

# **A feasibility study to inform the design of a randomised controlled trial to identify the most clinically effective and cost-effective length of Anticoagulation with Low-molecular-weight heparin In the treatment of Cancer-Associated Thrombosis (ALICAT)**

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## Scientific summary

### The ALICAT feasibility study

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# Scientific summary

## Background

Venous thromboembolism (VTE) is common in cancer patients, affecting up to 20% of cancer patients during their lifetime. The standard treatment of VTE is well established, consisting of 5 days' anticoagulation treatment with low-molecular-weight heparin (LMWH), followed by 3–6 months of warfarin. However, the management of cancer-associated thrombosis (CAT) presents several challenges with a higher rate of both re-thrombosis and bleeding among cancer patients compared with those with non-malignant disease. A strong evidence base and international guidelines recommend 6 months' anticoagulation treatment with LMWH. Current data recommend LMWH for anticoagulation as far as 6 months, yet guidelines recommend anticoagulation treatment beyond 6 months in patients who have ongoing or active cancer. This expert consensus recommendation, based on the theory that the presence of active cancer will confer an ongoing risk for VTE, has not been evaluated in a clinical study. A randomised controlled trial (RCT) to evaluate whether or not patients with ongoing cancer and VTE should be anticoagulated for longer than 6 months is clearly needed. However, there are concerns that such a study would be challenging to recruit to, since many clinicians already treat patients with anticoagulates longer than 6 months as standard practice. The ALICAT (Anticoagulation with Low-molecular-weight heparin In the treatment of Cancer-Associated Thrombosis) trial was undertaken to establish the feasibility of progressing to a full RCT to identify the most clinically and cost-effective length of anticoagulation with LMWH in the treatment of CAT.

## Study aims

The aims of the study were:

- to identify practicalities of conducting a full RCT with regard to recruitment, retention and outcome measurement
- to explore the barriers to progressing to a full RCT.

## Primary outcomes

The primary outcomes of the study were:

- i. number of eligible patients over 12 months
- ii. number of recruited patients over 12 months (target recruitment rate of 30% of eligible patients)
- iii. proportion of randomised participants with recurrent VTEs during follow-up.

## Secondary outcomes

The secondary outcomes of the study were:

- i. completion of a trial protocol
- ii. costs
- iii. quality of life
- iv. symptom assessment
- v. attitudes of clinicians and patients.

## Methods/design

The ALICAT trial was a randomised, multicentre, feasibility mixed-methods study with three components: (1) a RCT, (2) a nested qualitative study and (3) a UK survey.

### *Randomised controlled trial*

Patients with ongoing active or metastatic cancer who had received 6 months of LMWH for CAT, were invited to participate. Patients were randomised to continue LMWH for a further 6 months or to stop (usual licensed practice). Patients were reviewed at 3 months and 6 months from randomisation, and evaluated for recurrent VTE and bleeding. They completed quality-of-life, symptom and health resource usage questionnaires.

In order to identify the best clinical environment to recruit from, we designated three clinical settings as recruitment sites: oncology outpatients, haematology outpatients and primary care. This was an open-label, non-placebo controlled trial with 1 : 1 randomisation.

### *Nested qualitative study*

Patients who declined to participate in the study were invited to participate in a semistructured qualitative interview. Reasons for declining participation were explored.

Likewise, patients agreeing to randomisation were interviewed about their experiences of participating in the study including drivers for compliance and retention in the trial.

Focus groups were organised with clinicians from three clinical settings (oncology, haematology and primary care) to explore the following topics:

- attitudes to recruiting to the study in terms of recruitment, equipoise and acceptability of the intervention, and outcome measures
- their experiences of, and attitudes to, prescribing LMWH, including whether or not they would extend treatment past 6 months.

### *UK survey*

This component of the study comprised telephone and web-based surveys to identify the models of care in existence for CAT along with identifying variations in patient pathways.

## Results

### *Randomised controlled trial*

There were significant delays in opening recruitment sites, which, in part, reflected the complexity of the study, with the settings being across primary care, secondary care and under English and Welsh research processes. Key areas of delay included agreement of contracts between organisations, internal approval systems for each recruitment site and repetition of approval requirements between two research organisations.

On reviewing set-up processes and projected site opening times, it was agreed to close the study to primary care and focus on opening oncology and haematology sites. During the intended recruitment period, only the oncology sites were opened. The first haematology site opened just as the decision to close the overarching study was made.

Over a 6-month period, 5 out of 32 eligible participants consented to randomisation. This number was significantly below the target of 15 out of 62. It was therefore concluded that it was not feasible to progress to a full RCT.

### **Nested qualitative study**

Eight patients who had declined randomisation consented to a qualitative interview. Patients reported they had been given sufficient information and opportunity for questions about the study. They also understood the purposes of the study. However, their prior experiences of VTE had, in part, consolidated their attitudes to anticoagulation, be it to continue or to stop.

For those diagnosed with incidental or asymptomatic pulmonary emboli, there was a desire to stop the injections as soon as possible. As their diagnosis was not associated with distressing symptoms, they did not see any strong reason to continue. They did not want to enter the study and risk being randomised to continue LMWH.

Patients with symptomatic VTE often found the experience distressing and therefore associated the LMWH injections with making them better. Many of them feared a recurrence of VTE and as such were unwilling to stop the treatment. Likewise, they did not want to risk randomisation to stop LMWH.

Focus groups were conducted in primary care, haematology and oncology departments. Clinicians readily acknowledged the gap in clinical data and the rationale for the study. For many, however, anticoagulation beyond 6 months had already become custom and practice, and they were unwilling to recruit patients whom they believed were at risk of ongoing VTE. Clinicians did not believe the study had equipoise based on their clinical experience. Some suggested they would be willing to recruit certain subgroups of patients, thereby generating a biased sample. Some also considered whether or not a study that continued LMWH at a lower dose instead of stopping completely may be better.

### **UK survey**

Patient pathway modelling suggested that there is a broad heterogeneity of practice with respect to CAT management and co-ordination with no consensus on which specialty should best manage such cases.

## **Conclusion**

At the current time it is not feasible to recruit sufficient patients with advanced cancer and VTE to a RCT exploring the most effective way to manage CAT after 6 months' anticoagulation therapy with LMWH.

Several barriers have been identified. The process-related delays are not insurmountable, but allowing a longer run-in period would provide a greater likelihood of opening sites on time.

However, even with the most efficient processes in place, it appears that patients themselves are unwilling to participate in such a study since their experience of the index VTE event impacts considerably on how they view the necessity of LMWH. Clinicians, likewise, do not consider such a study holds true equipoise while readily identifying this view is largely based on intuition and less so hard data.

### **Study registration**

This study is registered as clinical trials.gov number NCT01817257 and International Standard Randomised Controlled Trial Number (ISRCTN) 37913976.

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