

Towards optimal use of antithrombotic therapy of people with cancer at the end of life

A research protocol for the development and implementation of the SERENITY shared decision support tool

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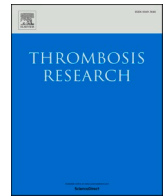
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Full Length Article

Towards optimal use of antithrombotic therapy of people with cancer at the end of life: A research protocol for the development and implementation of the SERENITY shared decision support tool

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ABSTRACT

Background: Even though antithrombotic therapy has probably little or even negative effects on the well-being of people with cancer during their last year of life, deprescribing antithrombotic therapy at the end of life is rare in practice. It is often continued until death, possibly resulting in excess bleeding, an increased disease burden and higher healthcare costs.

Methods: The SERENITY consortium comprises researchers and clinicians from eight European countries with specialties in different clinical fields, epidemiology and psychology. SERENITY will use a comprehensive approach combining a realist review, flash mob research, epidemiological studies, and qualitative interviews. The results of these studies will be used in a Delphi process to reach a consensus on the optimal design of the shared decision support tool. Next, the shared decision support tool will be tested in a randomised controlled trial. A targeted implementation and dissemination plan will be developed to enable the use of the SERENITY tool across Europe, as well as its incorporation in clinical guidelines and policies. The entire project is funded by Horizon Europe.

Results: SERENITY will develop an information-driven shared decision support tool that will facilitate treatment decisions regarding the appropriate use of antithrombotic therapy in people with cancer at the end of life.

Conclusions: We aim to develop an intervention that guides the appropriate use of antithrombotic therapy, prevents bleeding complications, and saves healthcare costs. Hopefully, usage of the tool leads to enhanced empowerment and improved quality of life and treatment satisfaction of people with advanced cancer and their care givers.

1. Introduction

Advance care planning (ACP) has become the preferred standard of care across Europe in people with cancer during the last phase of life. ACP means thinking ahead and having conversations between health care professionals, patients and their families on what the most appropriate choices are for treatments and care when the disease progresses [1]. One component of this process is a rationalisation of pharmacotherapy, including the deprescribing of medication that is potentially harmful and/or no longer necessary, such as antithrombotic therapy [2,3]. Approximately 30–50 % of people with cancer use anticoagulation or antiplatelet agents (i.e. antithrombotic therapy), rising to 80 % in elderly people with cancer [4–6]. Antithrombotic therapy is usually continued until the last day(s) before death. While the usage of antithrombotic therapy is associated with an absolute bleeding risk of 7–10 %, the risk of thromboembolic events, which should be diminished by the usage of antithrombotic therapy, is as low as 1 % in some of the antithrombotic therapy users [7]. Hence, antithrombotic therapy has possibly little benefit, or even negative effects on the well-being of people with advanced cancer [4,6–16].

Importantly, the use of antithrombotic therapy in people with cancer will almost certainly increase over the coming years due to several factors. First, with the progress in anticancer medicines, patients live longer with advanced disease and experience longer exposure to the risk of cardiovascular complications [17,18]. Second, the use of anticancer medicines, each conferring additional risk of cardiovascular complications including atrial fibrillation, continues to grow, resulting in a parallel rise in antithrombotic therapy indications [19–21]. Third, as patients' life expectancy expands, they face incremental age-related comorbidities including cardiovascular complications, sometimes even as a consequence of cancer-related treatment, again requiring antithrombotic therapy; the resulting polypharmacy increases the risk of drug-adverse events [22].

Despite the widespread and increasing use of antithrombotic therapy

in people with end-stage cancer, there is an overall lack of evidence in the efficacy and safety of them in this patient group. The only available guidance document on this matter solely refers to aspirin prescribed in the setting of primary cardiovascular prevention, which is no longer indicated in anyone (with or without cancer) in this setting. Antithrombotic therapy prescribed for atrial fibrillation or secondary prevention is not mentioned, but constitutes the vast majority of antithrombotic therapy prescriptions in people with cancer [23–25]. Hence, healthcare professionals may feel uncertain about the timing of antithrombotic therapy deprescription and lack the tools to objectively assess the relevant risks for a given patient, with the risk of overestimating the risk of cardiovascular complications in the short term, while underestimating the risk of bleeding events.

SERENITY is an international collaboration that aims to 1) gain an understanding of the use of antithrombotic therapy, its efficacy, safety, and deprescription in people with advanced cancer, and 2) to develop, test, validate, and widely implement a tool that will support informed decision-making for optimal antithrombotic therapy in people with cancer at the end of life. SERENITY stands for 'towardS cancer patiEnt empoweRment for optimal uSE of aNtithrombotic TherapY at the end of life' and will hopefully answer an important and highly relevant research question that is currently an area of clinical uncertainty, and that will become an even greater challenge in the coming years.

2. SERENITY consortium

The SERENITY consortium comprises researchers and clinicians from fourteen hospitals located in eight European countries with specialisations in oncology, cardiology, geriatrics, haemostasis, haematology, family medicine, palliative care, health economy, epidemiology, health communication and psychology. SERENITY attempts to solve the current clinical dilemmas around the use of antithrombotic therapy in people with cancer. It entails various types of research: a cross-sectional flashmob study, a realist review, nationwide epidemiological studies, qualitative studies, and consensus studies (Fig. 1). The studies will have a comprehensive and inclusive public involvement plan with an overall patient and public involvement (PPI) lead. Public Contributors will be

¹ Contributed equally.

invited to all workstreams to provide a lay perspective on our research processes and findings. Objectives of the studies conducted in the eight different work packages are summarised in Table 1. In the qualitative studies, data is collected through questionnaires for healthcare professionals and in-depth interviews with healthcare professionals and people with cancer. Here, the processes and factors that inform decisions around the deprescribing of medicines of discontinuing antithrombotic therapy are explored. In the epidemiological studies, current usage of antithrombotic therapy in people with cancer is described, and incidence rates of bleeding events and cardiovascular complications are established. Using the collected qualitative and epidemiological data, a user-friendly, easily accessible, web-based shared decision support tool (SDST) is developed, taking all relevant clinical, psychosocial, socioeconomic, cultural and religious patient values and preferences into account. Once the SERENITY intervention is developed, the implementation and effects will be tested in a randomised controlled trial, focusing on the quality of life (QoL), patient and carer satisfaction, and clinical and economic outcomes. Following this, a targeted dissemination and implementation plan will be created. The SERENITY intervention will be made available in a great variety of languages. Moreover, guidelines will be developed for the rational (de)prescription of antithrombotic therapy in people with advanced cancer, that are currently non-existent [26]. This paper presents our research design, one of the largest in end-of-life research. The entire project is funded by Horizon Europe.

3. Work packages

3.1. Phase 1: Laying the foundation

Phase one aims to understand and reach a consensus on the processes and factors that influence decisions around the optimal use of antithrombotic therapy in people with advanced cancer. All relevant data needed for phase two will be collected during this phase.

3.1.1. Work package 1: Assessing practice patterns

This work package comprises an extensive and thorough realist review of available evidence and a cross-sectional flash mob research (FMR) [27]. To improve understanding of the complexities of decision-

making in end-of-life care, different types of quantitative and qualitative knowledge are needed to integrate and take account of the impact of context. Realist review methodology provides an approach for systematically reviewing literature, that focuses on explaining an intervention instead of judging its effectiveness. A realist review explains how an intervention works, who it works for and in what circumstances it works. This way, a realist review works with (rather than attempting to factor out) complexity, and is therefore well-suited to address the challenges of understanding complex decision-making in end-of-life care [28,29]. Informed by Pawson's five iterative stages in realist reviews and the RAMESES quality and reporting standards [30,31], the SERENITY realist review will include studies describing the use and associated complications of antithrombotic therapy in people with cancer specifically, and that of deprescribing cardiovascular medication in end-of-life care in general, to evaluate all currently existing deprescribing tools and strategies. This enables the SDST design to be built on knowledge from adjacent areas of care, and to identify patient-centred important outcomes such as the personal impact of adverse events rather than proxy markers (e.g., presence or absence of polypharmacy, or numbers of adverse events) only.

In addition to the realist review described above, an FMR will be conducted where European healthcare professionals will be surveyed regarding their views, preferences, and practice, enabling assessment of potential loco-regional differences in views and values on end-of-life care and (de)prescription of antithrombotic therapy in people with cancer at the end of life, taking socioeconomic and cultural factors into account. Furthermore, a discrete choice experiment (DCE) will be incorporated, where the participating healthcare professionals are asked to reply to a few different hypothetical scenarios on decisions regarding deprescribing antithrombotic therapy in cancer patients, covering the whole range of settings where this decision is made (e.g. shorter or longer life expectancy, different indications for antithrombotic drugs and presence of risk factors of bleeding). Lastly, the healthcare professionals will be asked to share five actual case decisions regarding (de)prescription of medication in people with cancer receiving palliative care. Recommendations for performing FMR and DCE will be followed [32,33]. Using the consortium members' network and social media, we aim to recruit at least eight hundred healthcare professionals (one hundred per participating country) to participate in the FMR, allowing

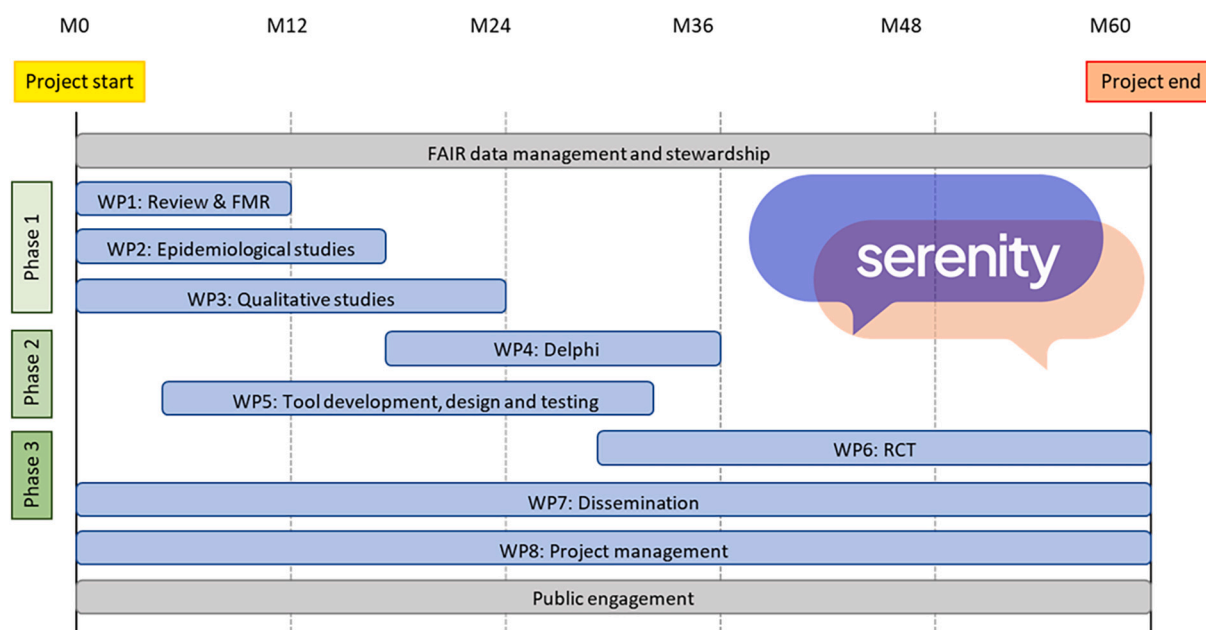


Fig. 1. SERENITY methodological framework.

M = month; FAIR = Findable, Accessible, Interoperable and Reusable; WP = work package; FMR = flashmob research; RCT = randomised controlled trial.

Table 1

Objectives of the research program per work package.

Work package 1: Assessing practice patterns
→ Further the understanding of how goal-concordant deprescribing interventions of antithrombotic therapy can be designed to improve shared decision-making in the last year of life of people with cancer (realist review)
→ Explore and describe current practice patterns across Europe with regard to the use of antithrombotic therapy in end-of-life care of people with cancer following flash mob research (FMR) methodology
→ Evaluate and understand the processes and factors that inform decisions around the deprescribing of medicines in the final year of life of people with cancer receiving antithrombotic therapy via a discrete choice experiment (DCE)
Work package 2: Epidemiological studies
→ Describe usage of antithrombotic therapy in people with cancer during the last year of life. This will be examined for the different antithrombotic therapy separately (direct oral anticoagulants, vitamin K antagonists, platelet inhibitors, low-molecular-weight-heparins), for different indications for the antithrombotic therapy (atrial fibrillation, valvular disease, venous thromboembolism (VTE), stroke, peripheral artery disease, and coronary artery disease) and for several cancer subtypes
→ Establish the absolute incidence of fatal, major, and relevant bleeding events, as well as fatal and non-fatal incident VTE, myocardial infarction, and stroke in people with cancer who never used antithrombotic therapy, who discontinued antithrombotic therapy in their last year of life or who were on antithrombotic therapy at baseline, for the different antithrombotic therapy groups, for the different indications for antithrombotic therapy, and different cancer subtypes
→ Identify prognostic factors that are associated with (dis)continuation of antithrombotic therapy and the occurrence of bleeding events or cardiovascular complications
Work package 3: Qualitative studies
→ Explore in detail and understand what influences current practice of deprescribing antithrombotic therapy in people with cancer, their care givers, and healthcare professionals
→ Identify potential barriers and facilitators to changing antithrombotic therapy in people with cancer at the end of life, using qualitative research
Work package 4: Consensus, Delphi analysis
→ Achieve consensus amongst a large group of experts from all relevant stakeholders on the optimal design and content of the shared decision support tool (SDST)
Work package 5: Design and development of the SDST
→ Design the optimal digital clinical decision tool for facilitating patient-involved decision-making regarding the use of antithrombotic therapy in last year of life care of people with cancer
→ Gain relevant insights on the usability of design
→ Develop a fully working alpha prototype release for alpha-testing in three languages (Italian, Dutch, English)
→ Run an alpha test on the SDST to a relevant provide input for the Beta-version
Work package 6: Demonstration, testing and evaluation of the intervention in an RCT
→ Deliver a beta-version of the tool to be used in the randomised controlled trial (RCT)
→ Evaluate pathways and processes involved in the successful implementation of the tool into clinical practice with particular focus on user acceptability
→ Establish the impact of using the tool on patient and carer short- and long-term satisfaction with clinical care and their quality of life, the incidence of major and relevant bleeding and/or venous and arterial thrombotic complications, as well as on the healthcare economic impact. Establish the impact of using the tool on deprescribing of antithrombotic therapy in cancer patients during the last year of life
Work package 7: Implementation and dissemination of the SDST
→ Present and publish the results of SERENITY to target groups
→ Develop guidelines, policy recommendations, and position papers on antithrombotic therapy in the last year of life of people with cancer
→ Provide educational materials (online, in print and in public lectures) for the intended users of the tool via national patient organisations
→ Provide training for medical professionals on the use of the tool
→ Engage in networking activities with other European Unions funded initiatives on this topic
→ Ensure long-term maintenance, implementation, and dissemination of the tool
Work package 8: Project management
→ Install all managerial bodies and procedures
→ Ensure and harmonise the development of activities across all work packages
→ Facilitate communication between partners as well as with the European Commission
→ Ensure good and effective project administration and progress management

us to estimate with sufficient accuracy the current proportion of cancer patients in whom deprescribing of antithrombotic therapy is considered and implemented.

3.1.2. Work package 2: Epidemiological studies

In work package two, population-based epidemiological data regarding the use of antithrombotic therapy in people with cancer and practice patterns of deprescribing in the last year of life will be collected. Various cohort studies will be performed in national data sources from Denmark, the Netherlands, and Wales. Taking into account the incidence of advanced cancer, the cohort size for each country is estimated at 90,000 to 200,000 unique patients. The usage and discontinuation of antithrombotic therapy in the last year of life of people with advanced cancer will be described. Moreover, the incidences of bleeding and cardiovascular complications (i.e., venous thromboembolism (VTE), myocardial infarction, and transient ischemic attack/stroke) and the association with numerous variables (e.g. type and stage of cancer, sex and age) and (dis)continued use of antithrombotic therapy will be determined. Additionally, we aim to identify patient profiles associated with these complications of antithrombotic therapy during end-stage cancer. These data are crucial to inform patients, their care givers and health professionals in making decisions on (dis)continuing antithrombotic therapy in their last phase of life.

3.1.3. Work package 3: Qualitative studies

The aim of this work package is to explore what influences the current practice of continuing and deprescribing antithrombotic therapy in people with cancer and identify potential barriers and facilitators to changing antithrombotic therapy at the end of life from the perspective of patients and clinicians. It will contribute to understanding the processes and factors behind decisions around the deprescribing of antithrombotic therapy. A multicentre qualitative interview study will explore experiences, values, and perspectives on antithrombotic therapy at the end of life of people with cancer. Moreover, clinicians' experiences of the current practice of continuing and deprescribing antithrombotic therapy in people with cancer and key facilitators and barriers to deprescribing will be identified.

Studies conducted in this work package will capture views on the best way to communicate important issues with patients and care givers. A total of 60 in-depth interviews with patients and between 72 and 96 with professionals will be equally conducted in four countries from the consortium (Denmark, United Kingdom, France and Spain). Data will be analysed using Framework Analysis following Ritchie and Spencer's five interconnected steps: (1) familiarisation with data; (2) identifying a thematic framework; (3) indexing the data; (4) charting; (5) mapping and interpretation [34]. A common protocol, interview schedule and analytic matrix will be used across the four European countries so that similarities and differences between nations may be observed.

3.2. Phase 2: Shared decision support tool development

In phase two, during the second and third year of the project, the information that has been acquired in phase one will be integrated in an SDST consistent with the shared decision-making guidelines and standards framework for shared decision-making support tools. [35,36]

3.2.1. Work package 4: Consensus

In work package four, a consensus agreement will be developed on the optimal introduction of the decision tool by clinicians, the interface, the content of the decision tool under development, and the likely ‘fit’ into the clinical care pathways of oncological and palliative care across European countries. Moreover, the primary outcome of the RCT in work package six will be determined.

In palliative care research, it is not always appropriate and/or possible to undertake clinical trials or large-scale observational research to derive evidence to support guidelines for ethical, economic, or practical reasons [37,38]. Many clinical guidelines on palliative care topics are therefore grounded in expert opinions and experiences, captured using consensus building processes such as the Delphi technique [39]. We will follow the reporting standard for Conducting and REporting of DELphi Studies in palliative care (CREDES), involving all consortium members as well as additional healthcare professionals, patients and care givers. This process will involve four methodological features: (1) an expert panel is questioned about the issue of interest; (2) the process is strictly anonymous in order to avoid social pressure and conformity to a dominant view; (3) the procedure is iterative in nature, comprising several rounds of enquiry; and (4) the design of subsequent rounds is informed by a summary of the group response of the previous round [40]. The Delphi method involves usually two or three rounds in order to achieve consensus. Considering the size of this project, we expect three rounds to achieve consensus, defined as >75 % agreement [41,42]. The criteria for the selection of experts and the process of the actual recruitment of the expert panel will be transparent and published on the SERENITY website. A total of 80 members is considered to be the maximum for this panel [40]. Assuming that the subject of our project is highly complex, we will aim for a 70- to 80-member panel. To ensure sufficient patient participation, at least one third of all panel members will be either a patient or a care giver. During the process, the actual content and interface of the decision tool are determined, covering factual information on the incidences of complications and how this information is provided, the potential to predict individual risks, clinical details, and key questions to take patient preferences into account. The optimal timing and frequency of using the tool will be decided as well, alongside the way in which the tool should be introduced.

3.2.2. Work package 5: Design and development of the SDST

From the consensus of work package four, a web-based SDST will be developed in close relation with patients and healthcare professionals to ensure its utility, usability, and acceptability in everyday practice. The tool will be adapted to facilitate its use across Europe. An expert reference group of clinicians and nurses in the field will be convened to advise on the application of the SDST in the clinical care pathway and on issues such as parallel minimum training in shared decision-making (following the UK NICE NG197 recommendations) [35]. An interactive element that identifies an individual’s levels of risk of complications due to antithrombotic therapy will be included. Flexibility will be built into the decision-making tool to ensure it is not ‘one size fits all’, taking into account for instance differences between sexes, ages, comorbidities, cancer types, religion and geographic location. It will be possible to print a summary in the form of a ‘brief decision aid’, which can be added to a medical chart. The tool will present options, with well-chosen descriptions and information about the pros and cons of those options. The prototype SDST will be subject to an iterative development process to refine the content, including feasibility and pilot studies, before finally being tested as part of an RCT, conducted in work package six.

Throughout testing, there will be a focus on usability, satisfaction, readiness to make decisions, and appraising the SDST under refinement according to the criteria and standards (essential and advanced) for high quality decision aids [43]. Upon finalisation of the SERENITY tool, the information will be presented in all 23 official EU languages as well as in Turkish, classic Arabic and Chinese (Mandarin). The design will take into account low (health) literacy, dyslexia, and social, cultural, and ethical aspects of the decision-making process.

3.3. Phase 3: Validation and implementation

In phase three, lasting from the third until the fifth year of the project, a feasibility study and an embedded pilot study are performed, followed by a cluster randomised controlled trial undertaken in five countries. The trial will formally evaluate the performance of the SDST, at the most appropriate time for ACP. When the SDST is considered ready for global use, an implementation and dissemination plan will be established. To increase inclusion, feasibility, dissemination, as well as validation and implementation of the results, we will use our networks to not only implement in hospital settings, but also in primary care and nursing home settings.

3.3.1. Work package 6: Demonstration, testing and evaluation of the intervention in an RCT

Work package six comprises the feasibility study, the pilot study and the RCT. The feasibility study will serve to optimise the study logistics with a particular focus on ensuring recruitment through specialist palliative care services, oncology clinics, primary care and/or nursing homes. It will allow for an estimation of recruitment and attrition rates. Moreover, the feasibility study will provide important preliminary data that will be used to refine the sample size calculation of the full trial. The embedded pilot study will be used to scrutinise study site openings and recruitment rates, to confirm that the trial will complete recruitment in time, in accordance with the recommendations of the United Kingdom’s National Institute for Health and Care Research (NIHR) evaluation, trials and studies coordinating centre (NETSCC) [44]. We shall identify patients facing the end of their lives by using the “surprise question” as an inclusion criterion. By asking the surprise question, “Would you be surprised if this patient dies within the next year?”, healthcare professionals can identify patients who might have palliative care needs and require specialist PC service [45]. It has been demonstrated that the surprise question is a feasible and effective tool to screen for people with cancer who have an increased mortality risk [46,47].

The primary outcome of the trial will be determined in phases one and two. The implementation of the tool and introduction by clinicians will be assessed and barriers for using the tool will be mapped. The impact of using the tool in daily practice will be determined by quantifying differences in the number of days participants used antithrombotic therapy, the prevalence of use of antithrombotic therapy each month before death, and the complications experienced after counselling. Furthermore, psychosocial intermediate and long-term outcomes will be studied, such as patient and carer immediate readiness and

Table 2

Steps undertaken to mitigate the risk of poor recruitment for the randomised controlled trial (RCT).

Steps undertaken to improve recruitment:
→ A pragmatic study design that replicates usual practice and minimises additional visits/follow ups
→ Identify and address challenges at the feasibility stage of the study
→ Broad inclusion criteria
→ Early involvement of recruitment site staff to ensure commitment to study
→ Pairing up of local clusters to share good practice and research nurse cross cover during absences
→ Learning approach from strong recruitment sites to ensure good practice is shared
→ Regular monitoring of recruitment activity in order to identify additional support/training needs

satisfaction with (the introduction of) the tool, alongside more long-term satisfaction with medical care, QoL, and symptom burden, while possible moderators (e.g. patients' personality or demographic variables) of these effects are explored [48]. Patient outcomes will be – where possible – related to the way clinicians introduced and discussed the tool, making use of coded audio- or video-taped interactions in a subset of the data [49]. Lastly, the economic impact of the application of the STSD will be evaluated by conducting a cost-effectiveness analysis, taking the medication costs, the palliative care as provided, and the medical costs for incident cardiovascular complications into account.

Recruitment of patients in the last year of life can be challenging, particularly when undertaken through palliative care services, many of which are funded by the charitable sector. Our consortium comprises a large number of clinicians, nurses and researchers, which will help facilitate recruitment, and several additional steps will be taken to mitigate the risks of poor recruitment (Table 2).

3.3.2. Work package 7: Implementation and dissemination

After the optimisation and evaluation of the SDST, we will be able to fully appreciate the (societal) impact of the tool, generate sufficient evidence to support guideline recommendations, and take the final step towards the implementation of the tool in daily practice. In work package seven, a targeted dissemination plan will be developed for the continuation of the SDST after the project ends. This will be carefully planned in collaboration with patient partner organisations and all consortium partners. The considered options are the establishment of a dedicated foundation that will exploit and update the tool or, alternatively, the hosting of this task by one of the consortium partners. This dissemination plan will include a financing model to accommodate for the regular updating of the app after the end of the project. For example, professional associations, policy makers, and national governments incorporating our guidelines into their quality frameworks and guidelines might be interested in contributing to its maintenance and further development. This dissemination package will enable us to achieve our long-term social and economic impacts.

3.3.3. Work package 8: Project management

A consortium manager will be assigned to establish the consortium structure, coordinate and steer SERENITY on scientific progress and output, and liaison with and report to the European Commission. Similarly, for the UK arm of the project, a manager will be employed to liaise with the consortium manager and also report to the United Kingdom Research and Innovation (UKRI). Detailed information about the studies' progress and results will be available on the consortiums website serenity-research.eu.

4. Conclusion

The conducted studies leading up to the development of the shared decision support tool will provide insights on the epidemiological aspects of antithrombotic therapy usage in people with cancer during their last phase of life. Moreover, current healthcare professionals' opinions on and practice patterns of deprescribing antithrombotic therapy, as well as patients' values and expectations concerning the use of antithrombotic therapy at the end of life will be identified. These insights will provide the foundation for the development of new policies and guidelines across Europe. Ultimately, we aim to provide a shared decision support tool that supports the healthcare professional, patient and care giver in decision-making around (dis)continuation of antithrombotic therapy, increases patient empowerment, improves quality of life in people with cancer during their final stage of life and reduces health costs.

CRedit authorship contribution statement

This protocol paper was primarily drafted by JG, FAK and SN. All

authors contributed to the development and drafting of the grant application, revised this manuscript critically for important intellectual content and approve of its submission. FM is a UK National Institute for Health and Care Research (NIHR) Senior Investigator. The views expressed in this article are those of the author(s) and not necessarily those of the UK NIHR, or the UK Department of Health and Social Care.

Declaration of competing interest

AAH reports grants, speaking, or consulting fees from Bayer, MSD, LEO-Pharma and Bristol-Myers Squibb/Pfizer. MS reports grants and consulting fees from Bayer. JJB is a speaker for Abbott and Edwards Lifesciences. GJG is vice-chair of the Dutch Federation of Thrombosis services, and reports grants from Bayer, BMS, Pfizer and Daiichi-Sankyo, The Dutch Research Council, The Netherlands Organisation for Health Research and Development, and the Dutch Heart Foundation, all unrelated to this work and paid to his institution. MVH reports grants from Dutch Heart Foundation, ZonMw, Bayer Health Care, Pfizer-BMS, and Leo Pharma, all unrelated to this work. FAK reports grants or contracts from Bayer, BMS, BSCI, MSD, Leo Pharma, Actelion, Varm-X, The Netherlands Organisation for Health Research and Development, the Dutch Thrombosis Association, The Dutch Heart Foundation and the Horizon Europe Program, all unrelated to this work and paid to his institution. AM reports advisory board honoraria from Bayer, BMS Sanofi and Pfizer, speaker's bureau for BMS and Bayer and an educational grant from Bayer. DM reports contracts from BMS, Leo Pharma, Pfizer and Sanofi. MJHAK reports grants from Sobi, The Netherlands Organisation for Health Research and Development and the Dutch Thrombosis Association and speakers fee from Roche, Sobi and BMS, all unrelated to this work and paid to his institution. FEMM reports grants from Yorkshire Cancer Research, Marie Curie Cancer Care, the UK National Institute of Health and Care Research, and Hull Clinical Commissioning Group, all unrelated to this work. LV reports a grant from the Dutch Cancer Society, the Netherlands Organization for Health Service Research and Development, and the Dutch Research Council, all unrelated to this work. All others report no conflicts of interest related to this project.

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