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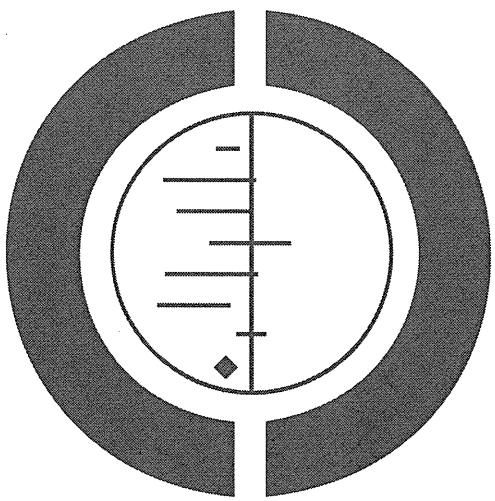
添付資料　14

Methods for administering subcutaneous heparin during pregnancy

Methods for administering subcutaneous heparin during pregnancy (Protocol)

Sasaki H, Yonemoto N, Mori R



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[Intervention Protocol]

Methods for administering subcutaneous heparin during pregnancy

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To compare the effectiveness and safety of different methods of administering subcutaneous heparin (UFH or LMWH) to pregnant women.

BACKGROUND

Description of the condition

The true incidence of thromboembolism (VTE) associated with pregnancy is unknown, yet there is a strong clinical indication of an increased risk when compared to non-pregnant individuals (Bates 2004). The estimated incidence varies from 0.76 to 1.72 per 1000 pregnancies, which is four times greater than among the non-pregnant population (Marik 2008).

The main reason for the increased risk of VTE in pregnancy is the hypercoagulability that occurs which protects women from haemorrhaging at the time of miscarriage or childbirth (James 2009). In developing countries, 20% to 34% of maternal mortality is due to haemorrhaging, while approximately 15% of maternal deaths in developed countries result from a pulmonary embolism (PE) (Khan 2006). Other risk factors for VTE in pregnancy include thrombophilia (an acquired or inherited tendency to develop thrombosis), a history of thrombosis, and antiphospholipid syndrome (a coagulation disorder that causes thrombosis in both arteries and veins) (James 2006). Acquired risk determinates include being aged over 35 years old, obesity, having a delivery by caesarean section, and a personal or family history of VTE (Bauersachs 2007).

Pregnancy leads to a temporary but more than three-fold increase in the risk of recurrent thrombosis compared to its occurrence among non-pregnant women (Pabinger 2002). Those women who develop VTE during their pregnancies require heparin (unfractionated heparin (UFH) or low-molecular weight heparin (LMWH)) as a treatment. Once they have passed through the treatment period, the dose or regimen will switch to a level that is necessary for prevention. Pregnant women requiring heparin prophylaxis are those with a history of VTE, antithrombin deficiency, and other risk factors for VTE such as a high-risk pregnancy.

VTE includes DVT (deep vein thrombosis) and PE. DVT is the result of an occlusive clot formation in the deep veins of the leg, from which parts of the clot frequently embolize to the lungs (PE) (Fauci 2008). From 75% to 80% of pregnancy-associated VTE comes in the form of DVT, while 20% to 25% is PE (James 2006). DVT and PE are life-threatening for both mother and fetus. Although maternal mortality from PE can be reduced by conducting a clinical investigation among symptomatic women and by treatment or prevention regimens in women with an increased risk of DVT, PE, or both, it is controversial because a clinical evaluation (e.g. a lung scan) exposes the fetus to radiation, and long-term treatment or prevention may be inconvenient and painful for patients. Administering heparin carries the risk of bleeding, osteoporosis and heparin-induced thrombocytopenia (HIT) (Bates 2004). However, James 2009 reported that the rate of recurrent VTE in women who did not receive anticoagulation with heparin varies from 2.4% to 12.2%, while the rate of recurrent VTE in women who did receive anticoagulation ranges from 0% to 2.4%. This shows that receiving heparin as an anticoagulant significantly reduced the risk of recurrent VTE during pregnancy.

The signs and symptoms of PE, such as dyspnoea, pleuritic chest pain, cough, and haemoptysis, are non-specific. The signs and symptoms of DVT, such as swelling, pain, redness, superficial venous dilatation, and Homan's sign (a pain in the calf or behind the knee on dorsiflexion of the ankle), are also non-specific (Fauci 2008). This is because some of the symptoms of DVT are similar to common symptoms that manifest themselves during pregnancy (Barbour 2001). Clinical suspicions are confirmed in 10% of pregnant women, compared with 25% of non-pregnant patients (Ginsberg 1998).

The classic gold standard for diagnosing PE is pulmonary angiography, which is an invasive method requiring expertise. Hence, similar to the developments that have occurred in the diagnosis of DVT, two (complementary) strategies have evolved. The first is the combination of the assessment of clinical probability (outcome) and the measurement of the D-dimer blood level; the second is the introduction of spiral CT of the chest. As regards DVT, ultrasonography with non-compressibility of the vein as the sole criterion has largely replaced contrast venography. This method has a very high sensitivity and specificity (95% to 100%) in symptomatic patients for proximal DVT (Fauci 2008). Compression ultrasonography carries no risk and is the preferred test in pregnant patients with suspected venous thromboembolism. Magnetic resonance imaging (MRI) also does not involve radiation exposure and is not harmful to the fetus. Unlike either ultrasonography or MRI, CT scanning is associated with fetal radiation exposure (Marik 2008).

Description of the intervention

UFH and LMWH are usually administered subcutaneously or intravenously for prophylaxis and treatment. These are the anticoagulant of choice during pregnancy, due to their established efficacy (Bates 2004) which has been demonstrated in pregnant women with DVT (Fauci 2008). Unlike other anticoagulants including vitamin K antagonists, warfarin and aspirin, both UFH and LMWH have no placental transfer (Bates 2008).

The potential risks of administering heparin - bleeding, osteoporosis and HIT - differ between UFH and LMWH. In one study (Ginsberg 1989) the rate of major bleeding in pregnant women receiving UFH was 2%, which is consistent with the reported rates of bleeding associated with administering heparin in non-pregnant women (Hull 1982a) and with warfarin therapy (Hull 1982b) when used for the treatment of DVT. In contrast, complications resulting from bleeding in pregnant women receiving LMWH are uncommon. Moreover, there was no statistically significant difference in bone loss between those who received LMWH and those who were untreated, suggesting that bone loss associated with prophylactic LMWH therapy is no different from the normal physiologic losses that occur during pregnancy (Carlin 2004). How-

ever, bone density was significantly lower in those receiving UFH compared with both those who were not treated and those who received delteparin (LMWH) (Monreal 1994). The risk of HIT with heparins is also low and may be lower with LMWH than with UFH, although as yet the actual risk is still unclear (Bates 2008). Even though the risk of severe adverse pregnancy outcomes is low, the use of subcutaneous heparin during pregnancy may cause pain, urticarial reaction, infection, and bruising due to repeated and long-term injections.

Heparin administration increases adverse pregnancy outcomes in women at risk. Women with thrombophilia are at a high risk of fetal loss, intrauterine growth restriction (IUGR), pre-eclampsia, placental abruption, and intrauterine death. Administering a combination of UFH and aspirin in women with thrombophilia has been shown to be effective for miscarriage compared with aspirin alone (Kutteh 1996; Rai 1997). The risk of thromboembolic complications in women with mechanical heart valves receiving heparin has varied across studies. Some studies (Al-Lawati 2002; Geelani 2005) have reported that there are fewer thromboembolic events among women receiving warfarin than in those treated with UFH, while other research (Nassar 2004) has reported conflicting results. The risk of maternal bleeding, congenital malformations, and fetal loss has been also reported in this high risk group (Bates 2008).

Methods of administering heparin subcutaneously include giving an intermittent injection, or using an indwelling catheter and an infusion pump. For prophylaxis with intermittent subcutaneous injections, UFH is usually given in fixed doses of 5000 U two or three times per day in non-pregnant patients. With these low doses, it is unnecessary to monitor coagulation, but monitoring is required when it is given for treatment (Fauci 2008). There is concern that this low dose may be insufficient in high-risk groups, including pregnant women with prior VTE, because it does not reliably produce detectable heparin (UFH) levels (Bates 2008).

The duration and doses of subcutaneous heparin LMWH during pregnancy vary depending on guidelines and studies. For prophylaxis, several dose regimens of LMWHs have been used, including administering subcutaneous enoxaparin 40 mg per 24 hours (Gates 2004), dalteparin 5000 U per 24 hours (Pettila 1999; Rey 2000), and an adjusted dose of LMWH to achieve a peak anti-Xa level of 0.2 to 0.4 U/ml (Dulitzki 1996; Blomback 1998).

Rey 2000 reported that dalteparin 5000 U per 24 hours was suitable for most pregnant women and did not need to be modified in the third trimester because anti-Xa activity levels did not vary significantly throughout pregnancy. In contrast, with the same regimen, where 5000 U of dalteparin was administered once daily, the mean anti-Xa level at 12, 24, and 36 week's gestation was significantly reduced at two hours post-injection when compared with postpartum (Sephton 2003). This suggests that there are inter- and intra- individual handling differences as pregnancy progresses. The Duke protocol (James 2005) reflects the increasing requirements for both UFH and LMWH as pregnancy progresses: UFH 5000 U subcutaneously per 12 hours before eight weeks, 7500 U subcutaneously per 12 hours from eight to 28 weeks then 10,000 U subcutaneously per 12 hours after 28 weeks or enoxaparin (LMWH) 30 mg twice-daily before 28 weeks then 40 mg twice daily after 28 weeks. Although higher dosages ranging from UFH 13,000 to 40,000 per 24 hours (mean 19,100 U per 24 hours) with 25 weeks of the average duration of prevention have been given, a 2.7% (five out of 184) recurrence of thrombotic events was recorded in spite of the high-dose prophylaxis (Dahlman 1993). Barbour 1995 also concluded that the adjusted high dose of UFH 7500 U to 10,000 per 12 hours may be reasonable in the second and third trimester as long as the activated partial thromboplastin time (aPPT) is not significantly elevated, while prophylaxis with low-dose anticoagulation is recommended for pregnant women with a history of thrombosis (Bates 2004).

One study (Anderson 1993) has investigated the comparative effectiveness and safety of using an indwelling Teflon catheter and a subcutaneous injection. Teflon catheters were inserted over an introducer steel needle at a 30 angle into the subcutaneous tissues of the abdomen by means of a sterile technique. After removal of the needle, the catheter was fixed in place with an adhesive foam pad. UFH was injected slowly, twice daily, through an external port at the proximal end of the indwelling Teflon catheter by means of an insulin syringe and a 25-gauge needle. The entire catheter was 3.5 cm in length with the Teflon portion that was inserted subcutaneously being 2 cm in length. Catheters were changed weekly to reduce the risk of infection. There were no differences in the mean heparin dose or aPPT between the two methods of heparin administration. The study also used a questionnaire to obtain information from patients about their preferred route of heparin administration. Of the 12 women interviewed, 11 reported that the catheter caused less pain and bruising than the subcutaneous injections given twice daily, although five patients developed urticarial reactions at the sites of the injections and these reactions tended to be more severe when the catheter was used.

Another method of subcutaneous heparin delivery, using a programmable external infusion pump, has been compared to the use of an intermittent subcutaneous injection. In a retrospective study (Floyd 1991), the mean daily dose of UFH when using a subcutaneous infusion pump was higher (29,445 versus 13,822 U), resulting in smoother, more therapeutic heparinization (mean aPTT, 20.6 versus 10.4 seconds above control) among the subcutaneous infusion pump group when compared to the intermittent subcutaneous injection group. There were two complications (hematoma, site infection) in the intermittent subcutaneous injection group, while none occurred in the subcutaneous infusion pump group. Although the results showed that there was no statistical significance in the smaller number of complications among the subcutaneous infusion pump group, when used in concert with weekly home visits, the subcutaneous infusion pump method nevertheless allowed the administration of the treatment to be more evenly controlled than did the use of intermittent subcutaneous

injections.

How the intervention might work

Heparin acts as an anticoagulant by activating antithrombin and accelerating the rate at which antithrombin inhibits clotting enzymes, particularly thrombin and factor Xa (Fauci 2008). The administration of heparin (UFH and LMWH) protects pregnant women against the risk of producing a thrombosis, which can develop into a DVT or PE.

Why it is important to do this review

Women requiring heparin during pregnancy, especially those with a history of VTE who are likely to be on lifelong anticoagulation, will require a switch from the administration of warfarin to heparin-related compounds (James 2007) when conception has occurred and been detected, because of the effects of warfarin on the fetus. Although administering subcutaneous heparin (UFH or LMWH) is the main option in the prevention of VTE during pregnancy, until now the management of thromboprophylaxis in pregnant women has mostly relied on the evidence from non-pregnant patients. Because of the discomfort and side effects due to repeated and long-term injections, some women discontinue administering heparin (UFH or LMWH) subcutaneously. Others may not self-administer heparin and must rely on others to give them their injections or else they discontinue the administration, thus exposing themselves to an increased risk of VTE (Anderson 1993). Women's satisfaction while administering subcutaneous heparin (UFH or LMWH) is highly important, since the effectiveness and safety of administering subcutaneous heparin during pregnancy using different methods is still not clear. This underscores the importance of conducting a systematic review to investigate the effectiveness and safety of different methods of administering subcutaneous heparin (UFH or LMWH) in this high-risk group of pregnant women.

OBJECTIVES

To compare the effectiveness and safety of different methods of administering subcutaneous heparin (UFH or LMWH) to pregnant women.

METHODS

Criteria for considering studies for this review

Types of studies

We will include all randomized controlled trials (individual and clustered) investigating methods for administering subcutaneous heparin (UFH or LMWH) during pregnancy. We will also include studies that have been reported only as abstracts but indicate that they are studies awaiting assessment, pending the full publication of their results. We will exclude quasi-randomized studies and crossover trials.

Types of participants

Participants will be women requiring heparin (UFH or LMWH) during pregnancy. We will not include pregnant women under intensive care.

Types of interventions

Intermittent injections versus indwelling catheters or programmable (auto) external infusion pumps, or any other devices to facilitate the subcutaneous administration of heparin (UFH or LMWH) during pregnancy.

Types of outcome measures

Primary outcomes

1. Women's satisfaction
2. Incidence of VTE

Secondary outcomes

1. Maternal death
2. Local and systemic bleeding (haemorrhage)
3. Pain
4. Urticarial reaction
5. Local and systemic infection and bruising
6. Withdrawal because of adverse events (discontinuation of heparin because of serious and threatened adverse events)
7. Pregnancy outcomes (e.g. miscarriage, fetal death)
8. Any adverse events reported by the included trials (e.g. osteoporosis, HIT)

Search methods for identification of studies

Electronic searches

We will contact the Trials Search Co-ordinator to search the Cochrane Pregnancy and Childbirth Group's Trials Register.
The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. weekly searches of EMBASE;
4. handsearches of 30 journals and the proceedings of major conferences;
5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE and EMBASE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

Searching other resources

(1) References from published studies

We will search the reference lists of relevant trials and reviews identified.

(2) Unpublished literature

If necessary, we will contact the authors for more details about the published trials/ongoing trials.

We will not apply any language restrictions.

Data collection and analysis

Selection of studies

Two review authors will independently assess the inclusion of all the potential studies we identify as a result of the search strategy. We will resolve any disagreement through discussion or, if required, we will consult the third review author.

Data extraction and management

We will design a form to extract data. For eligible studies, two review authors will extract the data using the agreed form. We will resolve discrepancies through discussion or, if required, we will consult an additional review author. We will enter data into the Review Manager software (RevMan 2008) and check for accuracy. When information regarding any of the above is unclear, we will attempt to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors will independently assess the risk of bias for each study, as well as for cluster-randomized and crossover trials separately using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreement by discussion or by involving an additional assessor.

(1) Random sequence generation (checking for possible selection bias)

We will describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We will assess the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator),
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number) or,
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We will describe for each included study the method used to conceal allocation to interventions prior to assignment and will assess whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We will assess the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We will describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We will consider that studies are at low risk of bias if they were blinded, or if we judge that the lack of blinding would be unlikely to affect results. We will assess blinding separately for different outcomes or classes of outcomes.

We will assess the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel;

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We will describe for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention

a participant received. We will assess blinding separately for different outcomes or classes of outcomes.
We will assess methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We will describe for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We will state whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported, or can be supplied by the trial authors, we will re-include missing data in the analyses which we undertake.
We will assess methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomization);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We will describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We will assess the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by 1 to 5 above)

We will describe for each included study any important concerns we have about other possible sources of bias.
We will assess whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

(7) Overall risk of bias

We will make explicit judgements about whether studies are at high risk of bias, according to the criteria given in the Handbook (Higgins 2011). With reference to (1) to (6) above, we will assess the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. We will explore the impact of the level of bias through undertaking sensitivity analyses - *see* 'Sensitivity analysis'.

Measures of treatment effect

Dichotomous data

For dichotomous data, we will present results as summary risk ratio with 95% confidence intervals.

Continuous data

For continuous data, we will use the mean difference if outcomes are measured in the same way between trials. We will use the standardized mean difference to combine trials that measure the same outcome, but use different methods.

Unit of analysis issues

Cluster-randomized trials

We will include cluster-randomized trials in the analyses, along with individually randomized trials and crossover trials. We will adjust their sample sizes using the methods described in the *Handbook* (Higgins 2011), using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), or from another source. If ICCs from other sources are used, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomized trials and individually-randomized trials, we plan to synthesize the relevant information. We will consider it reasonable to combine the results from both, if there is little heterogeneity between the study designs and an interaction between the effect of the intervention and the choice of the randomization unit is considered to be unlikely. We will also acknowledge heterogeneity in the randomization unit and perform a separate meta-analysis.

Dealing with missing data

For included studies, we will note the levels of attrition. We will explore the impact of including studies with high levels of missing data in the overall assessment of the treatment effect by using sensitivity analysis. For all outcomes, we will carry out analyses, as

far as possible, on an intention-to-treat basis, i.e. we will attempt to include all participants randomized to each group in the analyses, and all participants will be analyzed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial will be the number randomized minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

We will assess statistical heterogeneity in each meta-analysis using the T^2, I^2, and Chi^2 statistics. We will regard heterogeneity as substantial if I^2 is greater than 30% and either T^2 is greater than zero, or there is a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

If there are 10 or more studies in the meta-analysis we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually, and use formal tests for funnel plot asymmetry. For continuous outcomes we will use the test proposed by Egger 1997, and for dichotomous outcomes we will use the test proposed by Harbord 2006. If asymmetry is detected in any of these tests or is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We will carry out a statistical analysis using the Review Manager software (RevMan 2008). We will use a fixed-effect model for combining data where trials are examining the same intervention, and the trial's populations and methods are judged sufficiently similar. We will weight effect estimates by the inverse of their variance, giving greater weight to larger trials. If we suspect clinical or methodological heterogeneity between treatment effects, we will use a random-effects model. We will carry out meta-analysis by study type (randomized trial, cluster-randomized trial).
If we use random-effects analyses, we will present the results as the average treatment effect with its 95% confidence interval, and the estimates of T^2 and I^2.

Subgroup analysis and investigation of heterogeneity

If we identify substantial heterogeneity, we will investigate it using subgroup analyses and sensitivity analyses. We will consider whether an overall summary is meaningful, and if it is, use random-effects analysis to produce it.
If possible, we plan to carry out subgroup analyses for the primary outcomes and secondary outcomes as follows.

1. Type of heparin (UFH versus LMWH)
2. Previous VTE during pregnancy
3. A family history of VTE
4. Thrombophilia
5. Other risk factors (e.g. age, obesity, antiphospholipid syndrome)

For fixed-effect inverse variance meta-analyses we will assess differences between subgroups by interaction tests. For random-effects and fixed-effect meta-analyses using methods other than inverse variance, we will assess differences between subgroups by inspection of the subgroups' confidence intervals.

Sensitivity analysis

We will perform sensitivity analyses in order to explore the effect of trial quality for important outcomes in the review. If there is a risk of bias associated with a particular aspect of study quality (e.g. allocation concealment), we will explore this by sensitivity analysis. We will use primary and secondary outcomes in the sensitivity analysis.

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* *Indicates the major publication for the study*

HISTORY

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CONTRIBUTIONS OF AUTHORS

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DECLARATIONS OF INTEREST

None known.

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