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SYMPHONY consortium: Orchestrating personalized treatment for patients with bleeding disorders

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Essentials

- Treatment choices for individual patients with an inborn bleeding disorder are increasingly challenging due to increasing options and rising costs for society.
- The SYMPHONY consortium strives to orchestrate personalized treatment in patients with an inborn bleeding disorder, diagnosed and not yet diagnosed, by unravelling the mechanisms behind inter-individual variations of bleeding phenotype.
- Greater insight into these mechanisms will support individualization of treatment, potentially leading to regimens based more on individual bleeding tendency than on diagnosis.
- This will support personalization of health care innovations and shared decision making with regard to treatment choice, taking societal costs into account.

Abstract

Background

Treatment choices for individual patients with an inborn bleeding disorder are increasingly challenging due to increasing options and rising costs for society. We have initiated an integrated interdisciplinary national research programme.

Objectives

The SYMPHONY consortium strives to orchestrate personalized treatment in patients with an inborn bleeding disorder, by unravelling the mechanisms behind inter-individual variations of bleeding phenotype.

Patients

The SYMPHONY consortium will investigate patients with an inborn bleeding disorder, both diagnosed and not yet diagnosed.

Results

Research questions are categorized under the themes: 1) Diagnosis; 2) Treatment; and 3) Fundamental research and consist of workpackages addressing specific domains. Importantly, collaborations between patients and talented researchers from different areas of expertise promise to augment the impact of the SYMPHONY consortium, leading to unique interactions and intellectual property.

Conclusions

SYMPHONY will perform research on all aspects of care, treatment individualization in patients with inborn bleeding disorders as well as diagnostic innovations and results of molecular genetics and cellular model technology with regard to the hemostatic process. We believe that these research investments will lead to health care innovations with long-term clinical and societal impact.

This consortium has been made possible by a governmental, competitive grant from the Netherlands Organization for Scientific Research (NWO) within the framework of the NWA-ORC Call grant agreement NWA.1160.18.038.

Keywords

bleeding disorders, personalized treatment, proteomics, cellular models, pharmacokinetics, value-based health care

Introduction

Care for patients with an inborn bleeding disorder has improved drastically in the last decades. From high morbidity and mortality due to debilitating arthropathy and intracranial or gastrointestinal bleeds, to a normal life expectancy and high quality of life. [1,2] The introduction of factor replacement therapy in the 1970's for hemophilia has proved to be life changing and led to the concept of prophylaxis in severely affected patients.[3,4] However, long-term effect of intravenously administered prophylaxis on joint bleeds and joint damage was only shown in a randomized controlled trial in 2007.[5] The capacity to produce recombinant factor concentrates in the 1990's, instead of deriving them from human plasma further increased safety and quality of care by avoiding viral infections. Recombinant products in vials has made it possible to implement home treatment worldwide, attaining prophylactic trough levels >0.01 IU/ml. Meanwhile, hemophilia treatment has progressed further, being one of the first genetic diseases to develop and implement effective gene therapy.[6-9] Moreover, extended half-life factor concentrates and novel subcutaneously administered monoclonal antibodies with a long half-life and therefore infrequent infusions, have further advanced care and health outcomes for this patient group.[10,11]

These developments have concomitantly influenced research and treatment modalities in other inborn bleeding disorders concerning both the primary and secondary hemostasis, and/or fibrinolysis, such as von Willebrand disease, platelet function disorders, isolated factor deficiencies, fibrinolytic disorders and bleeding of unknown cause. Historically, the Netherlands has taken a leading position in advancing care for patients with bleeding disorders, initiating multicenter (inter)national clinical studies into symptoms, complications, pharmacokinetic-guided dosing of medication and quality of life.[1,12-18] Concomitantly, also improving diagnostic tests, and performing research into the etiology of hemostatic disorders and the development of inhibiting antibodies.[19] Notwithstanding this progress which has mainly benefited individuals with hemophilia, there are still unmet needs. As the unmet needs described in inborn bleeding disorders may be recognized by other rare diseases, the described approach in this design article may provide a valuable research framework for other fields as well. .

Knowledge gaps and unmet needs within the field of hemostasis can be structured according to the following four categories:

Presently, various novel expensive therapeutic approaches are emerging and becoming standard of care such as gene therapy and subcutaneously administered bispecific monoclonal antibodies[6,11,20] Potentially these will further improve patient outcomes but cost and benefit for patients and society are yet unclear. The effectiveness, (long term) side effects and therefore,

positioning and optimal use of these new treatments are still to be established.[21] In addition, we are obligated to identify which patients will benefit from which therapeutic approach. These new treatment options make personalized treatment for bleeding disorders not only possible, but mandatory.

Treatment strategies with intravenously administered factor concentrates and desmopressin, currently increasingly available in lower resource countries, are suboptimal and lead to both under- and overtreatment, as shown by the multicenter OPTI-CLOT studies, with subsequently either risk of bleeding, thrombosis and/or excessive costs.[12,22,23]

Patient and treatment outcomes are currently not monitored adequately. Systematic documentation of both patient-reported and patient-related outcomes and experience measures as well as treatment costs can determine which (future) treatment is best for each individual, taking costs for society into account.[24-26] This is momentarily needed to inform decision making by all involved stakeholders, including governmental health care institutions and insurance companies.

Despite the growing knowledge over the years there are still significant gaps in our knowledge of the hemostatic process. Knowledge on determinants of inter-individual variation in bleeding phenotype is lacking[27], but is crucial for personalization of treatment according to severity and defining necessity of more innovative, expensive therapies.[28] The limitations in health care management of inborn bleeding disorders warrants development of both novel diagnostic tests and investments in fundamental research to identify disease modifiers and more precisely establish therapeutic requirements. Techniques such as proteomic profiling, flow models, and cellular disease models are instrumental to gain more insight.

An integrated interdisciplinary research programme

The SYMPHONY consortium aims to personalize treatment in patients with inborn bleeding disorders, either due to defects in the known pathways (primary hemostasis, secondary hemostasis, and fibrinolysis), or due to not yet identified pathways. In order to achieve this aim, an integrated interdisciplinary national research programme in close collaboration with patients, was set up to gain greater insight into the mechanisms behind inter-individual variations in bleeding tendency. We believe that elucidation of these mechanisms will further personalize treatment, potentially leading to regimens that are increasingly based on individual bleeding tendency and needs than on diagnosis per se, as is now the case. Moreover, it will support development of algorithms for shared decision making with regard to best treatment choice for

each individual patient, taking societal costs into account and further personalize healthcare innovations and clinical management.

Research questions have been categorized according to a three-way approach in order to achieve precision diagnosis, to install safe, innovative and cost-effective treatment strategies by implementation of the results of enterprising fundamental research. The themes 1) Diagnosis; 2) Treatment; and 3) Fundamental research and respective workpackages (WPs), are depicted in Figure 1.

This interdisciplinary consortium provides a unique framework to implement health care innovations, and to harmonize and amplify results from earlier multicenter (inter)national studies in which clinical data and blood samples have been collected, [1,12-17,29] expanding and linking these to fundamental research on the biochemistry of hemostasis, molecular genetics, proteomics and cellular disease models. The patient perspective is well integrated in all SYMPHONY themes, especially those considering the realization and implementation of treatment and/or health care innovations.

We believe that these investments will lead to health care innovations and personalization of management and treatment with clinical and societal impact for patients with inborn bleeding disorders in patients, and provide an example for other patient groups with a rare disease.

Objective

The general research question we aim to answer in SYMPHONY is: How can we improve and personalize diagnosis and the treatment of inborn bleeding disorders at acceptable costs for society, by identifying, diagnosing and modifying the factors that define inter-individual variation in bleeding phenotype and treatment response?

Participants

Beneficiaries of the SYMPHONY consortium are Erasmus University Medical Center and Erasmus MC Sophia Children's Hospital, University Medical Center Rotterdam (Erasmus MC) (project leadership and coordination); Erasmus University Rotterdam (EUR); Sanquin Diagnostics; Sanquin Research; Amsterdam University Medical Centers (Amsterdam UMC); University Medical Center Groningen (UMCG); University Medical Center Utrecht (UMCU); Leiden University Medical Center (LUMC); Radboud University Medical Center (Radboud umc); Netherlands Society of Hemophilia Patients (NVHP); Netherlands Society for Thrombosis and Hemostasis (NVTH); Bayer B.V., CSL Behring B.V., Swedish Orphan Biovitrum (Belgium) BVBA/SPRL.

Patient involvement in SYMPHONY is key and represented by intense involvement of the NVHP patient society in especially the treatment WPs. Clinical care and research units involved in SYMPHONY include all Hemophilia Treatment Centers in the Netherlands as well as scientists from various Sanquin departments In addition, three pharmaceutical companies participate in the consortium, sharing their expertise with regard to therapeutics for bleeding disorders as well as knowledge on data sharing, marketing, and intellectual property. All partners and disciplines involved fulfill a specific need within the project for which they are valuable to the consortium.

The following disciplines and specialties are united within the SYMPHONY consortium: (pediatric) hematology, vascular medicine, clinical genetics, clinical pharmacology, (medical) psychology, ethics, epidemiology and methodology, mathematics, health care economics, laboratory medicine, information and data technology, biochemistry, molecular biology, molecular genetics, cell biology, (clinical) proteomics, expertise with regard to cellular (iPSC technology) and vascular endothelial cell models, business economics, marketing, sales, patient advocacy, and industrial design.

As a consortium, we have consciously focused on complementarity and diversity within the consortium, both in choices of participating co-applicants as well as cooperating partners, but also with regard to positions within the management structure. We have taken characteristics into account with regard to: professional experience (senior- and junior), area of expertise, educational background, gender, diversity and lastly type of institution, as well as representatives from small, large businesses and institutions, start-ups.

Patients and methods

Study population(s)

Within SYMPHONY all patients with a diagnosed and undiagnosed bleeding disorder can be included. SYMPHONY is a result of the expertise and experience of Dutch researchers, Dutch Hemophilia community, patients and caregivers. It builds on a number of (inter)national, multicenter initiatives of which the most important are named.

Existing national initiatives/ expertise's and their importance to SYMPHONY:

• *HemoNed*

National registry for hemophilia patients, developed in close collaboration with the patient organisation NVHP and patients. SYMPHONY will use HemoNed, and the App based registration of prophylaxis, bleeding episodes and treatment (Vasteprik®) as the digital platform to extend registration to other bleeding disorders and to implement proposed e-health modules for value based health care outcome registration and PK-PD guided dosing.[30]

• *OPTI-CLOT*

Multicenter studies which aim to optimize treatment by pharmacokinetic (PK) and ultimately PK-pharmacodynamic (PD)-guided dosing of factor concentrates and desmopressin and emicizumab in hemophilia by construction of population PK-PD models. Subsequent To WiN and DAVID studies specifically aim to improve treatment in von Willebrand and non-severe hemophilia A with a comparable approach.[16,31] SYMPHONY provides the opportunity to expand to prospective clinical trials[12] to achieve population PK-PD models which will finally associate coagulation factor levels with bleeding events which is urgently needed, and additionally to develop a user friendly PK-PD tool.[32]

• *Other clinical multicenter studies in bleeding disorders* initiated in The Netherlands:

Hemophilia in the Netherlands (HiN); von Willebrand in the Netherlands (WiN); Thrombocytopathy in the Netherlands (TiN); Rare bleeding disorders in the Netherlands (RBiN) and studies into bleeding of unknown cause (CRESCENDO). International studies initiated in the Netherlands, including INSIGHT/ RISE/ DYNAMO studies.[1,13-15,17,18,29] All studies provide interesting patient material to deepen our understanding of inter-individual differences. SYMPHONY provides the framework to maximize these collaborations and data sharing to its full potential.

• *Value based health care methodology/patient-reported outcome measures*

SYMPHONY will build on the expertise of several co-applicants, cooperating partners and external advisors with long term follow up of patient-important outcome measures. This will proceed in collaboration with International Consortium of Health care Outcome Measurements

(ICHOM) and KLIK (a Dutch initiative enabling long term follow up of quality of life parameters in children and parents/caregivers) and in cooperation with other groups specialized in value-based health care development and implementation.[33,34]

• All Dutch Hemophilia Treatment Centers, EAHAD-certified, and also accredited *European Reference Network (ERN)/ EuroBloodNet members* have joined forces in SYMPHONY. Therefore, cross border health care potential and knowledge utilization and dissemination both nationally and in Europe is able to take place. This is further supported by the important leading (inter)national clinical, scientific positions fulfilled by many co-applicants, cooperating partners in the field of hemostasis.

• *Participation in Phase II, III, and IV drug trials* of all clinical SYMPHONY members in for instance gene therapy for hemophilia A and B, long-acting EHL products, antibody-based therapy, novel coagulation factor bypassing therapies and previously untreated patients (PUP) studies, ensures knowledge of advantages and side-effects of novel therapies and dilemmas described.

Although previously collected cohorts are valuable, there is still a need to generate additional well characterized clinical cohorts with associated (longitudinally) collected biological materials (plasma, platelets, endothelial cells). Within the consortium a protocol for biomaterial will be created to ensure optimal efficient use of patient samples.

Study design

Within the three themes 1) Diagnosis; 2) Treatment; and 3) Fundamental research questions are addressed within defined work packages (WPs 1-12) and if applicable answered interactively. Titles of WPs are depicted in Figure 2. Overall objectives, methods and techniques per WP are described below.

Theme 0: Management, organisation and dissemination of results

WP01 Objective: Manage SYMPHONY professionally, ensuring optimal collaboration, communication and overall results. WP02 Objective: Assure good utilisation of knowledge and entrepreneurship. In WP01 and 02, we will manage the consortium accordingly and allocate sufficient funds for overall management and knowledge transfer.

Theme 1: Diagnosis

WP03 Objective: Develop reliable tests and flow models which more optimally quantify hemostatic potential and identify modifiers of hemostasis. In WP03, we will ensure results by the combined

expertise of biochemists on determinants of coagulation, fibrin and clot formation, and on development and validation of diagnostic tests and alternative hemostatic models. This will include detailed analyses of clot formation using the explicit expertise of thrombodynamics (Hemacore); modifications of thrombin generation and plasmin generation assays.[35,36] Experiments will optimise type and concentration of phospholipids, factor-deficient plasma and other specific alterations of procedures and develop a first flow model in collaboration with vascular endothelial cell model experts in WP12.

WP04 Objective: Develop precision tests that characterize platelet function disorders and compare results with current standard diagnostic and genetic techniques.

In WP04, we will apply novel diagnostic tests for analysis of platelet function to functionally characterize platelets from both adult and pediatric patients with inherited platelet disorders in the nationwide Thrombocytopathy in the Netherlands (TiN) study.[37] This will include measurement of platelet activation markers with flow cytometry, which has increased diagnostic range compared with the current gold standard for platelet function analysis, Light Transmission Aggregometry (LTA).[38] We will expand the current panel of platelet activation markers to improve sensitivity for platelet function disorders. Within the TiN study, whole exome sequencing (WES) data are collected on all patients with inherited platelet disorders. By combining WES data with extensive platelet phenotyping and the platelet proteome profiles determined in WP10, we aim to identify new genetic variants for inherited platelet disorders. Causality will subsequently be confirmed with induced pluripotent stem cell models in WP11.

Theme 2: Treatment

WP05 Objective: Improve quality of care by systematic measurement of outcomes that matter to patients. Implementation of value-based health care into the field of bleeding disorders is vital to balance both patient- and doctor reported health care outcomes with costs of treatment, especially in the light of emerging even more expensive therapeutic agents for bleeding disorders, especially hemophilia.[24] Value based health care comprises several advantages:1) patients may achieve a higher state of health at similar or lower costs; 2) health care providers are more efficient and succeed in achieving greater patient satisfaction; 3) payers (e.g. health insurance) are better able to control costs with reduction of risks; 4) suppliers can align prices with patient outcomes and 5) society as a whole becomes healthier while reducing overall healthcare spending.

WP06 Objective: Devise a dosing tool based on pharmacokinetic (PK) and pharmacodynamic (PD) principles instead of body weight, applicable in all patients with bleeding disorders to optimise quality of care and cost-effectiveness. In WP06, we will perform PK-PD modelling using non-linear mixed effects modelling (NONMEM). NONMEM is a statistical technique and recommended in FDA and EMA guidelines for the evaluation of population PK-PD of new drugs. Uniquely, NONMEM allows the analysis of population data obtained during clinical routine with often sparse and heterogeneous sampling from different treatment centres. The OPTI-CLOT research group has extensive experience with this technique and has applied NONMEM for the development of population PK models for factor VIII (FVIII), factor IX (FIX), von Willebrand factor (VWF)/FVIII, desmopressin and most recently also emicizumab.[12,39] They will apply these models in unique prospective multicenter trials in which doses are individualized on basis of individual patient PK using Bayesian statistical techniques.

WP07 Objective: Prioritize implementation of personalized care strategies and value-based health care principles by installing a personal communication platform for all patients with an inborn bleeding disorder. Persons with inborn bleeding disorders in the Netherlands receive comprehensive care at Hemophilia Treatment Centers, including psychosocial support with a strong emphasis on self-management and home treatment.[40] Data on patient-reported health outcomes is currently collected to enable personalized treatment. However, individuals' medical information is fragmented across health care information systems, digital treatment diaries and questionnaire portals, hampering integrated care. We intend to develop a nationwide digital personal health record for patients to manage and share relevant medical information in collaboration with existing initiatives the national hemophilia patient registry HemoNed and the digital PROM portal KLIK.

WP08 Objective: Calculate costs and cost effectiveness of treatment for standard and new treatment modalities. In WP08, we will use innovative quasi-experimental designs to study the effectiveness of the novel treatment options available for patients with bleeding disorders. In medicine, effectiveness of interventions is usually studied within RCTs with good internal validity but less feasibility or in observational data, the complete other end of the spectrum, with poor validity. Quasi-experimental designs form the optimal balance. These quasi-experimental designs will be combined with cost-effectiveness analysis to obtain cost-effectiveness estimates of the newer treatment options. Empirical data collection will be combined with a decision analytic

modelling approach to obtain -model based- estimates of the cost-effectiveness of the joint interventions.

WP09 Objective: Evaluate the patient's perspective on ethical dilemmas with regard to medical innovations. In WP09, we will take an empirical-ethical approach to bioethics. Such an approach starts from the assumption that ethical analysis and evaluation of a given practice does not occur in isolation of a certain context and that there is a certain wisdom in practices that needs to be taken into account for a thorough ethical analysis or evaluation. Several approaches exist within empirical-ethics. In this project, we will take a broad, pluralistic perspective on empirical-ethics by integrating an ethical- clinical and patient-participatory approach.

Theme 3: Fundamental research

WP10 Objective: Determine which modifying hemostatic plasma proteins are associated with the bleeding phenotype in hemophilia A, von Willebrand disease and Bleedings of Unknown Cause, as regularly performed in platelets. In WP10, we will apply nano-LC mass spectrometry approaches to identify hemostatic plasma and cellular protein signatures as determinants of bleeding. To this end, we assess protein expression and activation profiles of plasma and cellular systems of healthy individuals and patients with explained and unexplained bleedings. The full catalogue of profiles will assist in the identification as well as the understanding of the mechanisms behind the poorly understood bleedings.

WP11 Objective: Investigate if the new platelet-function-disorder mutations found in WP4 and previous studies are causative and if so, how do they affect megakaryopoiesis, platelet counts and/or platelet function? In WP11, we will generate induced pluripotent stem cells from patients or will introduce platelet-disorder specific mutations using CRISPR/Cas9 into iPS cell lines. Using these iPS cell lines as model systems, ideal conditions to study causality and mechanisms behind novel identified mutations in platelet function disorders can be obtained.[41] In addition, identified putative causative mutations can be investigated in both patient genomic- and patient independent genetic backgrounds. In general, iPS cell lines have been used as successful disease model systems in an array of pathologies both hematopoietic and non-hematopoietic.[42,43] For instance at Sanquin, differentiation of GFI1B mutated Grey platelet syndrome specific iPS recapitulated disease characteristics and uncovered mechanistic insights. Numerous patient specific and control iPS cell lines have been generated at the Sanquin iPS facility using integrative and non-integrative methodology.[43-45] The combined expertise, to generate, maintain, differentiate

and study megakaryopoiesis using both patient specific and de novo generated (CRISPR/CAS9) iPSC lines is only sparsely available, internationally. This allows for quick and adaptive responses to specific research questions.

WP12 Objective: Investigate if inter-individual variation in bleeding phenotype can be explained by cellular vascular endothelial mechanisms. In WP12, we will apply several state-of-the-art approaches to unravel the cellular mechanisms that are at the basis of (unexplained) bleeding abnormalities in patients. This will be done by isolating Endothelial Colony Forming Cells (ECFCs), in which patient-derived endothelial cell models of patients with various bleeding disorders are cultured.[46] This approach is particularly suited as it is capable of studying the effects of causative disease mutations in the endothelial context. We will construct a model system that reflects the patient's diseased-affected endothelium more accurately than has been done with general endothelial cell lines. In order to validate candidate disease modifiers we will use CRISPR/Cas9 gene editing in cord blood ECFCs. This research group was the first to establish a protocol to generate clonal CRISPR-engineered endothelial lines and the first to recapitulate a bleeding disorder (HPS-2) in endothelial cells using CRISPR/Cas9 gene editing of its causative gene, AP3B1, in cord blood ECFCs.[47]

Governance

The SYMPHONY consortium is managed at three levels as illustrated in Figure 3 and described below.

Management level 1: Action

The execution of each WP is managed at WP level under supervision of the respective WP leaders. The WP leaders communicate monthly with the project team on highlights and issues. The research WPs are split into two groups of five WPs (theme 1 and 3: WPs 03-04 and 10-12; Theme 2: WPs 05-09). These two groups report to the project team alternatively at three-monthly Theme meetings. *Management level 2: Management*

The project team is responsible for day-to-day management of the overall SYMPHONY research programme including monitoring of milestones and deliverables, intellectual property and ethics monitoring, dissemination strategy, publication policy and execution of the data management plan. It also manages contractual, legal, financial, and administrative affairs as well as safeguards SYMPHONY governance, knowledge transfer and utilisation, within and beyond the consortium.

Management level 3: Decision and advice

The executive committee is the ultimate decision making entity It consists of a representative from each institute involved in SYMPHONY, and is authorised to make binding decisions on behalf of his/her party. The advisory board consists of experts in the field. In addition, a patient panel assists the NVHP Working Group Care & Research to evaluate patient-related topics. Both the advisory board and the patient panel meet annually during the general assembly. Both advise the project team as stated in level 2. Independent advisors can be invited for specific topics.

Endpoints and reporting

Project endpoints are defined per WP as milestones and deliverables. Monthly reports are made by WP leaders and summarized in a yearly overview. Milestones and deliverables are reported to NWO by way of an impact plan as described by the theory of change,[48] which defines output, outcome and societal impact and addresses assumptions made between problem areas according to spheres of influence. Consortium output is regulated according to a communication, publication and authorship plan which defines how output is registered and safeguarded as well as how branding of NWO and SYMPHONY is organized.

Registration

This research received funding from the Netherlands Organization for Scientific Research (NWO) in the framework of the NWA-ORC Call grant agreement NWA.1160.18.038. Principal investigator: Dr. M.H. Cnossen. Project manager: Dr. S.H. Reitsma.

Conclusion

The coming years, SYMPHONY will produce cutting-edge papers on all aspects of care, treatment individualization in patients with inborn bleeding disorders as well as diagnostic innovations and results of molecular genetic and cellular model technology with regard to the hemostatic process. We believe that these research investments will lead to health care innovations with long-term clinical and societal impact. Moreover, we are convinced that rare diseases in general may benefit from SYMPHONY's pioneering example to innovate by integration of interdisciplinary efforts to improve health care and outcomes.

Author contributions

M.H. Cnossen and I. van Moort are the main authors of the manuscript. All authors substantially contributed to the writing, critically revised the manuscript, and approved the final draft. A complete overview of all collaborators is stated in the acknowledgments section.

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Disclosures

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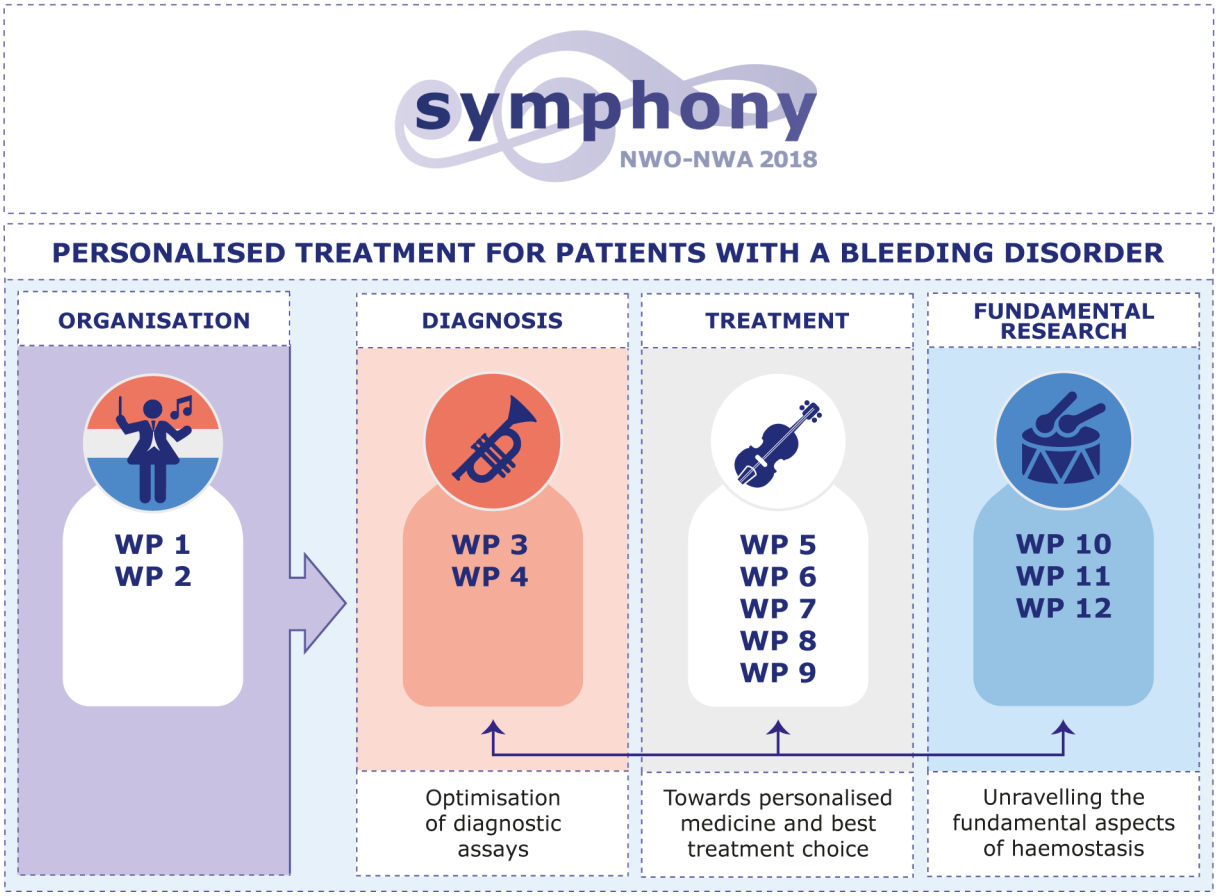

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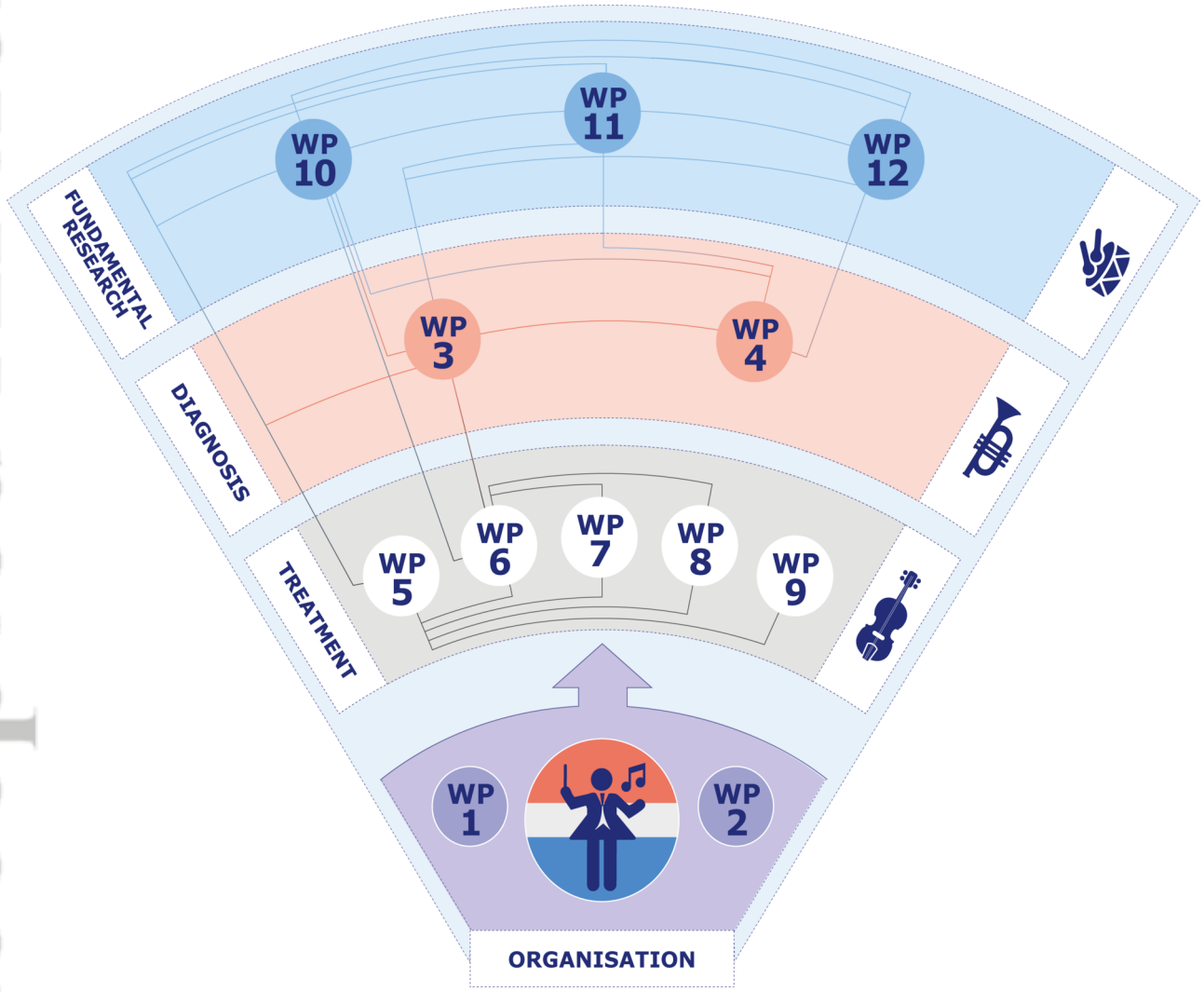

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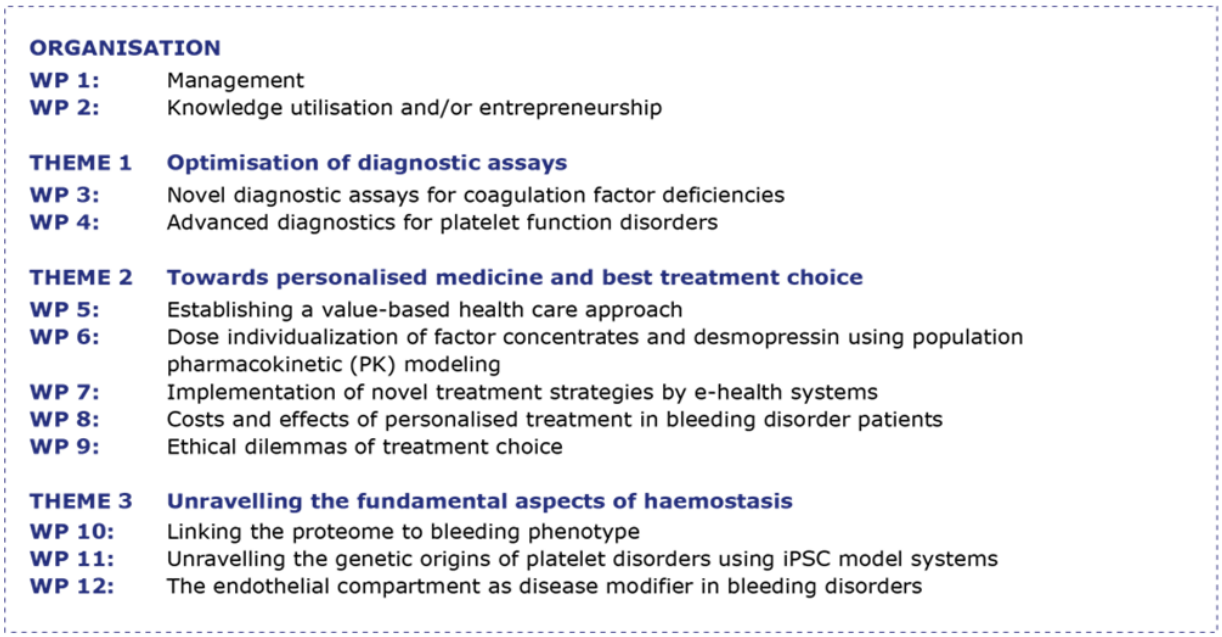

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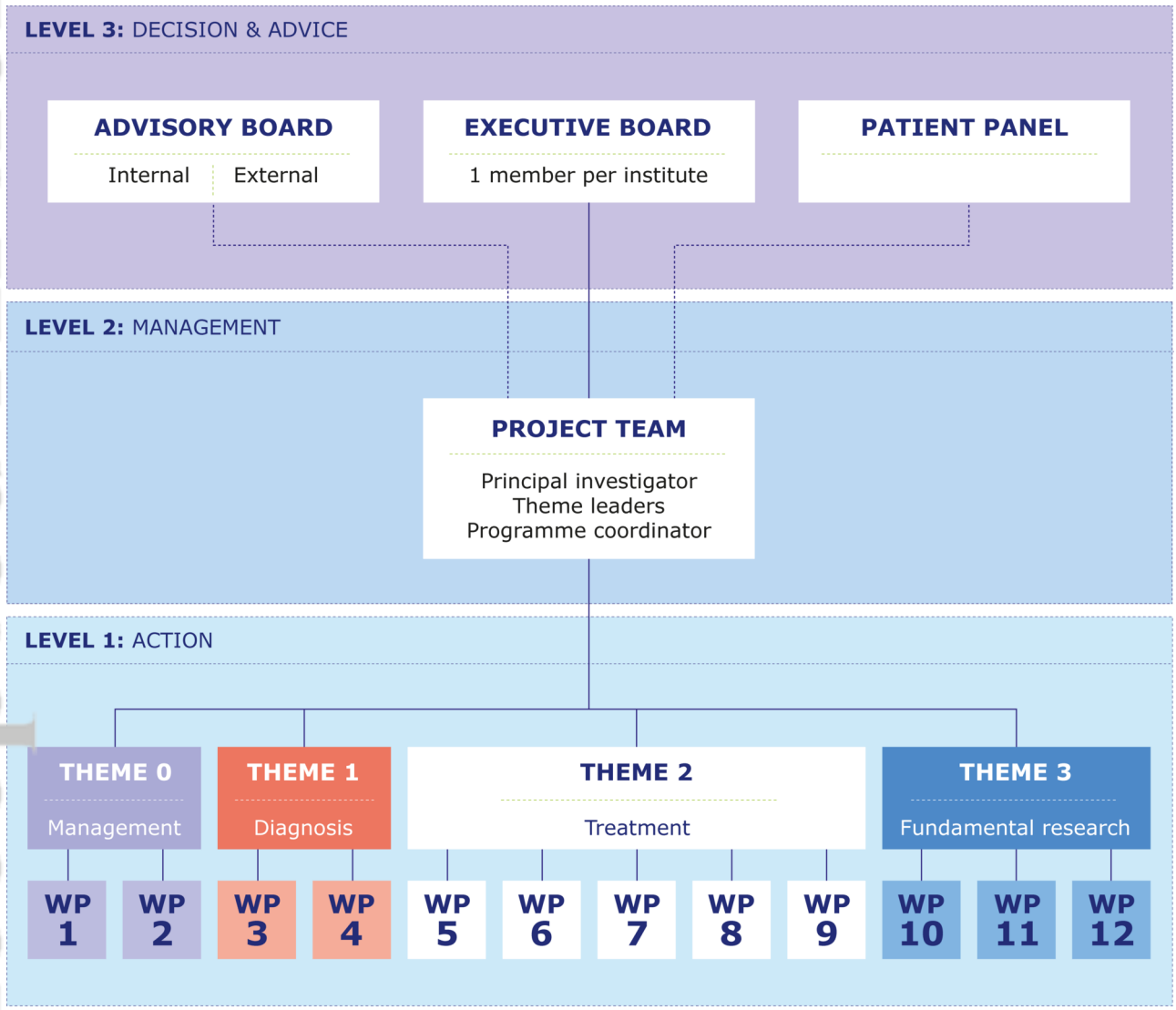

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