise conferences and workshops on gender	○	○	○	○	○
❑	Actions to improve work-life balance	○	○	○	○	○
○	Other:					

7. Was there a gender dimension associated with the research content – i.e. wherever people were the focus of the research as, for example, consumers, users, patients or in trials, was the issue of gender considered and addressed?

○ Yes- please specify

X No

E Synergies with Science Education

8. Did your project involve working with students and/or school pupils (e.g. open days, participation in science festivals and events, prizes/competitions or joint projects)?

○ Yes- please specify

X No

9. Did the project generate any science education material (e.g. kits, websites, explanatory booklets, DVDs)?

X Yes- please specify: Web-based e-learning tool for how to use the VHA software (WP7)

○ No

F Interdisciplinarity

10. Which disciplines (see list below) are involved in your project?

X Main discipline[10]: 3.2

X	Associated discipline[10]: 3.1	X	Associated discipline[10]: 1.1, 5.2

G Engaging with Civil society and policy makers

11a	**Did your project engage with societal actors beyond the research community?** *(if 'No', go to Question 14)*	○ X	Yes No

11b If yes, did you engage with citizens (citizens' panels / juries) or organised civil society (NGOs, patients' groups etc.)?

○ No

○ Yes- in determining what research should be performed

○ Yes - in implementing the research

○ Yes, in communicating /disseminating / using the results of the project

[10] Insert number from list below (Frascati Manual).

11c In doing so, did your project involve actors whose role is mainly to organise the dialogue with citizens and organised civil society (e.g. professional mediator; communication company, science museums)?	○ ○	Yes No

12. Did you engage with government / public bodies or policy makers (including international organisations)

- ○ No
- ○ Yes- in framing the research agenda
- ○ Yes - in implementing the research agenda
- ○ Yes, in communicating /disseminating / using the results of the project

13a Will the project generate outputs (expertise or scientific advice) which could be used by policy makers?

- X Yes – as a **primary** objective (please indicate areas below- multiple answers possible)
- ○ Yes – as a **secondary** objective (please indicate areas below - multiple answer possible)
- ○ No

13b If Yes, in which fields?

Agriculture		Energy		Human rights	
Audiovisual and Media		Enlargement		Information Society	
Budget		Enterprise		Institutional affairs	
Competition		Environment		Internal Market	
Consumers		External Relations		Justice, freedom and security	
Culture		External Trade		**Public Health**	
Customs		Fisheries and Maritime Affairs		Regional Policy	
Development Economic and Monetary Affairs		Food Safety		Research and Innovation	
		Foreign and Security Policy		Space	
Education, Training, Youth		Fraud		Taxation	
Employment and Social Affairs		Humanitarian aid		Transport	

13c If Yes, at which level?

- ○ Local / regional levels
- ○ National level
- X European level
- X International level

H Use and dissemination

14. How many Articles were published/accepted for publication in peer-reviewed journals?	**7**
To how many of these is open access[11] provided?	**5**
How many of these are published in open access journals?	**4**
How many of these are published in open repositories?	**1**
To how many of these is open access not provided?	**2**
Please check all applicable reasons for not providing open access:	
❑ publisher's licensing agreement would not permit publishing in a repository ❑ no suitable repository available ❑ no suitable open access journal available ❑ no funds available to publish in an open access journal ❑ lack of time and resources ❑ lack of information on open access x other[12]: by mistake	

15. How many new patent applications ('priority filings') have been made? *("Technologically unique": multiple applications for the same invention in different jurisdictions should be counted as just one application of grant).*		**0**
16. Indicate how many of the following Intellectual Property Rights were applied for (give number in each box).	Trademark	**0**
	Registered design	**0**
	Other	**0**
17. How many spin-off companies were created / are planned as a direct result of the project?		**0**
Indicate the approximate number of additional jobs in these companies:		

18. Please indicate whether your project has a potential impact on employment, in comparison with the situation before your project:

❑	Increase in employment, or	❑	In small & medium-sized enterprises
❑	Safeguard employment, or	❑	In large companies
❑	Decrease in employment,	❑	None of the above / not relevant to the project
X	Difficult to estimate / not possible to quantify		

19. For your project partnership please estimate the employment effect resulting directly from your participation in Full Time Equivalent (*FTE = one person working fulltime for a year*) jobs:	*Indicate figure:*

[11] Open Access is defined as free of charge access for anyone via Internet.
[12] For instance: classification for security project.

Difficult to estimate / not possible to quantify	X

I Media and Communication to the general public

20. As part of the project, were any of the beneficiaries professionals in communication or media relations?

○ Yes X No

21. As part of the project, have any beneficiaries received professional media / communication training / advice to improve communication with the general public?

○ Yes X No

22 Which of the following have been used to communicate information about your project to the general public, or have resulted from your project?

X	Press Release	❑	Coverage in specialist press
❑	Media briefing	❑	Coverage in general (non-specialist) press
❑	TV coverage / report	❑	Coverage in national press
❑	Radio coverage / report	❑	Coverage in international press
❑	Brochures /posters / flyers	X	Website for the general public / internet
❑	DVD /Film /Multimedia	❑	Event targeting general public (festival, conference, exhibition, science café)

23 In which languages are the information products for the general public produced?

X	Language of the coordinator	X	English
X	Other language(s)		

***Question F-10*:** Classification of Scientific Disciplines according to the Frascati Manual 2002 (Proposed Standard Practice for Surveys on Research and Experimental Development, OECD 2002):

FIELDS OF SCIENCE AND TECHNOLOGY

1. NATURAL SCIENCES

1.1 Mathematics and computer sciences [mathematics and other allied fields: computer sciences and other allied subjects (software development only; hardware development should be classified in the engineering fields)]

1.2 Physical sciences (astronomy and space sciences, physics and other allied subjects)

1.3 Chemical sciences (chemistry, other allied subjects)

1.4 Earth and related environmental sciences (geology, geophysics, mineralogy, physical geography and other geosciences, meteorology and other atmospheric sciences including climatic research, oceanography, vulcanology, palaeoecology, other allied sciences)

1.5 Biological sciences (biology, botany, bacteriology, microbiology, zoology, entomology, genetics, biochemistry, biophysics, other allied sciences, excluding clinical and veterinary sciences)

2 ENGINEERING AND TECHNOLOGY

2.1 Civil engineering (architecture engineering, building science and engineering, construction engineering, municipal and structural engineering and other allied subjects)

2.2 Electrical engineering, electronics [electrical engineering, electronics, communication engineering and systems, computer engineering (hardware only) and other allied subjects]

2.3. Other engineering sciences (such as chemical, aeronautical and space, mechanical, metallurgical and materials engineering, and their specialised subdivisions; forest products; applied sciences such as

geodesy, industrial chemistry, etc.; the science and technology of food production; specialised technologies of interdisciplinary fields, e.g. systems analysis, metallurgy, mining, textile technology and other applied subjects)

3. MEDICAL SCIENCES

3.1 Basic medicine (anatomy, cytology, physiology, genetics, pharmacy, pharmacology, toxicology, immunology and immunohaematology, clinical chemistry, clinical microbiology, pathology)

3.2 Clinical medicine (anaesthesiology, paediatrics, obstetrics and gynaecology, internal medicine, surgery, dentistry, neurology, psychiatry, radiology, therapeutics, otorhinolaryngology, ophthalmology)

3.3 Health sciences (public health services, social medicine, hygiene, nursing, epidemiology)

4. AGRICULTURAL SCIENCES

4.1 Agriculture, forestry, fisheries and allied sciences (agronomy, animal husbandry, fisheries, forestry, horticulture, other allied subjects)

4.2 Veterinary medicine

5. SOCIAL SCIENCES

5.1 Psychology

5.2 Economics

5.3 Educational sciences (education and training and other allied subjects)

5.4 Other social sciences [anthropology (social and cultural) and ethnology, demography, geography (human, economic and social), town and country planning, management, law, linguistics, political sciences, sociology, organisation and methods, miscellaneous social sciences and interdisciplinary , methodological and historical S1T activities relating to subjects in this group. Physical anthropology, physical geography and psychophysiology should normally be classified with the natural sciences].

6. HUMANITIES

6.1 History (history, prehistory and history, together with auxiliary historical disciplines such as archaeology, numismatics, palaeography, genealogy, etc.)

6.2 Languages and literature (ancient and modern)

6.3 Other humanities [philosophy (including the history of science and technology) arts, history of art, art criticism, painting, sculpture, musicology, dramatic art excluding artistic "research" of any kind, religion, theology, other fields and subjects pertaining to the humanities, methodological, historical and other S1T activities relating to the subjects in this group]