Anticoagulation Therapy in SELECTed Cancer Patients at Risk of Recurrence of Venous Thromboembolism

Chief Investigator

Annie Young

Authorised Signature:

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Sponsor: University of Warwick
Sponsor protocol number: RMRHS0095
Funding body: Bayer plc
### CONTACT DETAILS

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>University of Warwick</th>
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<tr>
<td>Sponsor</td>
<td>Dr Peter Hedges</td>
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<tr>
<td></td>
<td>Research Support Services</td>
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<td></td>
<td>University of Warwick</td>
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<td></td>
<td>University House</td>
</tr>
<tr>
<td></td>
<td>Coventry CV4 8UW</td>
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<tr>
<td></td>
<td>Tel: +44 (0)24 7652 3716</td>
</tr>
<tr>
<td></td>
<td>Fax: +44 (0)24 7652 4991</td>
</tr>
<tr>
<td></td>
<td><a href="mailto:p.a.hedges@warwick.ac.uk">p.a.hedges@warwick.ac.uk</a></td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Chief Investigator</th>
<th>Prof. Annie Young</th>
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<tbody>
<tr>
<td></td>
<td>Professor of Nursing</td>
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<td>Division of Health Sciences</td>
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<td>Tel: +44 (0)24 7615 1351</td>
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<tr>
<td></td>
<td>Fax: +44 (0)24 7652 8375</td>
</tr>
<tr>
<td></td>
<td><a href="mailto:annie.young@warwick.ac.uk">annie.young@warwick.ac.uk</a></td>
</tr>
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<table>
<thead>
<tr>
<th>Co-Investigator</th>
<th>Prof. Lord Ajay Kakkar</th>
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</thead>
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<tr>
<td></td>
<td>Director</td>
</tr>
<tr>
<td></td>
<td>Thrombosis Research Institute</td>
</tr>
<tr>
<td></td>
<td>Emmanuel Kaye Building</td>
</tr>
<tr>
<td></td>
<td>Manresa Road</td>
</tr>
<tr>
<td></td>
<td>Chelsea, London, SW3 6LR</td>
</tr>
<tr>
<td></td>
<td>Tel: +44 (0)207 351 8309</td>
</tr>
<tr>
<td></td>
<td><a href="mailto:akkakkar@tri-london.ac.uk">akkakkar@tri-london.ac.uk</a></td>
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<table>
<thead>
<tr>
<th>Co-Investigator</th>
<th>Dr Oliver Chapman</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Consultant Haematologist</td>
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<tr>
<td></td>
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<td>Tel: +44 (0)24 7696 5549</td>
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<tr>
<td></td>
<td><a href="mailto:oliver.chapman@uhcw.nhs.uk">oliver.chapman@uhcw.nhs.uk</a></td>
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<table>
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<tr>
<th>Co-Investigator</th>
<th>Prof. Chris Poole</th>
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<td></td>
<td>Professor of Medical Oncology</td>
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<td><a href="mailto:cjpoole@mac.com">cjpoole@mac.com</a></td>
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<tr>
<th>Co-Investigator</th>
<th>Prof. Bob Grieve</th>
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<td></td>
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<td><a href="mailto:robert.grieve@uhcw.nhs.uk">robert.grieve@uhcw.nhs.uk</a></td>
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<tr>
<th>Co-Investigator</th>
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<td></td>
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<th>Co-Investigator</th>
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<td></td>
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<tr>
<td></td>
<td><a href="mailto:richard.hobbs@phc.ox.ac.uk">richard.hobbs@phc.ox.ac.uk</a></td>
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<tr>
<th>Co-Investigator</th>
<th>Dr Veronica Wilkie</th>
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<th>Co-Investigator</th>
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</tr>
<tr>
<td></td>
<td><a href="mailto:s.petrou@warwick.ac.uk">s.petrou@warwick.ac.uk</a></td>
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## Co-Investigator
### User Involvement

<table>
<thead>
<tr>
<th>CTU Lead / Statistician</th>
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<th>Co-Investigator /select-d Trial Coordinator</th>
<th>QA Advisor</th>
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<tr>
<td>Prof. Janet Dunn</td>
<td>Dr Andrea Marshall</td>
<td>Miss Jenny Phillips</td>
<td>Ms Claire Daffern</td>
<td>Mrs Karen French</td>
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<tr>
<td>Head of Cancer Trials</td>
<td>Senior Statisticist</td>
<td>Clinical Trials Coordinator</td>
<td>QA Manager</td>
<td>VTE Nurse Specialist</td>
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<tr>
<td>Warwick Clinical Trials Unit</td>
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<td>Tel: +44 (0)24 7655 0176</td>
<td>Tel: +44 (0)24 7657 3315</td>
<td>Tel: +44 (0)24 7655 0117</td>
<td>Tel: +44 (0)24 7696 5508</td>
</tr>
<tr>
<td><a href="mailto:j.a.dunn@warwick.ac.uk">j.a.dunn@warwick.ac.uk</a></td>
<td><a href="mailto:andrea.marshall@warwick.ac.uk">andrea.marshall@warwick.ac.uk</a></td>
<td><a href="mailto:j.phillips@warwick.ac.uk">j.phillips@warwick.ac.uk</a></td>
<td><a href="mailto:c.daffern@warwick.ac.uk">c.daffern@warwick.ac.uk</a></td>
<td><a href="mailto:karen.french@uhcw.nhs.uk">karen.french@uhcw.nhs.uk</a></td>
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<th>Senior Project Manager</th>
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<th>QA Advisor</th>
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<tr>
<td>Mrs Jo Grumett</td>
<td>Warwick Clinical Trials Unit</td>
<td>Ms Claire Daffern</td>
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<tr>
<td>Senior Project Manager</td>
<td>Warwick Medical School</td>
<td>QA Manager</td>
</tr>
<tr>
<td>Warwick Clinical Trials Unit, Warwick Medical School, The University of Warwick, Coventry, CV4 7AL</td>
<td>Warwick Medical School</td>
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</tr>
<tr>
<td>Tel: +44 (0)24 7615 1082</td>
<td>University of Warwick</td>
<td>Coventry CV4 7AL</td>
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<tr>
<td><a href="mailto:joanne.grumett@warwick.ac.uk">joanne.grumett@warwick.ac.uk</a></td>
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<tr>
<td>Miss Asha Chauhan</td>
<td>Warwick Clinical Trials Unit</td>
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<td>Clinical Trials Administrator</td>
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</tr>
<tr>
<td>Tel: +44 (0)24 7657 3243</td>
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</tr>
<tr>
<td><a href="mailto:a.chauhan@warwick.ac.uk">a.chauhan@warwick.ac.uk</a></td>
<td><a href="mailto:c.daffern@warwick.ac.uk">c.daffern@warwick.ac.uk</a></td>
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<thead>
<tr>
<th>Pharmacy Advisor</th>
<th>Nursing Advisor</th>
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<tr>
<td>Mr Mojid Khan</td>
<td>Mrs Karen French</td>
</tr>
<tr>
<td>Specialist Pharmacist, Oncology Clinical Trials</td>
<td>VTE Nurse Specialist</td>
</tr>
<tr>
<td>University Hospital, UHCW</td>
<td>Department of Haematology</td>
</tr>
<tr>
<td>Coventry CV2 2DX</td>
<td>University Hospital, UHCW</td>
</tr>
<tr>
<td>Tel: +44 (0)24 7696 4000</td>
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</tr>
<tr>
<td>Fax: +44 (0)24 7696 6795</td>
<td>Tel: +44 (0)24 7696 5508</td>
</tr>
<tr>
<td><a href="mailto:mohammed.khan2@uhcw.nhs.uk">mohammed.khan2@uhcw.nhs.uk</a></td>
<td>Fax: +44 (0)24 7696 8798</td>
</tr>
<tr>
<td><a href="mailto:karen.french@uhcw.nhs.uk">karen.french@uhcw.nhs.uk</a></td>
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<tr>
<th>Translational Science Advisor</th>
<th>Translational Science Advisor</th>
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<tr>
<td>Prof. Wolfram Ruf</td>
<td>Dr Gloria Petralia</td>
</tr>
<tr>
<td>Margaret Thatcher Professor of Biological Chemistry (external)</td>
<td>Thrombosis Research Institute</td>
</tr>
<tr>
<td>Thrombosis Research Institute London SW3 6LR</td>
<td>Manresa Road</td>
</tr>
<tr>
<td>London SW3 6LR</td>
<td>Chelsea</td>
</tr>
<tr>
<td>Tel: +44 (0)207 351 8309</td>
<td>Tel: +44 (0)207 351 8309</td>
</tr>
<tr>
<td><a href="mailto:ruf@scripps.edu">ruf@scripps.edu</a></td>
<td><a href="mailto:petralia@tri-london.ac.uk">petralia@tri-london.ac.uk</a></td>
</tr>
</tbody>
</table>
TRIAL STEERING COMMITTEE

Chair
Professor Mark Levine
Chair, Department of Oncology
Department of Oncology, McMaster University
1st Floor, G Wing, Henderson Research Centre
711 Concession St.
Hamilton, Ontario, Canada L8V 1C3
Tel: +1 905 527-4322 ext 42176
mieleve@mcmaster.ca

Deputy Chair
Professor Gary Lyman
Professor of Medicine and Director,
Comparative Effectiveness and Outcomes Research – Oncology
Duke University School of Medicine
2424 Erwin Road, Suite 205, Durham, NC 27705
Tel: +1 919-681-1736; Fax: 919-681-7488;
gary.lyman@duke.edu

Member
Dr Peter MacCallum
Senior Lecturer in Haematology
Queen Mary London University
Mile End Road
London E1 4NS
Tel: +44 (0)20 788 26208
p.k.maccallum@qmul.ac.uk

Member
Dr Lisa Robinson
Consultant Haematologist
The County Hospital
Wye Valley NHS Trust
Stonebow Road
Hereford HR1 2BN
Tel: +44 (0)1432 355444
lisa.robinson@wvt.nhs.uk

Member
Dr Anthony Maraveyas
Consultant Medical Oncologist
Castle Hill Hospital
Hull and East Yorkshire Hospitals NHS Trust
Castle Road, Cottingham
East Yorkshire HU16 5JQ
Tel: +44 (0)1482 461318
anthony.maraveyas@hey.nhs.uk

Member
Prof. Jeremy Dale
Division of Health Sciences
Warwick Medical School
University of Warwick
Coventry CV4 7AL
Tel: +44 (0)24 7652 2891
jeremy.dale@warwick.ac.uk

Member
Dr Charles Hutchinson
Professor of Imaging
University of Warwick
UHCW Campus
Clifford Bridge Road
Coventry CV2 2DX
Tel: +44 (0)24 7696 8667
c.e.hutchinson@warwick.ac.uk

Member
Mrs Irene Singleton
select-d User Representative
c/o select-d Team
Warwick Medical School
University of Warwick
Coventry CV4 7AL
Tel: +44 (0)24 7615 1351
select-d@warwick.ac.uk

DATA AND SAFETY MONITORING COMMITTEE

Chair
Professor Keith Wheatley
Professor of Medical Statistics
Cancer Research UK Clinical Trials Unit
College of Medical and Dental Sciences
University of Birmingham
Birmingham B15 2TT
Tel: +44 (0)121 414 8040
k.wheatley@bham.ac.uk

Member
Dr Lisa Robinson
Consultant Haematologist
The County Hospital
Wye Valley NHS Trust
Stonebow Road
Hereford HR1 2BN
Tel: +44 (0)1432 355444
lisa.robinson@wvt.nhs.uk

Member
Dr Anthony Maraveyas
Consultant Medical Oncologist
Castle Hill Hospital
Hull and East Yorkshire Hospitals NHS Trust
Castle Road, Cottingham
East Yorkshire HU16 5JQ
Tel: +44 (0)1482 461318
anthony.maraveyas@hey.nhs.uk
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<td>Abbreviation</td>
<td>Explanation</td>
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<td>----------------------------------------------------------------</td>
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<tr>
<td>RVT</td>
<td>Residual Vein Thrombosis</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SAR</td>
<td>Serious Adverse Reaction</td>
</tr>
<tr>
<td>SC</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
</tr>
<tr>
<td>SSPE</td>
<td>Sub-Segmental Pulmonary Embolism</td>
</tr>
<tr>
<td>SUSAR</td>
<td>Suspected Unexpected Serious Adverse Reaction</td>
</tr>
<tr>
<td>TMG</td>
<td>Trial Management Group</td>
</tr>
<tr>
<td>TSC</td>
<td>Trial Steering Committee</td>
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<tr>
<td>ULN</td>
<td>Upper Limit of Normal</td>
</tr>
<tr>
<td>US</td>
<td>Ultrasound</td>
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<tr>
<td>VKA</td>
<td>Vitamin K Antagonist</td>
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<tr>
<td>VTE</td>
<td>Venous Thromboembolism</td>
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<tr>
<td>WBC</td>
<td>White Blood Cell</td>
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<tr>
<td>WCC</td>
<td>White Cell Count</td>
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<td>WCTU</td>
<td>Warwick Clinical Trials Unit</td>
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## 2. Trial Summary

<table>
<thead>
<tr>
<th>Title:</th>
<th>select:d: Anticoagulation Therapy in <strong>SELECTeD</strong> Cancer Patients at Risk of Recurrence of Venous Thromboembolism (VTE)</th>
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<tr>
<td>Design:</td>
<td>Prospective, randomised, open label, multicentre pilot study comparing dalteparin vs. rivaroxaban with a second placebo-controlled randomisation comparing the duration of anticoagulation therapy (6 months vs 12 months treatment) in Residual Vein Thrombosis [RVT] positive (+ve) patients.</td>
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</table>
| Inclusion criteria: | ● Patients with active cancer  
● Patients with a primary presentation of an objectively confirmed VTE - symptomatic lower extremity proximal DVT or symptomatic or incidental PE  
● ECOG Performance Status 0-2  
● Aged ≥18  
● Written informed consent given  
● Adequate haematological function (recommended levels – haemoglobin (Hb) > 10g/dl, white cell count (WCC) > 2x10⁹/l, platelets > 100 x10⁹/l)  
● Adequate hepatic and renal function – liver enzymes < x3 upper limit of normal (ULN); creatinine clearance >30ml per minute |
| Exclusion criteria: | ● Patients taking any anticoagulants (excluding any pre-treatment for this episode of VTE)  
● Patients taking >75 mg aspirin per day  
● Planned randomised treatment start time >72 hours after starting anticoagulant for this episode of VTE  
● Clinically significant liver disease (e.g. acute hepatitis, chronic active hepatitis, or cirrhosis) or an alanine aminotransferase level that is ≥ 3 times ULN range  
● Bacterial endocarditis  
● Active bleeding or at high risk of bleeding, contraindicating anticoagulant treatment  
● Systolic blood pressure > 180 mm Hg or Diastolic blood pressure > 110 mm Hg.  
*Control of blood pressure using anti-hypertensive drugs is permitted*  
● Of childbearing potential (both male and female participants) without a combination of adequate contraceptive measures, e.g. oral contraceptives, IUD, barrier methods of contraception (condom or occlusive cap with spermicide)  
● Pregnancy or breast-feeding  
● Concomitant use of strong cytochrome P-450 3A4 inhibitors (e.g. human immunodeficiency virus protease inhibitors or systemic ketoconazole) or inducers (e.g. rifampicin, carbamazepine, or phenytoin) or p-glycoprotein inhibitors/ inducers |
| Selection criteria for second randomisation: | ● Patients with DVT who are Residual Vein Thrombosis [RVT] positive (+ve) or patients presenting with a PE  
● ECOG performance status 0, 1 or 2  
● Still receiving initial trial treatment  
● No recurrence of VTE |
| Objectives: | Primary Objective:  
To assess VTE recurrence rates in SELECTed cancer patients at risk of recurrence of VTE treated with rivaroxaban or dalteparin  
Secondary Objectives:  
- To ensure the safety of the patients with regards to major bleeding in an internal safety study  
- To assess acceptability and compliance to randomisation and allocated treatment  
- To assess 6 months and 12 months anticoagulation treatment in patients with evidence of RVT following initial therapy, in terms of VTE recurrence rates  
- To assess the VTE recurrence rates in patients with evidence of RVT and those with no evidence of RVT |
| Outcome measures: | Primary Outcome:  
- VTE recurrence rates (including symptomatic VTE and incidental PE)  
Secondary Outcomes:  
- Symptomatic VTE and incidental PE recurrence rates  
- Major bleeding and clinically relevant non-major bleeding  
- Feasibility of conducting an economic evaluation  
- Tumour efficacy  
- Acceptability and compliance to randomisation and treatment  
- Patient experience  
- Quality of life  
- Progression-free survival (adjuvant patients) and overall survival  
- Biomarker correlation |
| Treatment: | Dalteparin (Fragmin®, Pfizer), a low molecular weight heparin, the only licensed anticoagulant in the UK for the extended treatment and prevention of recurrence of VTE in cancer patients  
Rivaroxaban (Xarelto®, Bayer), an oral direct Factor Xa inhibitor, licensed for the treatment of DVT and the prevention of recurrence of DVT and PE in adult patients. |
| Sample size: | A total of 530 patients will be recruited to provide reliable estimates of the primary outcome (VTE recurrence rates) to within a width of the 95% confidence interval of 8% assuming the VTE rates are 10% at six months. |
| Stratification: | FIRST RANDOMISATION (dalteparin versus rivaroxaban)  
- Stage of disease at randomisation [early/locally advanced disease; metastatic disease; not applicable]  
- Baseline platelet count [<350,000/µL; >350,000/µL]  
- Type of VTE [symptomatic VTE; incidental PE]  
- Risk of clotting by tumour type [high risk; low risk]  
SECOND RANDOMISATION (rivaroxaban versus placebo)  
- Treatment allocation at first randomisation [dalteparin; rivaroxaban]  
- Stage of disease at randomisation [early/locally advanced disease; metastatic disease; not applicable]  
- Platelet count at randomisation [<350,000/µL; >350,000/µL]  
- Type of VTE [symptomatic VTE; incidental PE]  
- Risk of clotting by tumour type [high risk; low risk] |
| Analysis: | Analysis will be performed after recruitment of 530 patients. Estimates of VTE recurrence and 95% confidence intervals will be obtained from constructing Kaplan-Meier curves to take into account censoring. The number of RVT positive patients continuing to the second randomisation will be evaluated. Compliance to treatment will be assessed by frequency of withdrawals of therapy and duration of therapy. Kaplan-Meier curves will be constructed and estimates obtained for the composite safety parameter, progression-free survival and overall survival. Quality of life will be reported descriptively using appropriate longitudinal analyses. Frequencies of adverse events and antitumour efficacy will be reported. A pre-planned safety analysis will be conducted after the first 200 patients randomised (100 on each treatment arm) and have been on study at least 6 months (i.e. completed initial therapy and considered for the second randomisation) to assess treatment compliance, RVT results, adverse events and power calculation assumptions. The trial will continue to 530 patients if safety study shows no excess adverse events over and above what is expected (i.e. around 5% major haematological bleeds with no more than 15% excess in rivaroxaban arm). |
3. Trial Schema

Eligibility
Patients with active cancer and VTE
with ECOG PS 0, 1, 2

RANDOMISATION 1
n=530

ARM A: Dalteparin
200IU/kg daily
s/c for 1 month
150IU/kg daily
s/c for 5 months
n=265

ARM B: Rivaroxaban
15mg twice daily
for 3 weeks
20mg daily for 6 months in total
n=265

STRATIFICATION VARIABLES
Stage of disease at randomisation [early/locally advanced disease; metastatic disease; N/A]
Baseline platelet count [<350,000/µL; >350,000/µL]
Type of VTE [symptomatic VTE; incidental PE]
Risk of clotting by tumour type [high; low]

At 5 months:
DVT patient Selection by US Assessment of RVT
[Continue treatment for total of 6 months]

No evidence of RVT
= 30% patients

STOP Treatment
n = 130

RVT+
(+PE on presentation)
= 70% patients

RANDOMISATION 2
(assuming 80% uptake)

STRATIFICATION VARIABLES
Stage of disease at randomisation [early/locally advanced disease; metastatic disease; N/A]
Platelet count at randomisation [<350,000/µL; >350,000/µL]
Type of VTE [symptomatic VTE; incidental PE]
Risk of clotting by tumour type [high; low]
First treatment [dalteparin; rivaroxaban]

Placebo
Daily for 6 months
n = 150

Community follow-up
for recurrence

Rivaroxaban
20mg oral daily for 6 months
n = 150

Patients on anticoagulation will discontinue treatments for unacceptable toxicity,
platelets <50,000/µL, recurrence of VTE, death or patient/physician decision

Safety Analysis
Pre-planned safety analysis after the first 200 patients randomised (100 in each arm)

Analysis
Estimates of VTE recurrence, assess compliance, RVT stratification, adverse events, quality of life, cost effectiveness

VTE: Venous Thromboembolism
RVT: Residual Vein Thrombosis
DVT: Deep Vein Thrombosis
PE: Pulmonary Embolism
4. Background

4.1 Introduction

The therapeutic ideal is to treat the right patient with the right drug at the right dose for the right length of time. The single most important component of this paradigm is patient selection. A more targeted approach to patient selection in identifying those patients with clinically relevant recurrent VTE is likely to have wider health economic benefits whilst reducing patient risk through over-treatment.

Rivaroxaban, along with other novel oral anticoagulants, is transforming the treatment of deep vein thrombosis (DVT) and prevention of recurrent DVT and pulmonary embolism (PE)\(^1\), the prophylaxis of venous thromboembolism (VTE) in patients undergoing orthopaedic surgery\(^2,3\), and the prevention of stroke and systemic embolism in people with atrial fibrillation\(^4\). Furthermore, research into the treatment of VTE in the cancer population was a highlighted research recommendation by the National Institute for Health and Clinical Excellence (NICE) in 2012\(^5,6\).

Rivaroxaban benefits from oral delivery, improved efficacy, a good safety profile and no need for monitoring by blood tests. Nevertheless, anticoagulation may reduce quality of life, and different models of anticoagulation management may have different impact on patient experience.

4.2 Venous Thromboembolism and Cancer

VTE (comprising DVT and PE) is a serious and potentially life-threatening condition, representing the second most common cause of death in cancer patients\(^7,8\). Cancer, chemotherapy and central venous catheters (CVCs) increase the risk of VTE\(^9\). Thrombosis and cancer are linked by multiple pathophysiological mechanisms; the tumour biology and coagulation processes are closely interconnected. In a prospective cohort study of 4000 patients with solid tumours and lymphoma, Kuderer et al showed that VTE is an independent risk factor for mortality during the initial months of chemotherapy in patients with cancer of all stages\(^10\).

Patients with malignancy not only have a four-fold increased risk of developing venous thromboembolism (VTE)\(^9\), they also have a three-fold risk of recurrent VTE and a three-fold to six-fold risk of major bleeding while receiving anticoagulant treatment with warfarin, relative to the general population\(^11\). The overall incidence of recurrent VTE in patients with cancer is 27.1 per 100 patient-years (18.9 per 100 patient-years with therapeutic warfarin) compared with 9.0 per 100 patient-years (7.2 per 100 patient-years with therapeutic warfarin) in patients without cancer\(^11\). Multiple factors need to be considered when attempting to calculate an individual cancer patient’s risk of developing thrombosis. The incidence of VTE among patients with cancer varies between tumour types\(^12,13\). The primary site of the cancer, receiving chemotherapy, and more recently, platelet count have been consistently identified as independent risk factors. Chemotherapy and hormone therapy are independent risk factors conferring a higher risk of VTE\(^9,13,14\). It has been suggested that performance status may also be a surrogate factor for age\(^15\).

The benefit/risk ratio between prevention of recurrence of thrombosis and bleeding is the all-important balance. The 12-month cumulative incidence of major bleeding in patients with and without cancer was found to be 12.4% and 4.9% respectively\(^11\). Thrombotic complications can delay or interfere with anticancer therapy, precipitate or prolong hospitalisation, and consume health care resources\(^16\). Optimal treatment of VTE is therefore crucial to minimising morbidity and mortality.

4.3 Rivaroxaban

Rivaroxaban is a highly selective direct Factor Xa inhibitor with oral bioavailability and rapid onset of action. Inhibition of Factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi\(^17\).
4.3.1 Treatment of VTE

Rivaroxaban is the most advanced oral Factor Xa inhibitor in terms of clinical trials, in which over 50,000 patients have been treated. An open-label, randomised, non-inferiority trial (EINSTEIN-DVT) comparing oral rivaroxaban alone (15 mg twice daily for 3 weeks, followed by 20 mg once daily) with subcutaneous enoxaparin followed by a vitamin K antagonist (VKA) for 3, 6 or 12 months in patients with acute symptomatic DVT has recently been published [7% of patients had active cancer]. A double-blind, randomised superiority study (EINSTEIN-Ext) that compared rivaroxaban alone (20 mg once daily) with placebo for an additional 6 or 12 months in patients who had completed 6 to 12 months of treatment for VTE was carried out in parallel [5% of patients had active cancer]. The primary efficacy outcome for both studies was recurrent VTE. Rivaroxaban had non-inferior efficacy compared to enoxaparin plus a VKA. The principal safety outcome of major bleeding or clinically relevant non-major bleeding occurred in 8.1% of the patients in each group of the treatment study. In the continued-treatment study (n=1196), rivaroxaban had superior efficacy (8 events [1.3%] vs. 42 [7.1%] with placebo; hazard ratio 0.18; 95% CI 0.09 to 0.39; P<0.001). Four patients in the rivaroxaban group had non-fatal major bleeding (0.7%), versus none in the placebo group (P=0.11). Thus, ‘extended’ treatment with rivaroxaban (6-12 months, after 6-12 months of anticoagulation) significantly reduces recurrent VTE compared to initial anticoagulation treatment. Further investigation of rivaroxaban in the cancer population was recommended in the paper.

Again in a general patient population, a randomised, double-blind comparison of extended anticoagulation with two doses of apixaban (2.5 mg and 5 mg, twice daily) with placebo in patients with VTE, demonstrated that both doses reduced the risk of recurrent venous thromboembolism without increasing the rate of major bleeding.

In a secondary analysis using data from a systematic review of long-term anticoagulation in patients with cancer and the effectiveness data from the cancer subgroup of EINSTEIN-DVT, rivaroxaban was shown to be less effective than LMWH at preventing VTE recurrence (HR 1.32; 95% CI 0.06 – 32.3) but induced fewer major bleeding events (OR 0.24; 95% CI 0.06-9.94). Caution should be exercised in the interpretation of these results; both the efficacy and safety results have wide confidence intervals. However, rivaroxaban should not be excluded as a treatment option for preventing VTE recurrence in people with cancer. Further prospective trials are therefore recommended. In July 2012, NICE recommended rivaroxaban as a possible treatment for adults with deep vein thrombosis, and to help prevent a pulmonary embolism or another deep vein thrombosis.

4.3.2 Pulmonary Emboli

A study (EINSTEIN-PE) of fixed-dose regimen of rivaroxaban alone demonstrated non-inferiority to standard therapy for the initial and long-term treatment of pulmonary embolism and had a potentially improved benefit–risk profile. There is, to our knowledge, no evidence on the optimal duration of anticoagulation treatment for cancer patients with PE and therefore select-d will allow us to assess recurrent VTE rates in those patients. The clinical relevance of emboli limited to the segmental or subsegmental pulmonary arteries and the role of anticoagulation have yet to be clarified. The location of the PE will be documented. The European Commission approved the extension of the rivaroxaban licence to the treatment of pulmonary embolism in November 2012, following a positive opinion of the European Medical Agency’s Committee for Medicinal Products for Human Use (CHMP) for the use of rivaroxaban for the treatment of PE and prevention of DVT and PE.

4.3.3 Thromboprophylaxis in Medically Ill Patients

A prospective, randomised, blinded, multicentre trial (MAGELLAN) for patients hospitalised with acute medical illness and at risk of venous thromboembolism, including patients with active cancer, demonstrated that those receiving enoxaparin had a significantly reduced rate of bleeding compared to those on rivaroxaban at both 10 and 35 days (1.2 percent of patients in the enoxaparin group experienced clinically relevant bleeding after 10 days compared to 2.8 percent in the rivaroxaban group; after 35 days 1.7 percent in the enoxaparin group suffered from clinically relevant bleeding compared to 4.1 percent in the rivaroxaban group). A clinical benefit with rivaroxaban compared to
enoxaparin could not be demonstrated in this heterogeneous study population. In summary, in the primary prophylaxis of VTE in acutely ill medical patients setting, rivaroxaban was non-inferior to enoxaparin for standard-duration (10 days) thromboprophylaxis. Extended-duration rivaroxaban (35 days) reduced the risk of venous thromboembolism. Rivaroxaban was associated with an increased risk of bleeding. Again, further analysis was recommended to identify which groups of patients in MAGELLAN may derive benefit from thromboprophylaxis with rivaroxaban.

4.4 Dalteparin

Dalteparin is the only licensed anticoagulant for the extended treatment and prevention of recurrence of VTE in cancer patients and thus is the gold standard treatment. As low molecular weight heparins are distinct entities, they should not be used interchangeably in clinical practice. Six months of dalteparin was found to be more effective than and as safe as VKAs (i.e. warfarin/coumarin) for patients with cancer and acute VTE, without significantly increasing the risk of major bleeding in cancer patients with acute VTE. Our Trials Steering Group (TSG) chair, Prof Mark Levine, was Chief Investigator of this formative trial (‘CLOT’; n=676). The authors concluded that ‘longer term’ dalteparin is safe in cancer patients.

4.5 Bleeding

Bleeding is the most important complication of anticoagulants and a major concern for both physicians and patients. Individual bleeding risk must be assessed for each patient. Bleeding is categorised as major, clinically relevant non-major, or minor bleeding and as the composite of major and clinically relevant non-major bleeding and each patient will be monitored stringently for bleeding.

Bleeding is defined as major if it is clinically overt and associated with a decrease in the haemoglobin level of 2.0 g per decilitre or more, if bleeding leads to the transfusion of 2 or more units of red cells, or if bleeding is intracranial or retroperitoneal, occurs in another critical site, or contributes to death. Clinically relevant non-major bleeding is defined as overt bleeding that does not meet the criteria for major bleeding but was associated with medical intervention, unscheduled contact with a physician, interruption or discontinuation of a study drug, or discomfort or impairment of activities of daily life.

4.6 Patient Selection by Residual Vein Thrombosis

Several testing strategies have been evaluated to identify subgroups of patients with VTE who are at highest risk of recurrence and who would gain the most benefit from prolonged anticoagulant therapy. The two most promising are d-dimer testing in patients with idiopathic VTE and evaluation for residual vein thrombosis (RVT) in patients with DVT.

D-dimer: D-dimer, a degradation product of fibrin, has been excluded as a patient selection strategy for select-d on account of two specific problems in cancer patients. Firstly D-dimer is commonly elevated in patients with cancer and predictive ability likely compromised as a result. Also anticoagulation treatment affects D-dimer levels and has to be interrupted for around one month in order to interpret levels. Any interruption of anticoagulant treatment may compromise safety in cancer patients at high risk of VTE. D-dimer levels will be measured in select-d patients as per local practice.

RVT: In a systematic review to determine the role of residual thrombosis in predicting recurrent VTE after acute proximal DVT in patients with and without malignancy, a positive relationship was demonstrated between residual thrombosis and recurrent VTE during follow up. The predictive effect was more pronounced in the pooled data of two studies of only cancer patients in which 33 of 177 had a recurrent VTE event. However, in a further systematic review of RVT as a predictor of recurrent thrombosis in all patients with DVT, RVT was associated with a modestly increased risk of recurrent VTE in patients with DVT (unprovoked and provoked). However, RVO did not seem to be a predictor of recurrent VTE in patients with unprovoked DVT following anticoagulation discontinuation. The value of RVT as a predictor of recurrent VTE after acute proximal DVT in the cancer patient population still requires prospective enquiry; the select-d design provides this platform.
‘Piovella’ criteria will be used for the measurement of RVT i.e. ‘consider residual thrombosis present if the ratio of vein diameter during compression x 100, divided by the vein diameter before compression is more than 40%’, as the criteria were utilised in two recent studies of cancer patients only\textsuperscript{35,37}; both confirming the value of measuring RVT to identify a low risk (of VTE recurrence) group. The trial by Siragusa et al investigating RVT as a predictor of recurrent VTE, showed that absence of RVT identifies a group of cancer patients at low risk for recurrent thrombosis who can safely stop LMWH after 6 months. This trial provides us with a means of enriching the patient group at risk of further VTE \textsuperscript{37} by identifying those (~70 %) with residual venous thrombosis (RVT) after the initial period of anticoagulation. The ~30% of patients with no evidence of RVT have a very low risk of further VTE [2.8% of patients]. This patient selection by presence of RVT, accompanied by a strong quality assurance programme, is deemed by the Trial Steering Committee to be the optimal method for ensuring that patients at low risk of VTE recurrence will \textit{not} be treated with anticoagulants unnecessarily.

\textit{Duration of Anticoagulation Using RVT:} The Siragusa trial investigating the role of RVT to establish duration of anticoagulation treatment in cancer patients (n=347) with VTE was powered for DVT recurrence by RVT assessment and not for duration of treatment\textsuperscript{37}. RVT was detected in 242 (69.7%) patients; recurrent events occurred in 21.9% of those randomised to discontinue and 14.2% of those who continued LMWH. In patients without RVT (Group B, n=105, 30.3%), recurrent events occurred in 3 cases (2.8%). The differences between 6 months treatment vs 12 months treatment (Group A2 vs A1) were non-significant, HR 1.58 (95% confidence interval [CI], 0.85-2.93; p = 0.145); five major bleeding events occurred in Group A1 and two events both in Group A2 and B. The duration (6 months vs 12 months treatment) question is therefore still unanswered for RVT +ve cancer patients.

4.7 Symptoms of DVT and PE

In the Multicenter Advanced Study for a Thromboembolism Registry (MASTER) study, a prospective cohort of 2,119 patients with VTE, the most common presenting symptoms and signs associated with deep venous thrombosis were reported as extremity oedema (80%), pain (75%) and erythema (26%). Patients with pulmonary embolism reported dyspnoea (85%), chest pain (40%), tachypnoea (30%) and tachycardia (23%). Syncope (10%), and haemoptysis (2%) were less common\textsuperscript{38}.

4.8 Incidental PE

Now that the quality of computed tomography (CT) imaging techniques has greatly improved with the introduction of thin section multi-detector row CT scanners, pulmonary embolism (PE) is increasingly diagnosed on routine CT examinations in the absence of a clinical suspicion. This phenomenon is often referred to as ‘incidental PE’\textsuperscript{39}. In a small case control study (n=19), incidental PE was not found to be less severe than symptomatic\textsuperscript{40}. In a worldwide survey of 183 physicians, most decided to treat a patient with incidental PE. However, uncertainty exists about the need for anticoagulant treatment in patients with incidental sub-segmental PE (SSPE)\textsuperscript{39}. Patients with incidental PE will be included and adjusted for, in select-d, to assess the benefits of treatments in an area of increasing prevalence where more research is needed\textsuperscript{41}. The select-d lead radiologists (or appropriate professionals) will suggest diagnostic criteria to classify incidental PE\textsuperscript{42,43}.

4.9 Health Economics

Some health economic analyses have recently been carried out by the manufacturer of rivaroxaban. Firstly, a cost minimisation analysis evaluating rivaroxaban in comparison to dalteparin for patients with active cancer has been reported where patients with cancer were assumed to be treated for 6 months. The cost of rivaroxaban was £4.20 per day for the first 21 days (2 tablets daily), followed by £2.10 per day (1 tablet daily). The cost of dalteparin was £8.47 per day for the first month and £7.06 per day for subsequent months. The total cost saving associated with rivaroxaban compared with LMWH (dalteparin) was found to be £903 for patients with cancer. Secondly, an exploratory cost-effectiveness analysis of the subgroup of patients with cancer has been reported, but the analysis may
be unreliable because of limited evidence in this subgroup\textsuperscript{6}. The select-d health economic evaluation (see section 18.5) will provide more robust estimates of cost-effectiveness for this group of patients.

5. Definitions

5.1 Venous Thromboembolism

Symptomatic DVT is defined as acute symptomatic, objectively confirmed proximal deep vein thrombosis, without symptomatic pulmonary embolism.

Symptomatic PE is defined as acute, symptomatic, objectively confirmed pulmonary embolism with or without symptomatic deep vein thrombosis.

‘Incidental’ pulmonary embolism is defined as incidentally diagnosed PE on CT scanning, in asymptomatic patients.

5.2 Active Cancer

Active cancer is defined as a diagnosis of cancer (other than basal-cell or squamous-cell carcinoma of the skin) within six months before enrolment, any treatment for cancer within the previous six months, or recurrent or metastatic cancer.

5.3 Stage of Disease at Randomisation for Solid Tumours and Lymphoma

Early/Locally Advanced or Metastatic\textsuperscript{44, 45}

In a large cohort study, cancer patients with the highest one-year incidence rate of VTE were found to be those with advanced disease of the brain, lung, uterus, bladder, pancreas, stomach and kidney. For these solid tumour histotypes, the rate of VTE was 4–13 times higher among patients with metastatic disease as compared with those with localised disease\textsuperscript{46}. We have therefore chosen ‘early/locally advanced disease’ and ‘metastatic disease’ as stratification groups for patients with solid tumours and lymphoma.

The same binary stratification is not applicable to haematological malignancies (excluding lymphoma) and therefore ‘not applicable’ will form a third stratification group.

5.4 Residual Vein Thrombosis (RVT)

Residual vein thrombosis will be considered present if the ratio of vein diameter during compression x 100, divided by the vein diameter before compression is more than 40\%\textsuperscript{35, 37}. Please see the DVD which will be issued to all participating sites.

6. Rationale

Rivaroxaban is a highly attractive alternative to the traditional oral anticoagulants, especially for cancer patients, as doses are fixed, laboratory monitoring is not required and they reportedly have few drug interactions. The low molecular weight heparins require daily subcutaneous injection. Further investigation of rivaroxaban in the cancer population was proposed after the trial of rivaroxaban vs enoxaparin, followed by a vitamin K antagonist in patients with symptomatic deep vein thrombosis (DVT)\textsuperscript{4}.

With regards to duration of therapy, international guidelines recommend “to consider 12 months anticoagulation” in the treatment of symptomatic VTE in patients who have advanced or metastatic cancer [American Society of Clinical Oncology (ASCO)\textsuperscript{47}; European Society of Medical Oncology (ESMO)\textsuperscript{48}; American College of Chest Physicians (ACCP)\textsuperscript{49}]. We do not know if clinicians comply with these guidelines. As this is an internal pilot trial, those patients presenting with DVT who are RVT +ve and patients presenting with PE, will be randomised to 6 versus 12 months duration of treatment.
In addition, in 15 of 16 trials included in a Cochrane review (2011) of the efficacy and safety of anticoagulation for the initial treatment of VTE in patients with cancer, patients received at least three months treatment [initial parenteral anticoagulation, followed by oral anticoagulation]⁵⁰. To our knowledge, no trial of duration of anticoagulation for cancer patients, treated in the adjuvant or advanced setting, with VTE, has been undertaken. Select-d is therefore timely.

7. Trial Design

Select-d is a prospective, randomised, open label, multicentre pilot study comparing dalteparin vs. rivaroxaban with a second placebo-controlled randomisation comparing the duration of anticoagulation therapy (6 months vs 12 months treatment) in patients with DVT who are Residual Vein Thrombosis [RVT] positive (+ve). All patients presenting with PE will be invited to participate in the second randomisation.

All procedures after identification of the patients (with the exception of the ultrasound or CT scan in hospital) will be carried out at a location of site feasibility – this could be at home, at the GP surgery, or at hospital outpatient clinics, and will ordinarily be coordinated by select-d link nurses.

8. Trial Objectives

8.1 Primary Objective

To assess VTE recurrence rates in SELECTeD cancer patients at risk of recurrence of VTE treated with rivaroxaban or dalteparin

8.2 Secondary Objectives

- To ensure the safety of the patients with regards to major bleeding in an internal safety study
- To assess acceptability and compliance to randomisation and allocated treatment
- To assess 6 months and 12 months anticoagulation treatment in patients with evidence of RVT following initial therapy, in terms of VTE recurrence rates
- To assess the VTE recurrence rates in patients with evidence of RVT and those with no evidence of RVT

9. Outcome Measures

9.1 Primary Outcome

- VTE recurrence rates (including symptomatic VTE and incidental PE)

9.1.1 Criteria for recurrence of VTE:

Symptomatic DVT confirmed using venous ultrasound as a new non-compressible venous segment or a substantial increase (4mm or more) in the diameter of the thrombus during full compression in a previously abnormal segment on ultrasonography or a new intraluminal filling defect on venography. When thrombosis of vessels proximal to the inguinal ligament is suspected, contrast-enhanced CT should be considered.

Non-fatal or fatal symptomatic or ‘incidental’ PE confirmed as a new intraluminal filling defect on spiral CT or pulmonary angiography, a cut-off of a vessel of more than 2.5mm in diameter on pulmonary angiography, a new perfusion defect of at least 75% of a segment with corresponding normal ventilation (high probability), a new non-high probability perfusion defect associated with deep vein thrombosis as documented by ultrasonography or venography. Fatal pulmonary
embo
ing is based on objective diagnostic testing, autopsy or death which could not be attributed to a documented cause and for which pulmonary embolism could not be ruled out (unexplained death)\textsuperscript{31}.

9.2 Secondary Outcomes

- Symptomatic VTE and “truly” incidental PE recurrence rates
- Major bleeding and clinically relevant non-major bleeding

The definition of major bleeding is acute, clinically overt bleeding accompanied by one or more of the following findings: a decrease in the haemoglobin level of 2 grams per decilitre or more over a 24-hour period; transfusion of 2 or more units of packed red cells; bleeding at a critical site (including intracranial, intra-spinal, intraocular, pericardial, and retroperitoneal bleeding); bleeding into the operated joint, necessitating reoperation or intervention; intramuscular bleeding with the compartment syndrome; or fatal bleeding. Clinically relevant non-major bleeding includes acute, clinically overt episodes such as wound hematoma, bruising or ecchymosis, gastrointestinal bleeding, haemoptysis, haematuria, or epistaxis that does not meet the criteria for major bleeding. Bleeding is categorised as minor if it is clinically overt but not adjudicated as major or clinically relevant non-major bleeding.

- Feasibility of conducting an economic evaluation
- Tumour efficacy using the RECIST Assessment [see Appendix 3]
- Acceptability and compliance to randomisation and treatment
- Patient experience using Anti-Clot Treatment Scale (ACTS) [see Appendix 4]
- Quality of life measured using the EuroQol (EQ-5D-5L) questionnaire
- Progression-free survival (adjuvant patients) and overall survival
- Biomarker correlation

10. Patient Selection & Eligibility

10.1 Target Population

Patients with active cancer (solid and haematological malignancies), presenting with a primary VTE.

10.2 Number of Patients

A total of 530 patients will be recruited into the pilot trial.

See section 18.3 for details as to how this sample size was calculated.

10.3 Inclusion Criteria

- Patients with active cancer
- Patients with a primary presentation of an objectively confirmed VTE - symptomatic lower extremity proximal DVT or symptomatic or incidental PE
- ECOG Performance Status 0-2
- Aged > 18
- Written informed consent given
- Adequate haematological function (recommended levels – haemoglobin (Hb) > 10g/dl, white cell count (WCC) > 2x10\textsuperscript{9}/l, platelets > 100 x10\textsuperscript{9}/l)
- Adequate hepatic and renal function – liver enzymes < x3 upper limit of normal (ULN); creatinine clearance > 30ml per minute
10.4 Exclusion Criteria

- Patients taking any anticoagulants (excluding any pre-treatment for this episode of VTE)
- Patients taking > 75 mg aspirin per day
- Planned randomised treatment start time > 72 hours after starting anticoagulant for this episode of VTE
- Clinically significant liver disease (e.g. acute hepatitis, chronic active hepatitis, or cirrhosis) or an alanine aminotransferase level that is ≥ 3 times ULN range
- Bacterial endocarditis
- Active bleeding or at high risk of bleeding, contraindicating anticoagulant treatment
- Systolic blood pressure > 180 mm Hg or Diastolic blood pressure > 110 mm Hg. Control of blood pressure using anti-hypertensive drugs is permitted
- Of childbearing potential (both male and female participants) without a combination of adequate contraceptive measures, e.g. oral contraceptives, IUD, barrier methods of contraception (condom or occlusive cap with spermicide)
- Pregnancy or breast-feeding
- Concomitant use of strong cytochrome P-450 3A4 inhibitors (e.g. human immunodeficiency virus protease inhibitors or systemic ketoconazole) or inducers (e.g. rifampicin, carbamazepine, or phenytoin) or p-glycoprotein inhibitors/inducers

10.5 Selection Criteria for Second Randomisation

- Patients with DVT who are Residual Vein Thrombosis [RVT] positive (+ve) or patients presenting with a PE
- ECOG performance status 0, 1 or 2
- Still receiving initial trial treatment
- No recurrence of VTE

10.6 Population Selection to Guide Randomisation using Assessment of RVT

Ultrasound assessment of RVT after 5 months of treatment for patients presenting with a DVT will be required, and will be backed up by a robust quality assurance programme. Patients who are RVT -ve will stop anticoagulation treatment and will be monitored as per standard practice for VTE recurrence and bleeding. Patients in the RVT +ve group will be randomised to placebo or continue anticoagulation treatment with rivaroxaban.

Patients who do not wish to participate in the second randomisation will be asked for reasons but should still be followed up for VTE as part of their initial randomisation for analysis – these patients should not be withdrawn from the study.

10.6.1 Compression Ultrasound

Compression Ultrasound (C-US) will be performed as per the select-d scanning protocol. The protocol and a DVD will be given to the site lead radiologist as part of the training programme.

10.6.2 Residual Vein Thrombosis

C-US of the affected leg should be performed, and transverse section images obtained as per DVD. Lumen compressibility should be evaluated by gentle pressure of the probe. RVT diameter is taken by measuring the distance between the anterior and posterior walls of the vein, during compression with the ultrasound probe. Measurements are taken at the common femoral vein, 1 cm below the inguinal ligament and at popliteal vein at the most prominent crease in the mid-popliteal fossa.
RVT is calculated as follows: RVT = vein diameter during compression x100/vein diameter before compression. RVT is scored as “absent” when ≤40% of vein diameter. Patients are considered to have RVT when a persistent thrombus was present in at least one of the two vein segments examined11.

10.7 Informed Consent

It is the responsibility of the local Principal Investigator (or designee as listed on the Site Signature and Delegation Log) to obtain written informed consent in compliance with national requirements from each patient prior to entry into the trial. The trial must be discussed in detail with the patient, and the patient provided with a copy of the Patient Information Sheet. Patients will be offered sufficient time to consider the trial, allowing time for discussion with family/friends/General Practitioner/etc. Patients wishing to consent immediately will be allowed to do so. The patient must be given the opportunity to ask questions and to be satisfied with the responses prior to written consent being given.

A copy of the signed Consent Form(s) must be given to the patient. The documents are available in electronic format to facilitate printing onto local headed paper. Original Consent Forms must be retained on site (it is recommended that the original is retained in the Trial Site File, with a copy filed in the relevant patient’s hospital notes). Completed Consent Forms must not be sent to the Trial Office at WCTU.

If the Patient Information Sheet and/or Consent Form(s) are modified during the course of the trial, sites will be notified of the procedure to follow for patients already consented and for prospective patients.

11. Randomisation Procedure

The randomisation system will ensure that there is no bias between the two treatment groups. Randomisations take place after written informed consent has been gained and baseline Quality of Life questionnaires have been completed. Subjects will be randomised strictly sequentially, as subjects are eligible for randomisation. Treatment allocation will be undertaken at a ratio of 1:1.

All participating sites will have the option of using electronic Remote Data Capture (eRDC) to randomise patients and subsequently enter data. This is the preferred method of data collection but will be dependent upon the capacity of the individual site. Sites opting to use eRDC will be provided with log-in details and will be trained appropriately. Full details will be available at the site set-up stage. Sites that are unable to use eRDC will be able to randomise patients and submit data on paper Case Report Forms (CRFs). Procedures outlined below are for paper CRFs.

After checking eligibility and recording baseline patient details, treatment will be allocated by computer using a minimisation algorithm.

Each patient will be allocated a unique trial number and this will be confirmed, with the treatment allocation, by WCTU to the randomising site. The patient’s trial number, initials and date of birth must be used on all subsequent CRFs and correspondence relating to that patient.

A similar procedure will be carried for the second randomisation once eligibility is confirmed and the appropriate documentation completed. Each patient will be then be allocated to rivaroxaban or to placebo, but will maintain the same trial number throughout the trial. Site staff and randomising staff at WCTU will not be given the treatment allocation – drug pack numbers will be used to ensure the second randomisation remains blinded.
11.1 Randomisation Documentation

After patients have been enrolled into the study, the investigator should send the patient’s General Practitioner (GP) a letter and copy of the Patient Information Sheet to inform them of their participation in the trial.

The completed Eligibility and Randomisation Forms must be sent to the Trial Office at WCTU with copies retained on site. The patient’s details must be entered onto the local site’s Patient ID Log.

A Screening Log must be maintained to document all patients considered for the trial but subsequently excluded. Where possible, the reason for non-entry to the trial must be documented. This must be faxed to Trial staff on a regular basis as requested. Patient names, hospital numbers or other personal identifiers must not be recorded on the Screening Log (use initials only).

12. Trial Therapy

12.1 ARM A: Dalteparin

12.1.1 Method of Administration

By subcutaneous injection, preferably into the abdominal subcutaneous tissue or into the lateral part of the thigh.

12.1.2 Dose

Month 1

Administer dalteparin 200 IU/kg total body weight subcutaneously (SC) once daily, using fixed dose syringes (see Table 1 below) for the first 30 days of treatment. The total daily dose must not exceed 18,000 IU daily.

Table 1 Month 1 - Dalteparin Doses by Weight

<table>
<thead>
<tr>
<th>Body weight (kg)</th>
<th>Scheduled dalteparin dose (IU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 46</td>
<td>7,500</td>
</tr>
<tr>
<td>47 to 56</td>
<td>10,000</td>
</tr>
<tr>
<td>57 to 68</td>
<td>12,500</td>
</tr>
<tr>
<td>69 to 82</td>
<td>15,000</td>
</tr>
<tr>
<td>≥ 83</td>
<td>18,000</td>
</tr>
</tbody>
</table>

Months 2-6

Dalteparin should be administered at a dose of approximately 150 IU/kg, subcutaneously, once daily using fixed dose syringes (see Table 2 below).

Table 2 Months 2-6 – Dalteparin Doses by Weight

<table>
<thead>
<tr>
<th>Body weight (kg)</th>
<th>Scheduled dalteparin dose (IU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 56</td>
<td>7,500</td>
</tr>
<tr>
<td>57 to 68</td>
<td>10,000</td>
</tr>
<tr>
<td>69 to 82</td>
<td>12,500</td>
</tr>
<tr>
<td>83 to 98</td>
<td>15,000</td>
</tr>
<tr>
<td>≥ 99</td>
<td>18,000</td>
</tr>
</tbody>
</table>

Duration of treatment: 6 months
12.1.3 Precautions and Dose Modifications

Month 1
In the case of chemotherapy-induced thrombocytopenia, dalteparin dose should be adopted as follows:
- In patients receiving dalteparin who experience platelet counts between 50,000 and 100,000/mm³, the daily dose of dalteparin should be reduced by 2,500 IU until the platelet count recovers to ≥100,000/mm³.
- In patients receiving dalteparin who experience platelet counts <50,000/mm³, dalteparin should be discontinued until the platelet count recovers above 50,000/mm³.

Months 2-6
In the case of chemotherapy-induced thrombocytopenia, frequent monitoring of peak anti-Factor Xa levels should be undertaken and the dalteparin dose should be adopted as follows:
- With platelet counts <50,000/mm³, dalteparin dosing should be interrupted until the platelet count recovers above 50,000/mm³.
- For platelet counts between 50,000 and 100,000/mm³, dalteparin should be reduced as illustrated in Table 3 below in accordance with the patient's weight. Once the platelet count has recovered to >100,000/mm³, dalteparin should be re-instituted at full dose.

Table 3: Dalteparin Dose Reduction for Platelet Counts between 50,000 and 100,000/mm³

<table>
<thead>
<tr>
<th>Body weight (kg)</th>
<th>Scheduled dalteparin dose (IU)</th>
<th>Reduced dalteparin dose (IU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 56</td>
<td>7,500</td>
<td>5,000</td>
</tr>
<tr>
<td>57 to 68</td>
<td>10,000</td>
<td>7,500</td>
</tr>
<tr>
<td>69 to 82</td>
<td>12,500</td>
<td>10,000</td>
</tr>
<tr>
<td>83 to 98</td>
<td>15,000</td>
<td>12,500</td>
</tr>
<tr>
<td>≥ 99</td>
<td>18,000</td>
<td>15,000</td>
</tr>
</tbody>
</table>

Renal failure:
In the case of significant renal failure once on study (as this is an exclusion criterion), defined as a creatinine clearance <30 ml/min, the dose of dalteparin should be adjusted based on anti-Factor Xa activity (target anti-Factor Xa 1.0 iu/ml). If the anti-Factor Xa level is below or above the desired range, the dose of dalteparin should be increased or reduced respectively, and the anti-Factor Xa measurement should be repeated after 3-4 new doses. This dose adjustment should be repeated until the desired anti-Factor Xa level is achieved.

12.1.4 Adverse Reactions
Common (≥1/100, <1/10) adverse reactions include haemorrhage (bleeding at any site), reversible mild non-immunologically-mediated thrombocytopenia (type I), transient elevation of liver transaminases (ASAT, ALAT) and subcutaneous haematoma at injection site.

The risk of bleeding is dependent on dose. Most bleedings are mild. Severe bleedings have been reported, and in some cases with fatal outcome.

12.1.5 Reversal of Dalteparin
The anticoagulant effect induced by dalteparin is inhibited partially by protamine. Since protamine itself has an inhibiting effect on primary haemostasis, it should be used only in an emergency.
12.2 ARM B: Rivaroxaban

12.2.1 Method of Administration

Oral

12.2.2 Dose

Initial treatment is 15 mg twice daily for the first three weeks. This is followed by 20 mg once daily for the remainder of the treatment period.

Duration of treatment: 6 months (first randomisation). Patients randomised in the second randomisation may receive a further 6 months of treatment, depending upon their allocation to receive either rivaroxaban or placebo.

12.2.3 Precautions

Use of rivaroxaban is not recommended with systemic azole-antimycotics (e.g. ketoconazole) or HIV protease inhibitors (e.g. ritonavir). These active substances are strong inhibitors of both CYP3A4 and P-gp and therefore may increase rivaroxaban plasma concentrations to a clinically relevant degree (2.6 fold on average) which may lead to an increased bleeding risk.

Care should be taken with drugs affecting haemostasis e.g. NSAIDs, aspirin (acetylsalicylic acid) and platelet aggregation inhibitors.

12.2.4 Dose Modifications

Renal Impairment

In patients with mild renal impairment (creatinine clearance 50-80 ml/min), no dose adjustment is necessary.

Patients with moderate creatinine clearance (30-49 ml/min) should be treated with 15mg twice daily for the first three weeks. Thereafter, the recommended dose is 20 mg once daily. A reduction of the dose from 20 mg once daily to 15 mg once daily should be considered if the patient's assessed risk for bleeding outweighs the risk for recurrent DVT and PE.

After entry into the trial, severe renal impairment (creatinine clearance 15-29 ml/min) indicates that rivaroxaban plasma concentrations are significantly increased, therefore rivaroxaban is to be used with caution in these patients.

In patients with creatinine clearance < 15 ml/min, the use of rivaroxaban is not recommended.

12.2.5 Overdose

At the time of protocol writing, there is no known antidote for rivaroxaban-induced bleeding. There are limited data in healthy volunteer subjects suggesting that use of prothrombin concentrates can reverse laboratory markers of coagulopathy e.g. prothrombin time, although any evidence of clinical benefit in humans has yet to be published.

12.2.6 Management of Bleeding Complications

Should a bleeding complication arise in a patient receiving rivaroxaban, the next administration should be delayed or treatment discontinued as appropriate. Rivaroxaban has a half-life of approximately 5 to 13 hours. Individualised bleeding management may include:

- Symptomatic treatment, such as mechanical compression, surgical intervention, fluid replacement
- Haemodynamic support, such as blood product or component transfusion

For life threatening bleeding that cannot be controlled by the above measures, administration of a specific procoagulant e.g. prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (r-FVIIa) is recommended. However, there is little clinical experience with these products.
12.2.7 Management of Recurrence of Venous Thromboembolism

The management of a recurrence of VTE (when the patient will be withdrawn from trial treatment) will be according to local practice. International guidance is available\(^{53}\).

12.3 Handling of Trial Medication

12.3.1 Investigational Medicinal Products (IMP)

Dalteparin sodium, rivaroxaban, and placebo are all classified as Investigational Medicinal Products (IMPs) in select-d.

12.3.2 Storage of IMP and Temperature Monitoring

Dalteparin, rivaroxaban and placebo should be stored at room temperature (15-25°C). Where stock is supplied by the trial, this should be kept segregated and used specifically for trial patients only. Sites will keep an inventory log of any trial stock received.

Temperature logs, which record the minimum and maximum temperature on a daily basis, should be kept at the location where IMP is stored.

In the event of a temperature excursion (i.e. stock stored outside of the recommended range), the affected stock should be quarantined. Sites should notify the Sponsor immediately of any temperature excursions, and if deemed appropriate, the Sponsor will advise if the stock can be used, returned or destroyed. All details of temperature excursions should be documented in the pharmacy site file or site master file.

12.4 Study Drugs: Ordering and Supply

12.4.1 Dalteparin

Dalteparin is the only licensed LMWH for use in cancer patients\(^{25}\) and is recommended as standard practice by the select-d steering group for use for treatment of VTE in cancer patients. Dalteparin will only be funded for sites that do not use dalteparin as standard for the treatment of VTE in cancer patients. These centres will order their own local supplies for the purpose of the select-d trial, and to subsequently invoice the WCTU to ensure that they are reimbursed accordingly. Accountability logs must be maintained throughout the trial.

12.4.2 Rivaroxaban

Bayer plc will supply rivaroxaban to the select-d distribution company, who will undertake distribution of supplies to the participating sites. Supplies will be in place prior to the randomisation of the first patient at a given site.

After the initial supply of drugs, further drug packs will be ordered on an automatic basis by the select-d database via the Trial Coordinator. If there are any concerns regarding drug supply, please contact the select-d Trial Coordinator.

Each bottle to be used in the second randomisation will bear a unique drug pack number and the randomisation system will allocate the bottles to a patient. Drugs will be supplied to the pharmacy in numbered bottles and the tablets and packaging will be indistinguishable by either the patient or their clinicians. Logistics of sending trial drugs/placebo to hospital pharmacies will be monitored by the Trial Co-ordinator.

Unused/returned or expired drugs will be returned by the research nurse to the hospital pharmacies and disposed of according to the instructions in the pharmacy site file. Accountability logs must be maintained throughout the trial.

12.4.3 Dispensing

Dispensing should be done via site pharmacies. Sites may create trial specific prescriptions.
The labelling of IMP will be in accordance with Volume 4 of Good Manufacturing Practices, Annex 13 (Manufacture of Investigational Medicinal Products).

12.4.4 Accountability Logs

Trial specific drug accountability logs will need to be maintained throughout the trial. The select-d Trial Office will provide sites with trial-specific accountability logs. Sites may use their own drug accountability logs (created locally) provided they allow full traceability of the IMP, as guide they should contain the following information:

- Trial name & EudraCT No, Site name and address, Drug name and strength, Quantity issued, Quantity returned, Manufacturer, Batch number, Expiry date, Patient trial number

All records will be maintained in accordance with current Good Clinical Practice (GCP) and in line with the Medicines for Human Use (Clinical Trials) Regulations 2004 and as amended in 2006 (SI 2004/1031; SI 2006/1928).

12.4.5 Destruction of IMP

Sites should not destroy any unused trial medication without the written permission of the Sponsor. For expired stock or stock that has been damaged or deemed unusable, sites should notify the select-d Trial Office at the earliest opportunity. Following written approval, sites may destroy this stock according to local destruction procedures (a copy of the local destruction procedures should be kept in the pharmacy site file or site master file).

12.5 Blinding and Unblinding

12.5.1 Methods for ensuring blinding

For the second randomisation, the rivaroxaban and placebo tablets will be packaged in coded but otherwise identical bottles. Neither the patient nor the clinical team responsible for the patient’s care will know which treatment the patient has been allocated. The treatment code can only be broken by the Emergency Scientific and Medical Services (eSMS) team at University Hospitals Coventry and Warwickshire.

12.5.2 Methods for unblinding the study

Emergency unblinding may be requested on grounds of safety by any clinician involved in the medical care of the patient. Emergency unblinding will be performed by telephone contact with the Emergency Scientific and Medical Services (eSMS) team at University Hospitals Coventry and Warwickshire. The phones will be manned 24 hours a day, 365 days a year. This option may be used ONLY if the patient’s future treatment requires knowledge of the treatment assignment. In the event of a suspected allergic reaction to the trial tablets, the trial tablets should be discontinued and unblinded if felt necessary for the safety of the patient.

Where possible, the Chief Investigator must be informed of any unblinding requests and authorise the unblinding if appropriate (or reject the request if appropriate). If the Chief Investigator is not available to discuss requests, information regarding the request and outcome will be given to the Chief Investigator as soon as possible. Details of any unblinding requests and outcomes will be documented in the Trial Master File. Information regarding unblinding will be disseminated to participating Principal Investigators as appropriate.

12.6 Concomitant Illness and Medication

Details of any concomitant illness (any illness present at the start of the trial) must be recorded appropriately on the CRFs. Details of any concomitant medication (any medication other than the trial product that is taken during the trial, including during screening and run-in periods) must be recorded. Any changes in concomitant medication should be recorded at each visit.
13. Suggested Patient Pathway

Patients with active solid or haematological cancers.
DVT/PE suspected by patient/GP/hospital doctor.
Referred to A&E/Treatment Centre: Baseline FBC; U&Es; LFTs; D-dimers (standard care).
Anticoagulation as per local DVT or PE practice.

Ultrasound (DVT) or CT/MRI (PE).
Diagnosis of VTE confirmed by radiologist.
Radiology Dept alert the referring doctor/DVT nurse/select-d link nurse.
DVT/select-d link nurse invite patient to join study.

Select-d link nurse follow-up phone call/meeting with patient (location of patient choice)

Patient eligibility reviewed by Principal Investigator or designee prior to consent

Select-d link nurse/research nurse/doctor consents patient to select-d.
First Randomisation
Patient given initial prescription of dalteparin (4 weeks) or rivaroxaban (3 weeks)

Select-d link nurse informs GP practice/relevant hospital personnel by letter, fax or e-mail that patient has been randomised. Patient will be given remaining dalteparin or rivaroxaban, and relevant instructions, as per standard practice.

For patients randomised to dalteparin: FBC (HIT) as standard practice

All patients: routine blood tests

3 monthly data request.
Bloods: FBC; U&Es; LFTs; medical review; QoL & Health Resource Use

All patients with DVT only on presentation: recall for US to look for RVT

Select-d link nurse sends results (RVT +ve or -ve) to patient, GP practice, relevant hospital personnel and WCTU.

Evidence of RVT/PE on presentation: Patients will enter Second Randomisation

STOP treatment at 6 months.
Patients will receive placebo.

CONTINUE treatment for a further 6 months.
Patients will receive rivaroxaban.

No evidence of RVT: inform patients to stop treatment at 6 months

5.5 Months +/- 3 days
Within 48 hrs of US test results

5 Months +

9 months & 12 months

18 months & 24 months

3 monthly data request.
Bloods: FBC; U&Es; LFTs; medical review; QoL & Health Resource Use

6 monthly data request.
Bloods: FBC; U&Es; LFTs; medical review; QoL & Health Resource Use
14. Data Collection

All participating sites will have the option of using electronic Remote Data Capture (eRDC) to enter data. This is the preferred method of data collection but will be dependent upon the capacity of the individual site. Sites opting to use eRDC will be provided with log-in details and will be trained appropriately. Full details will be available at the site set-up stage. Sites unable to use eRDC will be able to submit data on paper Case Report Forms (CRFs). Procedures outlined below are for paper CRFs.

Each site will be provided with an Investigator Site File containing Case Report Forms (CRFs). Data collected on each patient must be recorded by the local Principal Investigator, or designee, as accurately and completely as possible. The Principal Investigator is responsible for the timing, completeness, legibility, accuracy and signing of the CRFs and he/she will retain a copy of each completed form. The Principal Investigator must allow study staff access to any required background data from hospital records (source data, e.g. medical records) on request.

All fields MUST be completed. If a test or measurement was not done, please indicate why that was omitted on the CRF. Entries must be made in black ballpoint pen. Errors must be crossed out with a single line leaving the original data un-obscured (i.e. without overwriting), the correction inserted and the change initialled and dated. An explanatory note should be added if necessary. Correction fluid/tape/labels must not be used. All data submitted on CRFs must be verifiable in the source documentation. Any deviation from this must be explained appropriately.

Toxicities will be assessed using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. See Appendix 2 for further information.

14.1 Quality of life, patients’ experience and health resource use questionnaires

Anticoagulation may reduce quality of life, and different models of anticoagulation management might have different impacts on experience with this component of medical care. Therefore it is important to assess both patients’ quality of life and experience with the treatment. Patient experience will be investigated in select-d using the Anti-Clot Treatment Scale. Anticoagulation may reduce quality of life, and different models of anticoagulation management might have different impacts on experience with this component of medical care. Therefore it is important to assess both patients’ quality of life and experience with the treatment. Patient experience will be investigated in select-d using the Anti-Clot Treatment Scale. Patients will be asked to complete a QoL questionnaire booklet that will include the EuroQol EQ-5D-5L questionnaire and Anti-Clot Treatment Scale (ACTS), where applicable, and a health resource use questionnaire booklet. The baseline questionnaire booklet should be given to patients after written consent is obtained but prior to study randomisation. Further questionnaire booklets will be administered every 3 months from randomisation for the first 12 months, then again at both 18 months and 24 months. ACTS will be administered at 3 monthly intervals only until completion of anticoagulation treatment.

Each participating site will be responsible for providing patients with questionnaire booklets. The local researcher or their delegated individual must explain the requirements, ensure that the patient understands how to complete the questionnaires and the time-frames within which they are required, and (if the patient has completed them at home) ensure that the booklets are either returned to the local site, which should then submit them to the select-d Trial Office at WCTU, or returned directly to the Trial Office using the pre-paid envelopes provided. The member of staff responsible for this must be appropriately recorded on the Site Signature and Delegation Log.

Completed CRFs should be returned to:
select-d Trial Office
Warwick Clinical Trials Unit
Division of Health Sciences
Warwick Medical School
University of Warwick
Coventry CV4 7AL
United Kingdom
14.2 Follow-up

Select-d is a pilot study with a minimum follow-up of one year.

Patients will be assessed at three monthly intervals until month 12 (end of year 1) then 6 monthly until month 24 (end of year 2). Clinical examination (as clinically indicated), routine haematology and biochemistry will be performed at each visit. Tumour response assessments, including tumour markers where appropriate, will be obtained as part of usual care for patients on treatment. If the patient is not currently receiving anticancer treatment, then details of their most recent tumour response will be requested. Where appropriate, response should be measured using the RECIST criteria (see Appendix 3 for definition of response criteria). After the 5-6 month assessment, further CT scans and venous ultrasonography of upper/lower limbs will be performed if clinically indicated.

14.3 Clinical Monitoring

The monitoring of all select-d patients for bleeding will be stringent with locally agreed, proactive management, approved by the patient and their carer. After an information session with the select-d link nurse and the patient and their carer, the contact names of the select-d link nurse and an emergency contact number (acute oncology) will be given to the patient at first randomisation for the patient to call if concerned. All adverse events and serious adverse events will be reported to the Chief Investigator and co-investigators through the UKCRC-accredited University of Warwick Clinical Trials Unit pharmacovigilance team.

As part of this vigilant monitoring of any bleeding events, a blinded independent committee will be formed to adjudicate bleeding. Research staff will be asked to complete a Bleeding Occurrence Form with regards to any bleeding reported by the patient – the information provided on these will be provided to the Independent Bleeding Adjudication Panel, who will meet at regular intervals to review the information.

14.4 RVT Assessment by Ultrasound (US) Quality Assurance Programme

Dr Tom Goodfellow, Consultant Radiologist, UHCW and Professor Charles Hutchinson, Professor of Imaging, University of Warwick will lead the RVT assessment quality assurance programme. Dr Tom Goodfellow, Prof Hutchinson and their team at UHCW have completed a DVT imaging training programme to aid standardisation within the Trust, comprising a [DVT imaging] protocol, a written outline as to what is to be undertaken, a DVD demonstrating how to make the venous assessment and a sheet to annotate the measures made. This comprehensive training programme will be circulated to the select-d sites, to provide a basis of the training and to indicate the standard of the examination to be undertaken. It is important to note that everyone who receives the training is already fully versed in US techniques; the training is merely setting a standard for the procedure. Two select-d radiology leads will be identified from each cancer centre and the purpose-made DVD of RVT assessment by ultrasound [non-compressible venous segments in popliteal and common femoral veins] and a standard operating procedure (SOP) sent to each lead in the work-up phase of the trial. There is a standardised reporting system to maintain the quality of the venous assessment. A record of views will be saved.

A random sample of 10% of patients will have their ultrasound scans requested and sent to a central quality assurance panel, chaired by Dr Tom Goodfellow, for review and checking of adherence to the SOP. The results of this blinded review will be feedback to the radiology leads.

15. Biomarker Correlation

Almost all studied cancer types have been associated with haemostatic abnormalities including thrombocythaemia, activated platelets, variation in prothombin and activated partial thromboplastin times, demonstration of circulating activated coagulation factors and elevation of fibrinogen and markers of thrombin generation. Similarly, suppression of fibrinolytic activity has been noted.
Nevertheless, these markers do not yet correlate with prediction of thromboembolism or prognosis for the individual patient but exploratory studies have identified some ‘candidate’ biomarkers of thrombotic risk include D-dimer, soluble P-selectin, Prothrombin Fragments 1 and 2, C-reactive protein, and tissue factor (TF). Microparticles (MPS) are submicron membrane vesicles. They are statistically higher in cancer patients with VTE than those without VTE. Circulating MPS harbour molecular information related to cancer-related processes and may serve as a reservoir of prognostic and predictive biomarkers to monitor genetic tumour progression, angiogenesis, thrombosis, and responses to targeted therapies. Experimental pharmacological data in vivo demonstrate that TF-Vila-PAR2 signalling indeed plays a pivotal role in tumour progression. A broader selection of MP-associated biomarkers bearing highly active procoagulant and pro-fibrinolytic/tissue degradation functions and the resulting balance between pro- and anti-coagulant functions may constitute a powerful biomarker of the hyper- or hypo-coagulant tendency in cancer patients which may prove a powerful screening tool for recurrent VTE in cancer patients. There is some expertise in the University of Warwick team of measuring levels of circulating endothelial cells (CECs) and endothelial progenitor cells (EPECs), which play a vital role in neo-angiogenesis in malignancy. A selection of these biomarkers will be measured in the patients randomised into select-d.

Biomarker analyses, with the exception of CECs, will be carried out at a central expert laboratory in the UK. Bloods will be requested at baseline (before any anticoagulation treatment). Further bloods will be requested at 3 months, 6 months, and at 12 months for those patients entered into the second randomisation. Two blood samples will be collected at each specified visit, each sample will consist of approximately 7ml of whole blood. In addition, original tumour tissue will be requested for all patients.

16. Safety & Adverse Event Management

16.1 Definitions

16.1.1 Adverse Event (AE)

An AE is defined as any untoward medical occurrence in a subject (administered a medicinal product) and which does not necessarily have a causal relationship with this treatment.

16.1.2 Adverse Reaction (AR)

An AR is an unintended response to a medicinal product, related to any dose. The term is used to describe events that have a ‘possible’, ‘probable’ or ‘definite’ causal relationship with the product. This may also be referred to as an Adverse Drug Reaction (ADR).

16.1.3 Serious Adverse Event (SAE)

An SAE is an AE that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening*
- Requires hospitalisation or prolongation of existing hospitalisation**
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical condition***

* In this context, the term ‘life threatening’ refers to an event in which the patient was at risk of death at the time of the event. It does not refer to a hypothetical event that might have caused death if it had been more severe.

** Hospitalisation is defined as an inpatient admission, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisation for a pre-existing condition, including elective procedures, without complications, would not fulfil the criteria for an SAE.
*** Other events may be considered an SAE when, based upon medical judgement, the event may require medical or surgical intervention to prevent one of the outcomes listed above.

16.1.4 Serious Adverse Reaction (SAR)

A SAR is defined as an SAE that has a definite, probable or possible causal relationship to the trial drug. The causality of SAEs (i.e. relationship to trial medication) must be assessed by the local investigator(s) on the SAE Form.

16.1.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Suspected Unexpected Serious Adverse Reactions (SUSARs) are SAEs that are unexpected (i.e. their nature or severity is not consistent with the Investigator Brochure/Summary of Product Characteristics) and are considered to be caused by the trial drug. [All SUSARs will be reported by the Trial Office to the Medicines and Healthcare Products Regulatory Agency (MHRA), main Research Ethics Committee, and the trial Sponsor in accordance with regulatory requirements and WCTU SOPs].

16.2 AR Reporting

All ARs must be reviewed and reported on the relevant CRF(s) using Version 4 of the Common Terminology Criteria for Adverse Events (CTCAE). See Appendix 2 for further information.

Any toxicity incurred but not categorised by the CTCAE should be graded by the clinician and be recorded using a scale of mild (1), moderate (2), or severe (3) on the relevant CRF.

All adverse events must be followed until resolution or for at least 30 days after discontinuation of study medication (whichever comes first), or until toxicity has resolved to baseline or < Grade 1, or until the toxicity is considered to be irreversible. Perceived lack of efficacy is not an adverse event.

An exacerbation of a pre-existing condition is an adverse event.

All adverse events and toxicities must be graded according to the NCI Common Terminology Criteria for adverse events (NCI-CTCAE) Version 4.0.

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

Abnormal laboratory test results that are deemed clinically significant by the Investigator and that lead to a change in the dosage of trial treatment or temporary or permanent discontinuation of trial treatment, or require intervention or diagnostic evaluation to assess the risk to the subject should be recorded as adverse events and instigate further investigation and follow up as appropriate.

16.3 SAE Reporting

All SAEs that occur between trial entry and 30 days after the end of the trial treatment will be reported. If an unreported event from this time period is identified at a later date, retrospective reporting must occur immediately. Events occurring outside of this time period may still be reported if the Investigator feels that it is medically important.

SAEs will be reported using the SAE Form. The local Principal Investigator must report any SAEs to the Trial Office within 24 hours of becoming aware of the event. Do not delay reporting in order to identify causality or expectedness, which can be identified at a later stage and the report updated.

The SAE Form must be completed and faxed to the Warwick Clinical Trials Unit on:

+44 (0)24 7615 0549

In the absence of a responsible Investigator (as named on the Site Signature and Delegation Log), the SAE Form must be completed and signed by a member of the site trial team. The SAE Form must be checked by the responsible Investigator, signed and re-faxed as soon as possible.
The patient must be followed up until clinical recovery is complete and laboratory results have returned to normal, or until the patient’s status is unlikely to change further. Trial staff will liaise with the site to compile all of the necessary information and to resolve queries as necessary.

The Trial Office is responsible for reporting relevant events to the Sponsor, ethics committee and MHRA within required timelines in accordance with trial procedures and regulatory requirements. The PI is responsible for reporting events to local parties (e.g. R&D Department), in accordance with local practice.

All reportable events - serious and unexpected and drug related/relationship unknown, and any others as advised by the main REC, will be sent to Investigators for submission to relevant parties in accordance with local practice.

Trial staff will send a safety report to the main REC, MHRA and to the Sponsor annually. Sites should forward this report to their local R&D department in accordance with local practice and regulatory requirements.

If the event leads to the patient being withdrawn from trial medication, the appropriate CRF(s) must be completed in accordance with the CRF schedule. All SAEs will be subjected to a clinical review by the Chief Investigator (CI) and a clinical coordinator from WCTU to determine whether sufficient information has been provided and whether any further information should be requested. The Chief Investigator will review all adverse reactions for increased severity/frequency on a quarterly basis. Adverse event data will also be reviewed periodically by the Independent Data and Safety Monitoring Committee (IDSMC).

The following events do not require to be reported as SAEs:
- Hospitalisation or death due to disease progression
- Hospitalisation for planned investigations
- Hospitalisation for study drug administration, palliative care, terminal care or elective surgery

16.4 Death/Life-Threatening Events

In the case of death or life-threatening events, on the day of becoming aware of the event, please telephone or fax the Trial Office. The appropriate CRFs must be submitted in accordance with the CRF schedule.

In the case of death, where possible, a copy of the death certificate and post-mortem report (if applicable) should be submitted to the Trial Office as soon as possible. Names and hospital numbers must not be visible on these documents. The patient’s trial number and initials must be clearly added to the document using black ball-point ink.

16.5 Investigator Assessment

Seriousness

When an AE/AR occurs, the responsible investigator must assess whether the event is classified as serious (i.e. an SAE).

Expectedness

An expected event is defined as a known toxicity as listed in the Investigator Brochure/Summary of Product Characteristics at the same severity/frequency.

Causality

The Investigator must assess the causality of all SAEs/SARs in relation to the trial medication using the definitions below. The Sponsor will not be permitted to downgrade investigators’ causality assessments (e.g. to change an investigator’s assessment of an event from ‘possible relationship’ to ‘unlikely to be related’). Events categorised as ‘possible relationship’, ‘probable relationship’ or ‘definitely related’ will be recorded and processed as ‘related events’.
16.6 Procedures in case of pregnancy

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the trial medication may have interfered with the effectiveness of a contraceptive medication. However, the outcome of all pregnancies and pregnancies of the partners of those patients recruited into the trial (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the trial. A Pregnancy Notification Form should be completed and submitted to the Trial Office. Follow-up information may be requested as necessary.

All reports of congenital abnormalities/birth defects must be reported and followed up as per the procedures for an SAE.

17. Post Randomisation Withdrawals and Moves Out of Region

Patients have the right to withdraw from the trial at any time for any reason. Patients may be withdrawn from the trial at the discretion of the Investigator and/or Trial Steering Committee due to safety concerns.

Full details of the reasons for withdrawal should be recorded on the relevant CRF(s) where possible.

Patients should be encouraged to remain within the trial. However, for patients wishing to withdraw, every effort should be made to identify the following:

- Reason for withdrawal
- Whether the patient gives consent to collect follow-up information on survival and quality of life
- Whether the patient withdraws completely from the trial, and does not want any further data to be collected on them (and the patient’s wishes regarding data already collected)

If the patient is only withdrawn from trial treatment, they must be followed-up in accordance with the protocol.

<table>
<thead>
<tr>
<th>Relationship to study medication</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unrelated</strong></td>
<td>There is no evidence of any causal relationship</td>
</tr>
<tr>
<td><strong>Unlikely to be related</strong></td>
<td>There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication or device). There is another reasonable explanation for the event (e.g. the patient’s clinical condition, other concomitant treatment)</td>
</tr>
<tr>
<td><strong>Possible relationship</strong></td>
<td>There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication or device). However, the influence of other factors may have contributed to the event (e.g. the patient’s clinical condition, other concomitant treatments)</td>
</tr>
<tr>
<td><strong>Probable relationship</strong></td>
<td>There is evidence to suggest a causal relationship and the influence of other factors is unlikely</td>
</tr>
<tr>
<td><strong>Definitely related</strong></td>
<td>There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out</td>
</tr>
</tbody>
</table>
In the case of any withdrawal, the Trial Office should be notified immediately. Patients moving away from the region of the local site should NOT be withdrawn from the trial. Should this occur, please contact WCTU with the relevant details, and they will endeavour to assign the patient’s follow-up to a site close to their new location.

If there are patients who choose not to participate in the second randomisation, we will ask them the reasons why, also informing them that there is no necessity to answer. In such circumstances, continue to follow these patients up in the same manner as those who are randomised a second time to enable assessment of the primary outcome. We can also explore reasons for non-participation and trends that we may be able to address in a subsequent study.

18. Statistical Considerations

18.1 Stratification

To ensure a balance across trial arms, treatments at the first randomisation will be allocated using a minimisation algorithm stratified by the following priority confounding variables for risk of VTE in this population:

- Stage of disease at randomisation [early/locally advanced disease; metastatic disease; not applicable] (see section 5.3)
- Baseline platelet count \([\leq 350,000/\mu\text{L}; >350,000/\mu\text{L}]\) (pre-chemotherapy count for those patients on chemotherapy)\(^{55, 56}\)
- Type of VTE [symptomatic VTE; incidental PE]\(^{43}\)
- Risk of clotting by tumour type [high risk; low risk]\(^{15}\) (see Appendix 5)

The treatments at the second randomisation will be stratified by the below factors to ensure a balance between patients stopping and continuing treatment on each therapy:

- Treatment allocation at first randomisation [dalteparin; rivaroxaban]
- Stage of disease at randomisation [early/locally advanced disease; metastatic disease; not applicable] (see section 5.3)
- Platelet count at randomisation \([\leq 350,000/\mu\text{L}; >350,000/\mu\text{L}]\) (latest pre-chemotherapy count for those patients on chemotherapy)\(^{55, 56}\)
- Type of VTE [symptomatic VTE; incidental PE]\(^{43}\)
- Risk of clotting by tumour type [high risk; low risk]\(^{15}\) (see Appendix 5)

18.2 Endpoints

- VTE recurrence rates will be calculated from the date of randomisation to the date of first VTE recurrence event (either symptomatic VTE or incidental PE, whichever occurs first), or censored at the date last known to be VTE recurrence free.
- Symptomatic VTE recurrence rates will be calculated from the date of randomisation to the date of first symptomatic VTE recurrence event, or censored at the date last known to be symptomatic VTE recurrence free.
- “Truly” incidental PE recurrence rates for all patients will be calculated from the date of randomisation to the date of first incidental PE recurrence event, or censored at the date last known to be incidental PE recurrence free.
• Major bleeding and clinically relevant non-major bleeding (see section 9.2 for definition): The time to a major bleed or clinically relevant non-major bleed will be calculated from the date of randomisation or censored at the date last known to be free from a major bleed.

• Feasibility of conducting an economic evaluation (see section 18.5 for details)

• Tumour efficacy using the RECIST assessment (see Appendix 3)

• Acceptability of the study assessed by the numbers randomised and screening logs for reasons for non-randomisation

• Compliance to treatment assessed by the frequency of withdrawals of therapy and duration of therapy

• Patient Experience using Anti-Clot Treatment Scale (ACTS)

• Quality of Life measured using the EuroQol EQ-5D-5L questionnaire

• Progression-free survival (adjuvant patients) will be calculated from the date of randomisation to the date of first progression or death from any cause, or censored at the date last known to be alive and progression free.

• Overall survival will be calculated from the date of randomisation to the date of death from any cause, or censored at the date last known to be alive.

• Biomarker correlation

### 18.3 Power and sample size

A safety analysis of 200 patients (100 on the dalteparin treatment arm and 100 on the rivaroxaban treatment arm) would be sufficient to detect an excess of 15% in the major bleeding and clinically relevant non-major bleeding rate with 80% power and a 5% two-sided significance level assuming a 5% rate on the control arm.

A total of 530 patients will be recruited to provide reliable estimates of the primary endpoint (VTE recurrence rates) to within a width of the 95% confidence interval (95% CI) of 8% assuming the VTE rates are 10% at six months.

It is expected that approximately 70% of these 530 patients (370 in total (185 on each arm)) will be RVT+ve/PE and eligible for the treatment duration randomisation, and 80% of these will participate in the second randomisation, resulting in a total of 300 patients being randomised (150 on each arm).

### 18.4 Analysis plan

Estimates of VTE recurrence rates and 95% CIs will be obtained from constructing Kaplan-Meier curves to take into account censoring for the primary comparison of dalteparin versus rivaroxaban. Similar analyses will be conducted for the secondary comparison of 12 months versus 6 months anticoagulation treatment and for those in the RVT negative cohort. The number of RVT+ve/PE patients continuing to the second randomisation will be evaluated. Compliance to treatment will be assessed by frequency of withdrawals of therapy and duration of therapy. Kaplan-Meier survival curves will also be constructed for the time to event secondary outcomes of progression-free survival, overall survival and the composite safety parameter. Quality of life and patient experience analyses will be carried out using appropriate longitudinal analyses. Frequencies of adverse events and antitumour efficacy will be reported. The prevalence of measured biomarkers will be reported. All analyses will be performed on an intention-to-treat basis.

A pre-planned safety analysis will be conducted after the first 200 patients have been randomised (100 on each treatment arm) and have been on study at least 6 months (i.e. completed initial therapy and considered for the second randomisation) to assess treatment compliance, RVT results, adverse events and power calculation assumptions. The trial will continue to 530 patients if the safety study shows no
excess adverse events over and above what is expected (i.e. around 5% major haematological bleeds with no more than 15% excess in the rivaroxaban arm).

18.5 Health Economic Evaluation

The feasibility of conducting an economic evaluation of the alternative anticoagulant therapy packages will be assessed during the course of this study. This will involve consideration of the practicalities and difficulties associated with an assessment of the costs to providers, individuals and, more broadly, to society entailed by the introduction of the alternative anticoagulant therapy packages. As part of the pilot study, we will evaluate the performance of alternative client service receipt inventories in collecting resource utilisation data. We will also test the processes for identifying major adverse events and procedures, as well as inpatient admissions and outpatient consultations, from hospital records and routine data collection systems. The feasibility study will also involve an identification of the appropriate sources of unit cost data for potential resource consequences and an assessment of how much primary costing research will be required. An assessment will be made of the best possible way of expressing the cost-effectiveness of the alternative anticoagulant therapy packages. Outcome measures such as rates of venous thrombosis preclude cost-effectiveness comparisons with health interventions more broadly. Moreover, they overlook the potential consequences of anticoagulant therapy on broader aspects of health-related quality of life and individuals’ preferences for those broader consequences. A review will be conducted of the psychometric properties of the disease-specific measures and health related quality of life/multi-attribute utility measures (e.g. EQ-5D-5L) in this population group. Other trials and observational datasets held by the research team will be used as test beds for the study of the psychometric properties of these outcome measures. An important methodological issue that will have to be resolved during the course of the feasibility study is the appropriate time horizon of the subsequent, definitive, economic evaluation. Anticoagulant therapy may have consequences beyond the time horizon of the trial itself in terms of health status and health service utilisation. Therefore, the period of the feasibility study will be used to plan a long-term cost-effectiveness analysis with estimates of the patients’ subsequent health status and health care costs over a lifetime time horizon. This will almost certainly require the development of a baseline decision-analytic model, which will allow important elements of resource use and costs and gaps in the evidence to be identified. The baseline decision analytic model will ultimately be used to extrapolate the cost and effectiveness parameters beyond the data observed in a future RCT, as well as allow extrapolation to other settings.

18.6 Trial timetable and milestones

Details of all patients approached to participate but who refuse will be documented along with reasons for refusal via screening logs.

The pilot trial aims to recruit 530 patients over a 2 year recruitment period from at least 40 centres across the UK, with a strong and committed history of support for the UK’s national cancer trials portfolio.

0-6 months  Trial and centre set up
3 months  Trial Steering Committee (TSC) meeting to review protocol and timelines
6 months  IDSMC meeting
8 months  First patient randomised
16 months  Recruitment of 100 patients and IDSMC followed by TSC
20 months  Recruitment of first 200 patients
26 months  Perform safety study analysis on first 200 patients recruited, and IDSMC followed by TSC review
32 months  Recruitment of 530 patients
32 months  IDSMC followed by TSC review and decision to extend to full phase III study
38 months  Analysis of 530 patients with a minimum of 6 months follow-up

18.7  Phase III Trial

It is anticipated that if the analysis of the pilot study of 530 patients identifies that no excess of major haematological bleeds have been observed and at least 56% of patients are able to continue with the second randomisation then consideration will be given to extending recruitment to 770 patients in total, subject to additional funding.

18.7.1  Primary Objectives of Phase III Trial

- To compare VTE recurrence rates in cancer patients treated with rivaroxaban or dalteparin.
- To compare 6 months and 12 months of treatment with rivaroxaban in patients with evidence of RVT, following initial therapy in terms of VTE recurrence rates.
- To establish the cost-effectiveness of rivaroxaban treatment compared to dalteparin, and 6 months of anticoagulation treatment compared to 12 months.

18.7.2  Sample Size Calculations for Full Phase III Trial

The power calculations for the primary outcome assume a 6 month VTE recurrence free rate of 90% in the control arm and a 3 year recruitment period with a minimum of 6 months follow-up on all patients. On this basis, randomising 770 patients (385 patients to dalteparin and 385 to rivaroxaban) will allow demonstration of non-inferiority of the experimental arm, defining non-inferiority as “no worse than 5% below the 6 month VTE recurrence free rate for the control arm, with a 2.5% 1 sided level of significance and 90% power. This allows for a 10% drop out rate.

It is expected that approximately 70% of these 770 patients (540 in total (270 on each arm)) will be RVT positive and eligible for the second randomisation, and 80% of these will agree to participate in this second randomisation, resulting in a total of 432 patients being randomised (216 on each arm). If the VTE recurrence free rate at 12 months is around 85% with 6 months treatment, then 216 patients on each arm (432 in total) are required to detect a 7% difference with 12 months treatment with 90% power and 5% 2-sided significance level, allowing for 7% dropouts and assuming a 3 year recruitment period and 1 year follow-up on all patients.

The above assumptions will be verified within the pilot study.

19. Data Management & Patient Confidentiality

19.1  Data Acquisition

Personal data collected during the trial will be handled and stored in accordance with the 1998 Data Protection Act and WCTU SOPs. The Case Report Forms (CRFs) will be designed by the Trial Co-ordinator in conjunction with the Chief Investigator and Statistician. Original CRFs must be sent to the coordinating team at WCTU and copies retained on site.

19.2  Monitoring and Audit

19.2.1  Data quality monitoring

On receipt, all forms will be checked for completeness and congruity. Forms containing empty data fields or data anomalies will be queried with the site for resolution. Data will be entered onto the trial database and any further anomalies will be identified and queried with the site. Periodically, data will undergo additional checks to ensure consistency between data submitted on CRFs.

Trial staff will maintain regular communication with sites, through routine calls, mailings and/or meetings. In the event of persistent issues with the quality and/or quantity of data submitted, an on-
site monitoring visit may be arranged. In such circumstances, patient notes and the investigator site file must be available during the visit. The representative from the Trial Office will work with the site staff to resolve issues, offer appropriate training if necessary, and determine the site’s future participation in the trial.

An audit may be arranged at a site if the Trial Management Group feels it is appropriate. Audits will be conducted by an independent team, determined by the Trial Management Group.

If a regulatory inspection is planned at a participating site, site staff should contact the Trial Office to discuss any action necessary.

19.2.2 Pharmacy

Pharmacy departments at sites will be monitored depending on recruitment. High recruiting sites may be monitored more frequently. Monitoring of sites may be done remotely by requesting fax/email copies of accountability, site inventory, temperature, training and delegation logs, or by visiting the site if necessary.

Sites will be provided with written notification if a pharmacy monitoring visit is planned.

19.3 Confidentiality

The personal data recorded on all documents will be regarded as strictly confidential. To preserve the patient’s anonymity, only their initials, date of birth and hospital number (or similar details) will be recorded on the CRFs. With the patient’s permission, their initials, date of birth and health service (NHS) number/Community Health Index (CHI) number, if applicable, will be collected by the trial management team at Warwick Clinical Trials Unit at randomisation to allow sample tracking. Patients should be assured that their confidentiality will be respected at all times.

The local investigator must maintain documents that are not submitted to the trials unit (e.g. patients’ written consent forms) in strict confidence. In the case of special problems and/or governmental queries, it will be necessary to have access to the complete trial records, provided that patient confidentiality is protected. Warwick Clinical Trials Unit will maintain the confidentiality of all patient data and will not disclose information by which patients may be identified to any third party, other than those directly involved in patients’ treatment.

If information contained in a participant’s response on a trial form indicates an issue which may jeopardise the safety of the participant or another person, this should be reported to the CI who will decide on the appropriate action.

This may necessitate a breach of participant confidentiality in order to maintain their safety or to maintain the safety of others. If the CI considers it is necessary to breach confidentiality, the appropriate details will be communicated to the TMG. In such circumstances the participant will be informed that information will be shared with a third party. The nature of the information to be shared will also be disclosed to the participant, unless the CI feels that it would be unsafe to do so.

The database will be set up by the Programming Team at WCTU and all specifications (i.e. database variables, validation checks, screens) will be agreed between the programmer, statistician and trial coordinator.

19.4 Data Storage & Archiving

All essential documentation and trial records will be stored by WCTU in conformance with the applicable regulatory requirements and access to stored information will be restricted to authorised personnel.

Trial documentation and data will be archived for at least five years after completion of the trial in accordance with WCTU SOPs.
20. Trial Organisation

20.1 Trial Management Group (TMG)

The TMG includes a multidisciplinary team of clinicians and researchers who have considerable expertise in all aspects of trial design, conduct, analysis and quality assurance.

20.2 Trial Steering Committee (TSC)

The TSC will have an independent Chairperson. Meetings will be held at regular intervals determined by need but not less than once a year. Routine business is conducted by email, post or teleconferencing. Members of the TMG will be co-opted onto the TSC as appropriate.

The Trial Steering Committee, in the development of this protocol and throughout the trial, will take responsibility for:

- Major decisions such as a need to change the protocol for any reason
- Monitoring and supervising the progress of the trial
- Reviewing relevant information from other sources
- Considering recommendations from the IDSMC
- Informing and advising on all aspects of the trial

20.3 Independent Data & Safety Monitoring Committee (IDSMC)

An independent data and safety monitoring committee will be established for this trial. Their main objective will be to advise the Trial Steering Committee as to whether there is evidence or reason why the trial should be amended or terminated based on recruitment rates, compliance, safety or efficacy. The IDSMC will meet after the first 100 patients have been recruited and regularly thereafter.

Confidential reports containing recruitment, protocol compliance, safety data and interim assessments of outcomes will be reviewed by the IDSMC. Members of the IDSMC will accept and sign the IDSMC Charter. This will include a declaration that they will maintain confidentiality and that they have no conflicts of interest. The trial statistical analysis plan will be agreed with the IDSMC.

20.4 Administration

The Chief Investigator for the trial is Prof. Annie Young. The trial will be co-ordinated from the Trial Office at Warwick Clinical Trials Unit (WCTU), under the direction of Prof. Janet Dunn. Clinical responsibility will be undertaken by the Lead Investigators of the Trial Management Group.

The Trial Office will be responsible for ethical submissions, study site coordination (including training and accreditation), document design and production, monitoring trial procedures, trial meeting organisation, data queries, data monitoring, randomising patients, and safety reporting. Statistical analysis, database cleaning and the writing of the final study report will be performed by statisticians at the Warwick Clinical Trials Unit.

20.5 Site Staff Training

Prior to activating a site to recruitment, it is necessary for all staff members working on the trial to participate in an induction session. This will be carried out during an initial launch meeting. For sites unable to attend the trial launch, or for sites opening to recruitment at a later date, this will be carried out via teleconference or by a site initiation visit.

An accreditation checklist will be completed for all sites to confirm that pre-activation activities have been completed and all relevant staff members are able to participate.
Support will be offered to staff at participating sites to ensure they remain fully aware of trial procedures and requirements. Additional support and training will be offered to sites as appropriate where necessary (e.g. if the recruitment rate is lower than expected).

21. Patient Protection & Ethical Conduct

The trial will be conducted in accordance with the principles and guidelines of the International Conference on Harmonisation Good Clinical Practice (ICH GCP), UK legislation, Warwick Clinical Trials Unit SOPs and the protocol. GCP-trained personnel will conduct the trial. Free GCP training will be given, through the local National Cancer Research Networks (NCRN), to sites who do not have experience in conducting randomised, prospective, controlled clinical trials.

Before enrolling patients into the trial, each trial site must ensure that the local conduct of the trial has the approval of the relevant Trust Research and Development (R&D) department. Sites will not be permitted to enrol patients into the trial until written confirmation of R&D approval is received by Warwick Clinical Trials Unit, and a Site Agreement is in place.

Patients’ participation in the trial must be documented in the patient notes and must be communicated to the patient’s GP using the provided GP Letter.

21.1 Indemnity

NHS indemnity (Clinical Negligence Scheme for Trusts) covers negligent harm caused to patients whenever they are subjects of clinical research. NHS indemnity covers NHS staff and staff with honorary contracts with the NHS conducting the trial in the UK. All sites should ensure that they carry insurance allowing them to conduct studies including this one.

The University of Warwick will indemnify the trial in relation to the design and management of the research.

21.2 Ethical & Regulatory Review

The trial has obtained ethics approval from NRES Committee West Midlands – Coventry & Warwickshire Research Ethics Committee (main REC) and the MHRA in the UK. The local Principal Investigator must submit this protocol, any supporting documentation and any amendments to the R&D Office at the Trust as appropriate in accordance with local requirements and recommendations made by the main REC.

21.3 Annual Report

The trial staff will send an annual trial update report to the main REC, which will be distributed to all sites. It is the responsibility of each site to send a copy of this report to the R&D Office in accordance with local requirements and recommendations made by the main REC. Any additional local information required must also be submitted. Additional data required by NHS Trusts are available from the Trial Office on request. An annual Development Safety Update Report (DSUR) will be sent to the MHRA and main Research Ethics Committee by the Trial Office.

21.4 Protocol Amendments

All substantial amendments to the protocol will be documented by the Trial Office and will be submitted to the main REC/MHRA for approval prior to circulation to local parties as appropriate. Each trial site must ensure that they are using the most up to date version of the protocol, the Patient Information Sheet and Consent Form. All previous versions of the protocol and other trial documents should be crossed out with ‘this version is now superseded’ written on the cover page, and retained in the Trial Master File/Investigator Site File.
22. Research Governance

22.1 Sponsor

The University of Warwick is the Sponsor of the trial.

22.2 Essential Documentation

A Trial Master File will be set up and held securely at the WCTU, in accordance with WCTU SOPs.

WCTU will produce and provide each Investigator Site with an Investigator Site File. Any updates to essential trial documentation will be circulated to all participating sites – it is the responsibility of the site to update their Investigator Site File as necessary.

22.3 End of Trial

The end of trial is defined as the date of completion of all trial procedures for participants.

The trial will be stopped prematurely if:

- Mandated by the Ethics Committee
- Mandated by the Medicines and Healthcare products Regulatory Agency (MHRA)
- Following recommendations from the IDSMC
- Funding for the trial ceases

The main Research Ethics Committee (main REC) and the MHRA will be notified in writing within 15 days if the trial is concluded or terminated early.

22.4 Financial Support

Select-d is an investigator-led trial, funded by Bayer plc.

23. Dissemination & Publication

The results of the trial will be reported first to trial collaborators. The main report will be drafted by the trial co-ordinating team at WCTU and the final version will be agreed by the TSC before submission for publication, on behalf of the collaboration.

The success of the trial depends on the input of national and international collaborators. Equal credit will be given to those who have wholeheartedly collaborated in the trial.

The trial will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines (www.consort-statement.org).
### 24. Schedule of Delivery

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>10 days</th>
<th>3-4 wks</th>
<th>3 mths</th>
<th>5 mths</th>
<th>6 mths</th>
<th>9 mths</th>
<th>12 mths</th>
<th>18 mths</th>
<th>24 mths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria satisfied</td>
<td>✔</td>
<td></td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Informed consent taken</td>
<td>✔</td>
<td></td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Sample of original tumour tissue (submitted to central laboratory)</td>
<td>✔</td>
<td></td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Initial medication provided to patient¹</td>
<td>✔</td>
<td></td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Diagnostic scan: CT/MRI²,³ / US</td>
<td>✔</td>
<td></td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Medical review (including ECOG PS, weight, clinical assessments)</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Blood tests – haematology, biochemistry, cancer markers etc</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Biomarker blood samples</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Ultrasound scan / Venous Ultrasonography</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Toxicity by CTCAE</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Quality of Life (EQ-5D-5L)</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Health Resource Use</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>ACTS</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
</tbody>
</table>

Notes:

N.B. All highlighted fields are research related activities only.

1. Patient provided with initial medication – remainder of medication for first six months distributed as per local procedures
2. CT and/or MRI scans will be carried out as clinically indicated
3. Subsequent response assessments will be obtained as part of usual care for patients on anti-cancer treatment
4. Patients in second randomisation only
5. Patients receiving dalteparin only
6. Patients with DVT on presentation only
25. References


58. NCI. Common Terminology Criteria for Adverse Events (CTCAE) and Common Toxicity Criteria (CTC). US National Institutes of Health; 2009.


## Appendix 1: ECOG Performance Status

<table>
<thead>
<tr>
<th>Grade</th>
<th>ECOG Performance Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g. light house work, office work)</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self care, confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any self care. Totally confined to bed or chair</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
</tr>
</tbody>
</table>

* As published in Am. J. Clin. Oncol 57
Appendix 2: Common Terminology Criteria for Averse Events [CTCAE] v4.0

CTCAE version 4.0\textsuperscript{58} can be found through the following link:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40
Appendix 3: Response Criteria – RECIST v1.1

These criteria will be used where objective response, an assessment of stable disease or tumour progression are appropriate.

The new response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1) can be found through the following link:

## Appendix 4: The Anti-Clot Treatment Scale (ACTS)

### Anti-Clot Treatment Scale

We are interested in your experiences of anti-clot treatment. We would be grateful if you could help us by filling out this questionnaire. The questions below ask about your experiences of anti-clot treatment during the past 4 weeks. All of the information you provide is COMPLETELY CONFIDENTIAL. Please be sure to answer all questions.

**INSTRUCTIONS:** We are interested in your experiences of anti-clot treatment during the **past 4 weeks**. Please circle the number in the box that best describes your views.

<table>
<thead>
<tr>
<th>During the <strong>past 4 weeks</strong>...</th>
<th>Not at all</th>
<th>A little</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. How much does the possibility of bleeding as a result of your anti-clot treatment limit you from taking part in vigorous physical activities (e.g. exercise, sports, dancing, etc.)?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>2. How much does the possibility of bleeding as a result of your anti-clot treatment limit you from taking part in your usual activities (e.g. work, shopping, housework etc.)?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>3. How bothered are you by the possibility of bruising as a result of your anti-clot treatment?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>4. How bothered are you by having to avoid other medicines (e.g. aspirin) as a result of your anti-clot treatment?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>5. How much does your anti-clot treatment limit what you eat and drink (including alcohol)?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>6. How much of a hassle (inconvenience) are the <strong>daily</strong> aspects of your anti-clot treatment (e.g. remembering to take your medicine at a certain time, taking the correct dose of your medicine, limiting what you eat and drink (including alcohol), etc.)?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>7. How much of a hassle (inconvenience) are the <strong>occasional</strong> aspects of your anti-clot treatment (e.g. the need for blood tests, going to or contacting the hospital/doctor, making arrangements for treatment while travelling etc.)?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
Now I want to ask you about daily and occasional aspects of your anti-clot treatment during the past 4 weeks…

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at all</th>
<th>A little</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>8. How difficult is it to follow your anti-clot treatment?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>9. How time-consuming is your anti-clot treatment?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>10. How much do you worry about your anti-clot treatment?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>11. How frustrating is your anti-clot treatment?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>12. How much of a burden is your anti-clot treatment?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>13. <strong>Overall</strong>, how much of a negative impact has your anti-clot treatment had on your life?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>14. How confident are you that your anti-clot treatment will protect your health (e.g. prevent blood clots, stroke, heart attack, DVT, embolism)?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>15. How reassured do you feel because of your anti-clot treatment?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>16. How satisfied are you with your anti-clot treatment?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>17. <strong>Overall</strong>, how much of a positive impact has your anti-clot treatment had on your life?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

THANK YOU FOR YOUR HELP
Appendix 5: High / Low Risk Tumour Type Stratification

The incidence of these thrombotic events in patients with solid or haematological malignancies is greatly variable and is influenced by many factors, including the type of disease, the type of chemotherapy and the use of a central venous catheter. A number of clinical risk factors have been identified and contribute to the increasing thrombotic rate. Biologic properties of the tumour cells can influence the hypercoagulable state of patients with these malignancies by several mechanisms. However, for the purposes of the select-d trial, the thrombotic risk of VTE by tumour type is taken from the findings of a population case control study, a cancer registry and a review of VTE in the haematologic malignancies.

<table>
<thead>
<tr>
<th>HIGH RISK</th>
<th>LOW RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>Breast</td>
</tr>
<tr>
<td>Colorectal</td>
<td>Bone</td>
</tr>
<tr>
<td>Kidney</td>
<td>Nasopharygeal and oral</td>
</tr>
<tr>
<td>Acute leukaemias</td>
<td>Prostate</td>
</tr>
<tr>
<td>Lung</td>
<td>Skin</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>Other</td>
</tr>
<tr>
<td>Multiple myeloma (treated with thalidomide or derivative + dexamethasone)</td>
<td></td>
</tr>
<tr>
<td>Ovarian</td>
<td>Upper GI</td>
</tr>
</tbody>
</table>


Appendix 6: Cockroft-Gault Formula

Creatinine clearance should be calculated using the Cockroft-Gault Formula\textsuperscript{62}, which is given below:

\[
\text{Males: } 1.25 \times (140 - \text{age}) \times \text{weight (kg)} \\
\text{Females: } 1.05 \times (140 - \text{age}) \times \text{weight (kg)}
\]

\[
\begin{align*}
\text{Serum creatinine (µmol/l)} \\
\text{Serum creatinine (µmol/l)}
\end{align*}
\]