ist PROTOCOL

International Stroke Trial

DOES EARLY ANTITHROMBOTIC THERAPY FOR ACUTE STROKE SAVE LIVES AND REDUCE DISABILITY IN SURVIVORS?

The fundamental aim of the IST collaborative group is to assess reliably the balance of the risks and benefits for simple widely practicable treatments that might produce moderate but worthwhile mortality reductions (and reductions in disability of survivors) in patients with acute ischaemic stroke.

Substantial numbers of lives might be saved by such treatments, but benefits of the size that can realistically be expected will be reliably detected only by randomised trials involving some tens of thousands of patients. In order to recruit such numbers, the IST involves almost no extra work for collaborators: hence, busy general hospitals - where the majority of patients with acute ischaemic stroke are actually treated - can take part easily. The ability of the IST to yield clear, reliable answers depends entirely on the collaboration of many doctors and nurses in the participating hospitals. For this reason, publication of the final results will be in the names of all the collaborators.

LARGE SIMPLE STUDY OF THE EFFECTS OF ASPIRIN, AND OF LOW-DOSE OR MEDIUM-DOSE SUBCUTANEOUS HEPARIN

All patients, with mild, moderate and severe deficits, presenting within 48 hours of the onset of suspected acute ischaemic stroke are eligible for the IST, provided the responsible physician does not initially consider there are any clear indications for, or clear contraindications to, any one of the trial treatments: aspirin, low-dose or medium-dose subcutaneous heparin. If a CT scan has excluded intracranial haemorrhage (ICH) or if the clinician considers the probability of ICH is low, patients are randomised between: (i) a policy of 'begin oral (or rectal or intravenous) aspirin immediately' or 'avoid aspirin' and (ii) 'begin low-dose subcutaneous heparin immediately' or 'begin medium-dose subcutaneous heparin immediately' or 'avoid heparin'. The allocated treatment policy is continued for two weeks or until discharge (or transfer) from the randomising hospital, if that occurs sooner. (NB Patients already on aspirin and patients who have already received some heparin can still be entered.)

In this trial, two different treatments will be evaluated simultaneously in a "3x2 factorial design". At first glance this may appear to complicate the results, but in fact, appropriate statistical analysis of this "factorial" design will allow all the patients to contribute fully to assessment of the separate effects of each treatment (whilst also providing important information about the combined effects).

Apart from giving the trial treatments, all other aspects of individual patient management are left entirely to the responsible physician to decide. Many physicians will wish to start aspirin therapy for long-term secondary prevention of serious vascular events at about two weeks after stroke onset or at hospital discharge. This is strongly encouraged. The IST will provide good evidence about the effects of adding the trial treatments to various standard treatments during the acute phase of ischaemic stroke. By including many different types of patient from many different types of hospital, with wide variation in ancillary management (which is anyway unavoidable), the IST results will be of direct clinical relevance to the heterogeneous realities of clinical practice worldwide.

United Kingdom 1992
ISTUK/P/1/1

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(Major organisation and policy decisions)

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CONTENTS

1. CAN SIMPLE WIDELY PRACTICABLE TREATMENTS SAVE LIVES, AND REDUCE DISABILITY IN SURVIVORS?

Acute stroke is a substantial public health problem; over the next decade in Europe and USA alone there will be about 15 million patients with acute ischaemic stroke, many of whom will present to hospital within 48 hours of onset. At present, antithrombotic treatments are used haphazardly in the early treatment of such patients, with no clear evidence that they are either effective or safe[1]. On the other hand, **if** early antithrombotic therapy in acute ischaemic stroke were proven to be safe and effective, and even if it reduced early mortality by 'only' one sixth (from 12% to 10%), widespread use in Europe and USA alone, over the next decade, might avoid a few hundred thousand early deaths after stroke. Furthermore, early antithrombotic treatment might reduce the volume of brain damaged by ischaemia and might therefore increase the probability of survival free of serious disability[2-13]. Convincing evidence from a large trial, that such simple treatment saves lives **and** reduces disability in survivors, might really change clinical practice (for example, the ISIS-2 trial[14] completely changed clinical practice in the use of aspirin and streptokinase in the management of acute myocardial infarction).

2. CHOICE OF TREATMENTS TO STUDY

The chief aim of the IST is the reliable assessment of the separate and combined effect on mortality (and on disability in survivors) of two widely practicable antithrombotic regimens: (i) "start aspirin therapy immediately" compared with "delay starting aspirin therapy for two weeks"; (ii) "begin subcutaneous heparin immediately" compared with "avoid heparin therapy for the first two weeks", for a wide range of patients in the acute phase of ischaemic stroke (with severe as well as with mild neurological deficits). Early intervention with antithrombotic agents might reduce the volume of brain damaged by cerebral ischaemia and thereby reduce the neurological deficit and reduce disability in survivors.

Acute ischaemic stroke begins with the occlusion of a cerebral blood vessel by thrombus or embolus[2]. This initial event triggers a cascade of secondary events, all of which may cause increasing damage to the surrounding neural tissue[2,6-13]: a) platelet activation and aggregation with release of serotonin and calcium: b) activation of the coagulation cascade: c) biosynthesis of thrombogenic and neurotoxic eicosanoids: d) endothelial damage: e) breakdown of the blood brain barrier: f) diffusion of these products into surrounding brain: g) reduced microvascular flow in the ischaemic penumbra around the initial focus. In the core of the cerebral infarct, some neurones are irrevocably damaged soon after the initial occlusion of the primary vessel, but around the core, cascade reactions may cause rather gradual and increasing neuronal death over some hours after the initial insult. Thus the "time window" for therapeutic benefit from antithrombotic agents may be surprisingly long. In experimental models of focal cerebral and spinal cord ischaemia, inhibition of platelet cyclo-oxygenase with aspirin, indomethacin or similar agents has: promoted spontaneous lysis of the occluding cerebral thrombus[5]; inhibited platelet aggregation at the site of the initial occlusion[13]; inhibited biosynthesis of thrombogenic and neurotoxic eicosanoids[8,11]; improved microvascular circulation in the ischaemic penumbra[8]; and prevented the 'post-ischaemic no reflow' phenomenon[6]. In addition, heparin alone, or in combination with aspirin, indomethacin or fibrinolytic agents has reduced ischaemic damage in experimental models of ischaemic stroke[5,7,13], and promoted lysis of the occluding thrombus[5].

A practicable antiplatelet regimen: once daily 300 mg oral (or rectal or equivalent intravenous) aspirin for two weeks.

BENEFITS IN LONG -TERM SECONDARY PREVENTION: A worldwide overview of over 200 trials provided clear evidence that long-term antiplatelet therapy, started some weeks or months **after** an acute myocardial or cerebral infarct and given for two years or so, reduces serious vascular events (stroke, myocardial infarction and vascular death) by about a quarter[15] (Table 1).

Reason for high risk	Total number randomised	Reduction in vascular events (% ±SD)	2p
History of myocardial infarction	19,000	25% ±4	<0.00001
History of stroke or TIA	10,000	23% ±4	<0.00001
Other reason*	22,000	30% ±4	<0.00001

***TABLE 1**: Worldwide overview of over 200 Trials of antiplatelet therapy (Antiplatelet Trialists' Collaboration). Reductions in serious vascular events (stroke, myocardial infarction or vascular death) when antiplatelet therapy is given for long term secondary prevention in patients with a history of symptomatic vascular disease[15]. * Other reasons include a history of : peripheral vascular disease; surgery on the coronary or peripheral arterial circulation; atrial fibrillation.*

BENEFITS IN THE ACUTE PHASE OF MYOCARDIAL INFARCTION: There is clear evidence from the ISIS -2 study that aspirin therapy, started as soon a possible after the onset of chest pain, reduces early mortality (Table 2). The reduction is equivalent to the avoidance of 24 deaths per 1000 patients treated. The effect of aspirin (as a treatment for the acute phase) on early mortality after cerebral infarction is unknown[4,5].

	Total number randomised	Reduction in early mortality (% ±SD)	2p
Acute myocardial infarction	17,000	23% ±4	<0.00001
Acute cerebral infarction	few	Not known	–

***TABLE 2:** Effect of antiplatelet therapy when used as a treatment for the acute phase of myocardial or cerebral infarction[4,5,14].*

PREVENTION OF ARTERIAL OCCLUSION: The Antiplatelet Trialists' Collaboration also examined data from 41 trials of antiplatelet therapy in 8,000 patients, mostly undergoing arterial grafting in the coronary or lower limb circulations, which showed that antiplatelet treatment provided useful protection against graft occlusion, reducing the risk by about 40%[16]. A similar protective effect in the brain could prevent propagation of thrombus in cerebral arteries and reduce the volume of ischaemic brain damage (and hence might reduce neurological disability in survivors).

PREVENTION OF VENOUS THROMBOEMBOLISM: An overview of the 55 trials of antiplatelet therapy in the prevention of deep venous thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing surgical procedures, showed that treatment significantly reduced both DVT by about 40% and pulmonary embolism by about 65%[17]. This effect is clearly relevant in acute stroke where DVT occurs in about half of all hemiplegic patients[4,18], PE occurs in about 6% of all strokes[4] and PE accounts for about 5% of all stroke deaths[19].

OPTIMUM ASPIRIN DOSE: In long-term secondary prevention, doses of aspirin between 30 mg and 160 mg daily are effective[15]. Higher doses (160 mg - 300 mg) are required in the treatment of acute myocardial infarction and probably also in acute cerebral infarction to achieve the most rapid and complete inhibition of thromboxane biosynthesis[11,14].

RISKS OF ASPIRIN THERAPY IN THE ACUTE PHASE OF CEREBRAL INFARCTION: Aspirin therapy can have potentially serious side- effects. Long-term antiplatelet therapy was associated with a 20% excess of intracerebral haemorrhages, which was outweighed by a larger reduction in the risk of ischaemic strokes[15]. Aspirin, given to rabbits in an experimental model of acute ischaemic stroke induced by injection of small thrombi, caused a substantial increase in fatal intracerebral haemorrhage[5]. No data from randomised controlled clinical trials in the acute phase of stroke on the risks of serious cerebral bleeds with aspirin have yet been published[4,5].

A practicable anticoagulant regimen: twice daily subcutaneous heparin

An overview of the 10 small randomised trials of heparin in patients with acute ischaemic stroke showed that, whilst heparin therapy was associated with a highly significant 81% reduction in DVT ($2p < 0.00001$), there was no reliable evidence on whether treatment reduced pulmonary embolism[4]. Only 173 deaths occurred, so although an 18% (SD ± 16) reduction in mortality was observed, it was not conventionally significant, and an excess of about 10-20 deaths per 1,000 patients treated could not be excluded. No data on the effect of early heparin treatment on long-term disability in survivors were reported by any of the trials.

	Reduction (% ± SD)	2p
Deep venous thrombosis	**81% ± 8**	**< 0.00001**
Death	**18% ±16**	**NS**
Cerebral haemorrhage	**12% excess**	**NS**
Disability in survivors	**no data available**	**—**

TABLE 2: *Reductions in DVT and death in an overview of 10 small trials of heparin in acute ischaemic stroke[4]*

The risk of major cerebral haemorrhage (ie severe haemorrhagic transformation of the infarct) was low in controls 7/102 (6.9%), and somewhat higher in heparin-allocated patients 8/106 (7.5%), a non-significant 12% (SD ± 56) increase. Because there were so few events, the data from the overview were wholly inadequate to determine reliably whether or not heparin treatment of acute ischaemic stroke was associated with an increased risk of major cerebral haemorrhage. Until reliable evidence on the risk of this rare, but potentially fatal or disabling complication of heparin therapy emerges from large trials such as the IST, routine use of heparin in the acute phase of ischaemic stroke cannot be recommended. Even if the routine use of low-dose subcutaneous heparin for DVT prophylaxis caused only a few fatal or disabling cerebral haemorrhages, such serious adverse effects might offset any benefits from reductions in non-fatal DVT and PE.

Low dose heparin should carry the lowest risk of cerebral bleeding and a low dose should be sufficient to reduce **venous** thromboembolism after stroke, yet it might be inadequate to prevent neurological disability due to cerebral **arterial** occlusion. Rapid and complete anticoagulation with adjusted dose intravenous heparin might be more likely to prevent cerebral arterial thrombosis, but might carry an unacceptably high risk of bleeding. Medium fixed-dose regimens of subcutaneous heparin (12,500 units twice daily) provide greater efficacy in the prevention of left ventricular thrombus after myocardial infarction than low dose regimens, without any apparent major excess of serious bleeding complications[20]. The safety and efficacy of medium-dose subcutaneous heparin is not importantly different to intravenous adjusted dose heparin[21]. Regimens involving rapid anticoagulation with intravenous heparin are difficult to administer and maintain within the therapeutic range[21-24]. Compliance with therapy is likely to be better with a simple twice daily subcutaneous regimen[23]. Subcutaneous heparin has many practical advantages: it is simpler for the collaborating doctors[25], and it achieves moderate anticoagulation without the need for monitoring[20]. Thus the simpler, more easily administered medium-dose subcutaneous regimen should be tested in acute ischaemic stroke, but should also be compared with the potentially safer (but possibly less effective) lower dose subcutaneous regimen of 5,000 units twice daily, and because of the risk of disabling or fatal cerebral bleeding, active heparin therapy should be compared with control[4].

Flexibility in all other aspects of management

In general, physicians who definitely want to use either of the trial drugs (aspirin or heparin) in a particular patient should do so, and should **not** randomise that patient. All other aspects of patient management (such as the use of glycerol, mannitol, cortico-steroids, calcium antagonists and other agents) are entirely at the discretion of the responsible physician, because the needs of individual patients and the preferred methods of different physicians vary widely. The wide variation in the ancillary management of trial patients that will result (and which is anyway unavoidable) is advantageous since it helps to make the IST result more directly relevant to heterogeneous clinical practice worldwide. Hence the IST will provide good evidence about the effects of adding aspirin and subcutaneous heparin to currently standard treatment.

The treatment to be prescribed at the end of the two week trial period (or at discharge or transfer from the randomising hospital if that occurs sooner) is also at the discretion of the responsible physician, but it is **recommended** that all patients be given (if there are no contraindications) aspirin as long term therapy for secondary prevention. There is good evidence that, given for a few years after an ischaemic stroke, low-to-medium dose (30-300 mg) aspirin reduces the risk of serious vascular events by about one quarter[15].

3. SIZE OF DIFFERENCE TO BE MEASURABLE: 20-30 DEATHS PER 1000 PATIENTS TREATED

Reliable assessment of the effects of aspirin and heparin on mortality may require at least 20,000 patients to be randomised.

If early administration of antithrombotic drugs reduced two week mortality by 'only' one sixth, routine use in patients with acute ischaemic stroke over the next decade might save several hundred thousand lives worldwide. Although a study with 10,000 subjects might be sufficient to detect effects of this size, it might well not be (whereas a trial twice this size definitely would be). For example, a 15% difference in mortality in a trial of 10,000 patients (eg 430 deaths among 5,000 treated patients and 500 deaths among controls) would be statistically significant ($2p = 0.02$). But, even if treatment really does reduce the risk by 15%, the play of chance could make the **observed** difference in a trial of 10,000 patients somewhat less extreme and hence not conventionally significant (eg 440 vs 490 deaths, NS). Given the wide relevance of the questions addressed by the IST, this chance of failing to recognise a treatment that really does reduce mortality by 15% is not a reasonable risk to take.

The aim in the IST, therefore, is to randomise **at least** 20,000 patients to ensure that the risk of such a false negative trial is negligible. Of course, if some of the differences are greater than 15%, then the trial is likely to yield statistically definite results for one or more of the treatment comparisons before its scheduled end. That particular comparison would then be stopped early so that later patients in IST and elsewhere could benefit. In planning for the size of IST, it is not sensible to let over-optimism lead to failure to recognise moderate mortality differences since these could still be medically worthwhile with such simple and inexpensive treatments. The principal secondary aim of the IST is reliably to assess the **safety** of early antithrombotic therapy. The most important complication is severe (ie fatal or disabling) haemorrhagic transformation of the cerebral infarct. The study must have sufficient statistical power to detect even moderate increases in this rare but often serious event[26].

Full efficiency: the IST factorial design allows the separate assessment of more than one treatment without any material effect on study size requirements.

In the IST, patients will be randomised between: aspirin vs open control, and low-dose heparin vs medium-dose heparin vs open control. If as is hoped, a total of 20,000 patients are randomised, then there will be about 5,000 patients in each of the four main treatment groups (aspirin vs control, heparin vs control). Group sizes of 5,000 may not be large enough to yield statistically reliable results, so it may at first sight appear that this factorial design needs far more patients than would have been needed by a simple design that randomised only one treatment comparison. This is not the case, however, because the way in which the results from such a factorial design can be analysed allows each main question to be answered about as reliably as if the other questions were not being asked (as in ISIS-2 for aspirin and streptokinase[14]: see "Analysis" page 13).

4. ELIGIBILITY: MILD, MODERATE AND SEVERE ISCHAEMIC STROKE

Simple eligibility: stroke with: onset ≤ 48 hrs ago, a deficit unlikely to resolve within the next few hours, no known intracranial haemorrhage, no clear indications for, or clear contraindications to, aspirin or subcutaneous heparin.

All patients, with mild, moderate or severe deficit, are eligible if, in the view of the responsible physician:

- **There are symptoms or signs of an acute stroke; and**
- **The patient is not known to have intracranial haemorrhage; and**
- **There are considered to be no CLEAR indications for, or CLEAR contraindications to, any of the trial treatments (aspirin or subcutaneous heparin).**

Diagnosis of stroke and exclusion of patients with TIAs.

The diagnosis of stroke is a clinical one and patients should be considered for the IST if they have had: a sudden onset of a new focal neurological deficit which is presumed to have a vascular cause, and symptoms which are not resolving quickly. The conventional definition of stroke, which states that symptoms must last more than 24 hours, is impossible to apply to patients seen within 24 hours of the onset of symptoms. However, if symptoms are still present a few hours after onset, they are unlikely to resolve completely within 24 hours (and therefore, such patients are likely to be eligible for the trial).

The need to exclude intracranial haemorrhage by CT scanning before randomisation.

CT scanning **before** randomisation to exclude intracranial haemorrhage is **strongly recommended** and is **mandatory** in comatose patients, (in whom the probability that the stroke is due to cerebral haemorrhage is high). Clinical scoring systems may help in differentiating those with a high or a low probability of haemorrhagic stroke; though clinical methods alone are unreliable, CT scanning may not always be immediately available to exclude cerebral haemorrhage before antithrombotic treatment begins. Even if CT is readily available, a policy of "mandatory pre-treatment CT scanning" for all non-comatose patients might, for some patients, delay treatment unduly (beyond the time when benefit is plausible). If undue delay in CT scanning seems likely, a more pragmatic policy would allow patients, in whom haemorrhagic stroke is considered unlikely on clinical grounds, to be randomised and be given one or two doses of treatment while CT scanning is organised. Treatment would be stopped if the initial stroke proved to be a primary intracerebral haemorrhage. The balance of benefit (earlier treatment of some ischaemic strokes) and risk (one or two doses of antihaemostatic treatment for a few patients with primary intracerebral haemorrhage) would be measured and monitored during the progress of the study. (NB: Any randomised patient who is later found to have an intracranial haemorrhage will not be excluded from any follow-up or from analysis of the trial results. **All** randomised patients must be followed-up, **irrespective of CT scan or autopsy findings**).

The intent is to randomise patients as **promptly** as possible after admission to hospital. If the patient is not considered eligible for randomisation because of some contraindications they should be reassessed a few hours later, and may then be eligible if trial treatments are no longer thought to be contraindicated and it is still within 48 hours of the onset of symptoms. **(NB A patient can be entered once and only once in the IST.)**

Onset of symptoms ≤ 48 hrs

In theory, to derive maximal benefit, antihaemostatic treatments like aspirin and heparin should be given as soon as possible after the onset of cerebral ischaemia, but we have no idea of how long the 'time window' could be. We do not know exactly when such treatment may be dangerous and precipitate haemorrhagic transformation of an ischaemic infarct. It would, therefore, be most informative to admit patients as soon as possible after stroke onset, accepting that patients would enter at various times. This would allow us to examine whether the balance of risks and benefits alters with increasing delay of starting treatment after stroke onset in prespecified subgroups (eg 0-3, 3-6, 6-12, 12-24 and 24-48 hours delay after onset).

Contraindications are specified not by the protocol but by the responsible physician.

The fundamental criterion for entry in the study is that the responsible physician is **substantially uncertain** whether or not to use the trial treatments in **that particular patient**. Reasons for not entering patients in the trial by the responsible physician **might** include:

either only a small likelihood of worthwhile benefit, such as:

- symptoms considered likely to resolve **completely** within the **next few hours**
- patient was already dependent on others for everyday activities (to dress, wash, bath, eat, walk or use toilet) **prior to** the onset of the present stroke

or a high risk of adverse effects of treatment, such as:

- known hypersensitivity to aspirin or heparin
- history of currently active peptic ulceration or recent gastrointestinal bleeding
- patient already on long-term oral anticoagulants.

Patients who, at the time of the onset of stroke symptoms, were already on long-term aspirin for some other reason (eg history of possible myocardial infarction many years previously) or who have received a few doses of heparin after hospital admission, but prior to consideration for trial entry, may be eligible for IST, if the responsible physician is **substantially uncertain** whether to stop or to continue such therapy. On the other hand, for example, many physicians may consider that a stroke patient with a history of acute myocardial infarction within the past few days has a clear indication for aspirin or anticoagulant therapy; such a patient would not be eligible for IST.

Any consent required should be sought before randomisation

Patients who have had a stroke are likely to be frightened and upset by their illness. Trial medications may be more effective the sooner they are started, and it may not be considered appropriate to delay the start of treatment by discussing with the patient the various treatment options in prolonged detail. The degree and timing of consent is, therefore, left entirely to individual doctors to decide **for individual patients**, in the light of local requirements and advice from any relevant ethical committees. This may result in a range of practices, ranging from at one extreme, formal written consent, through various degrees of verbal consent to, at the opposite extreme, some mention of the trial intended just to offer patients an easy opportunity to initiate any discussion they may want. An information sheet for patients and carers can be useful (Appendix A). For patients who are drowsy or dysphasic, consent obtained (as above) from the next of kin is appropriate. Written consent may distress some patients, may be a practical impossibility in others, and may not be considered ethical by some physicians.

5. OUTLINE OF PRACTICAL PROCEDURES

IST "log" of all patients with acute stroke admitted to hospital.

All patients admitted to hospital with suspected or confirmed acute stroke should be considered for the trial, and a note made for each in the IST log. Whether the patient was randomised in IST, or if not, the main reason(s) for not randomising (eg not stroke, ≥ 48 hrs, definite intracranial haemorrhage etc.) should be recorded.

ist International Stroke Trial

IST LOG: Hospital name and code number: ____________ ☐☐☐
For **all** patients admitted with suspected acute stroke **either** record if randomised, **or** main reason(s) for not randomising.

				RANDOMISED IN IST		MAIN REASON(S) NOT IN IST					
Patient's initials	Date of birth	Date of admission/ randomisation	Ward	YES	NO	Not stroke	>48 hrs from onset	Intra-cranial haemorrhage	Already on oral anticoagulant	Dependent prior to stroke	Other reason; specify:
______	__/__/__	__/__/__	______	☐	☐	☐	☐	☐	☐	☐	______
______	__/__/__	__/__/__	______	☐	☐	☐	☐	☐	☐	☐	______
______	__/__/__	__/__/__	______	☐	☐	☐	☐	☐	☐	☐	______
______	__/__/__	__/__/__	______	☐	☐	☐	☐	☐	☐	☐	______
______	__/__/__	__/__/__	______	☐	☐	☐	☐	☐	☐	☐	______

Telephone randomisation: use the IST notepads.

No entry form is needed for the IST, and no special tests have to be done. In most countries patients are entered into the trial by means of a telephone call to a 24 hour randomisation service in Oxford - but see the back of the protocol for details. IST randomisation notepads are used to prepare for the questions you will be asked.

The hospital code number is marked on the back of the randomisation pad and on the trial folder. If it is not available, please give the hospital name.

ist
International Stroke Trial

INTERNATIONAL STROKE TRIAL - RANDOMISATION NOTEPAD (UK)

Patients are eligible if:

- **Less than 48 hours since onset of symptoms of acute stroke**
- **No known intracranial haemorrhage**
- **No CLEAR indication for, or CLEAR contraindications to, aspirin or heparin**

To randomise (24 hour service) See back page of protocol for number to call

PLEASE ASSEMBLE THE FOLLOWING INFORMATION BEFORE YOU MAKE THE TELEPHONE CALL:
NB. A patient can be entered ONCE only in IST

COUNTRY _____

HOSPITAL CODE NUMBER ☐☐☐ _____
(see back of pad) (or give hospital name if number not available)

HOURS from symptoms first noted ☐☐ hours (must be 48 hours or less)
(to nearest hour; round half hours up)

CONSCIOUS LEVEL NOW (Tick ✓ one box only)

Fully alert ☐ Drowsy ☐ Unresponsive coma ☐ (If unconscious, the patient **MUST** have a CT scan **BEFORE** randomisation to exclude intracranial haemorrhage)

PATIENT IDENTIFIERS AND OTHER DETAILS

Family name _____

Given names _____

Date of birth Day_____/ Month _____/Year_____

Sex (Male/Female) ☐

	YES	NO or UNCERTAIN (Tick ✓ one box on each line)
Stroke first noted on waking from overnight sleep	☐	☐
Atrial fibrillation present	☐	☐
Received any heparin in previous 24 hours	☐	☐
Received any aspirin in previous 3 days	☐	☐
CT scan performed after stroke onset	☐	☐ If intracranial haemorrhage on CT DO NOT RANDOMISE
Infarct visible on CT	☐	☐
Systolic blood pressure	☐☐☐ mm Hg	

STATUS NOW: (Tick ✓ one box on EACH line)

			YES	NO	CAN'T ASSESS
1	Unilateral weakness (and/or sensory deficit) affecting face	1	☐	☐	☐
2	Unilateral weakness (and/or sensory deficit) affecting arm/hand	2	☐	☐	☐
3	Unilateral weakness (and/or sensory deficit) affecting leg/foot	3	☐	☐	☐
4	Dysphasia	4	☐	☐	☐
5	Homonymous hemianopia	5	☐	☐	☐
6	Visuospatial disorder e.g. sensory inattention	6	☐	☐	☐
7	Brainstem/cerebellar signs	7	☐	☐	☐
8	Other deficit	8	☐	☐	☐

NAME OF DOCTOR RANDOMISING _____ **WARD** _____ **TODAY'S DATE** ☐☐ ☐☐ ☐☐☐☐ (Day Month Year)

PLEASE SEND THIS FORM TO THE IST MEDICAL COORDINATOR IN YOUR HOSPITAL AFTER USE

THE IST MEDICAL COORDINATOR IN YOUR HOSPITAL IS _____

TREATMENT ALLOCATION - START IMMEDIATELY AFTER RANDOMISATION

ASPIRIN ALLOCATION (Tick ✓ ONE box on this line)

☐ **ASPIRIN**
If patient able to swallow, give 300 mg oral aspirin daily for 14 days. If unable to swallow give aspirin for 14 days as:
EITHER one 300mg aspirin tablet, crushed or dissolved via nasogastric tube daily
OR one 300 mg aspirin suppository per rectum daily
OR 100 mg lysine salt of aspirin i.v. in 100 ml saline over 60 minutes daily

☐ **AVOID ASPIRIN**
Stop any prescription for regular aspirin. Avoid aspirin use for 14 days. Use paracetamol if needed for analgesic

HEPARIN ALLOCATION (Tick ✓ ONE box on this line)

☐ **LOW-DOSE HEPARIN**
5,000 units twice daily subcutaneously for 14 days, or to prior discharge

☐ **MEDIUM-DOSE HEPARIN**
12,500 units twice daily subcutaneously for 14 days, or to prior discharge

☐ **AVOID HEPARIN**
Stop any prescription for heparin. Avoid heparin or oral anticoagulants for 14 days

When treatment period ends at 14 days after randomisation (or at discharge/transfer from randomising hospital if sooner), stop any heparin and give daily aspirin for long term secondary prevention if indicated.

ISTUK/R/1

At the end of the telephone call, after all the pre-randomisation details have been provided, the randomisation service gives the aspirin and heparin allocation for that patient. All patients who are given a treatment allocation are then irrevocably in the trial (whether or not they **should** have been entered and whether or not they **actually** receive the allocated trial treatments, since the principal analyses will be "intention-to-treat"[27]). The operator will ask you to record the name of the ward the patient has been admitted to, and the date of randomisation. The operator will then give you the name of the medical coordinator for IST in your hospital; please send the completed form to him/her (this allows the coordinator to check that hospital discharge forms are completed on time).

Trial treatment supplies

The IST does **not** provide special trial drug packs. The drugs should be obtained in the normal way from your hospital pharmacy. The treatment policies are given below, along with the answers to some common questions about how the trial treatments are administered.

When should the treatment policy begin?

Immediately after randomisation. If the allocation is to active aspirin or heparin (or both together), give the first dose immediately. If the patient was prescribed regular aspirin or heparin prior to randomisation but is allocated to 'avoid aspirin' or to 'avoid heparin', ensure that the prescription is discontinued immediately.

How long must the treatment policy continue?

Allocated treatment should continue for two weeks after randomisation, if at all possible. If the patient is discharged home less than two weeks after randomisation, then the trial treatment policy may be discontinued on the day of discharge. If the patient is transferred to another hospital, and it is practicable to continue the trial treatment policy for the full two weeks, this should be arranged. Please ensure that, at two weeks or at hospital discharge (if sooner), ALL patients are considered for long term antiplatelet therapy with aspirin.

ASPIRIN

What dose and formulation of aspirin?

300 mg daily by mouth, preferably in an enteric coated formulation (if available). For patients who develop dyspepsia, the dose may be reduced. If enteric coated tablets are used, the first tablet must be chewed or crushed before giving, to ensure rapid onset of action.

How do you give aspirin if the patient is unable to swallow?

Tablets may be crushed or dissolved and given via a nasogastric tube. If a nasogastric tube is unacceptable or the patient cannot tolerate a tube, 300mg aspirin may be given rectally as a suppository; the bioavailability is satisfactory[28,29]. If neither oral nor rectal aspirin is practicable, an intravenous formulation of aspirin (the lysine salt of acetyl salicylic acid) is available in some countries; 100 mg is the equivalent intravenous dose (de Gaetano, personal communication); it should be dissolved in 100 ml of saline and administered over 60 minutes.

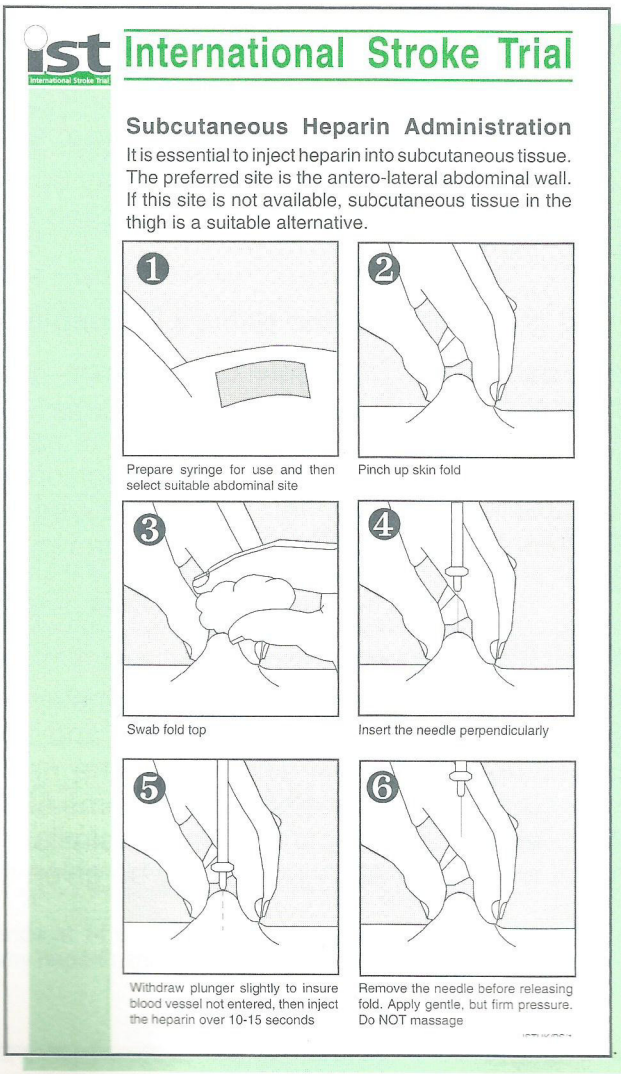
AVOID ASPIRIN

If the patient is allocated to this policy, please ensure that any prescription for regular aspirin is stopped immediately after randomisation and that the patient is not prescribed any aspirin-containing tablets or medicines for the next 14 days, unless a CLEAR clinical indication for such therapy develops at some time AFTER randomisation (eg onset of acute myocardial infarction). Use paracetamol or similar non-aspirin preparation for mild pain. Non-steroidal antinflammatory drugs may be given if clinically indicated (eg for arthritis).

HEPARIN

Use standard unfractionated calcium heparin. Do NOT use low molecular weight heparin or heparinoids. Please use the following technique:

- Withdraw required dose into a 1ml syringe. If the required volume is in excess of 1ml the drug must be given in divided dosage in more than one site. Select site for injection. (Fig 1). (Note: where there is an abdominal incision, heparin may be administered in the outer aspect of the thigh).
- Pick up skin fold. (Fig 2). It is important to take great care to avoid damaging the skin and subcutaneous fat at the site of the injection so that the risk of haematoma formation is minimised.
- Raise the skin fold between thumb and forefinger on the anterior abdominal wall near the iliac crest. Swab skin fold top. (Fig 3).
- Insert the needle perpendicularly (ie at a right angle to the skin). The needle should be a 25 G (1/2" or 1cm long). (Fig 4).
- Withdraw the syringe plunger slightly to ensure that a blood vessel has not been punctured, then make the injection slowly over a period of 10-15 seconds holding the syringe firm and still throughout.(Fig 5).
- When the injection has been made, withdraw the needle at the same angle at which it was inserted. After the needle has been withdrawn, apply **gentle** but **firm** pressure over the area. **Do not massage**. (Fig 6).
- When possible, injection sites should be alternated between right and left side of the anterior abdominal wall. If the abdominal wall is not suitable, the subcutaneous tissue of the thigh is a reasonable alternative.



HEPARIN: low-dose

5,000 units of unfractionated calcium heparin should be given into the subcutaneous fat over the abdomen every 12 hours.

HEPARIN: medium-dose

12,500 units of unfractionated calcium heparin should be given into the subcutaneous fat over the abdomen every 12 hours.

AVOID HEPARIN

If allocated this policy, please ensure that any prescription for regular heparin is stopped immediately after randomisation, and the patient is not prescribed any heparin or other anticoagulant drugs for the next 14 days, unless a CLEAR clinical indication for such therapy develops at some time AFTER randomisation (eg definite deep vein thrombosis with confirmed pulmonary embolism).

What should happen if a CT scan shows intracranial haemorrhage?

If the patient is randomised before a CT scan has been performed, a CT scan must be done as soon as possible thereafter. If this CT excludes intracranial haemorrhage, continue allocated trial treatment policy; if CT shows intracranial haemorrhage, it may be advisable to stop all antithrombotic treatment. Whatever the CT scan shows and whether or not treatment is stopped, the patient is irrevocably in the trial and must be followed up.

Routine non-trial investigation, management and patient monitoring at the discretion of the responsible physician

Unless clear contraindications develop, the trial treatments should be given as specified, and varied only if the responsible physician believes there is a **definite** need to do so. Routine monitoring of the coagulation profile and platelet count in patients allocated heparin is not required for the purposes of the trial; physicians are free to undertake such monitoring if they feel it is clinically indicated. All other aspects of patient management and monitoring are entirely at the discretion of the patient's own doctor. Patients are managed in whatever way appears best for them, with **no** special treatments, **no** special investigations, and **no** delay of discharge. If desired, the patient's family doctor can be written to (perhaps by using, or modifying the standard letter in Appendix B: copies of this are supplied in the IST trial folders).

No extra follow-up

The information routinely recorded in the normal clinical notes (with no special extra records or investigations) should be sufficient for completion of the one-page discharge form (Appendix C). This simple list of questions is to be completed just once for each patient after 14 days, discharge, or death, whichever occurs first. Please return the top copy using the pre-addressed envelopes supplied. The discharge forms (supplied in the IST trial folders) are printed on duplicating paper so that completion of the top copy for the coordinating centre automatically produces a copy for the hospital records.

The arrangements for further follow-up of patients in IST after 14 days vary from country to country. In many countries, this will be undertaken by the National Coordinator, who will contact patients known to be alive at six months and assess their functional outcome by means of a simple questionnaire (Appendix D) which can be administered by either postal questionnaire or by telephone interview; both methods have been validated against a 'gold standard' (a face-to-face interview by a trained assessor administering the Oxford Handicap Score and the Barthel Scale)[30]. In a few countries, follow-up at six months is undertaken by the randomising clinician. Details of the follow-up method to be used in your country are given on the back cover of the protocol.

6. ANALYSIS

Main analyses

The main comparisons will be of:

1. **Death during the first two weeks** and **poor long-term outcome.** (i.e. at about six months, the patient is **either** dead **or** alive but needing help in everyday activities: to wash, bathe, dress, feed or walk) between:

i) all those allocated 'aspirin' versus all those allocated 'avoid aspirin'.

ii) all those allocated 'heparin' (to either low-dose or to medium-dose heparin) versus all those allocated 'avoid heparin'.

The most important subsidiary analyses of two-week mortality and poor long-term outcome involve:

i) a comparison of all those allocated 'medium-dose heparin' with all those allocated 'low-dose heparin' with all those allocated 'avoid heparin'.

ii) a comparison of all those allocated 'aspirin' with all those allocated 'avoid aspirin', subdivided by prior aspirin use recorded at randomisation.

iii) a comparison of all those allocated 'heparin' versus all those allocated 'avoid heparin', subdivided by prior heparin use recorded at randomisation.

iv) a comparison of the effects of antithrombotic therapy, subdivided by the timing of the first CT scan (before randomisation, after randomisation, and no CT performed at all).

v) a comparison of all those allocated 'aspirin' with all those allocated 'avoid aspirin', subdivided by the number of hours between onset and randomisation: 0-3, 3-6, 6-12, 12-24, 24-48 hours.

vi) a comparison of all those allocated 'heparin' with all those allocated 'avoid heparin', subdivided by the number of hours between onset and randomisation: 0-3, 3-6, 6-12, 12-24, 24-48 hours.

vii) assessment of whether the group allocated the combination of aspirin with heparin had an outcome that was significantly different from what might have been expected from the separate effects of the two agents.

Other aspects of functional outcome will be examined by similar comparisons of: the proportion of patients who, at about six months, are alive and consider that they have made a complete recovery from their stroke; the proportion of patients who, at about six months, are alive and living in their own home. Various analyses to assess the safety of treatment will be undertaken with particular attention to any serious bleeding complications thought likely to be due to trial treatment during the first two weeks; any deaths within two weeks attributed to confirmed intracranial haemorrhage and any confirmed intracranial haemorrhages with symptom onset within two weeks associated with subsequent poor outcome (see above).

In addition, many other exploratory analyses will be performed and presented, often for descriptive purposes, with due allowance for their exploratory nature. Appropriate analyses to determine whether treatment is particularly beneficial or particularly hazardous in certain clinically-defined categories of patient will also be reported, for example in patients suspected of having large cerebral vessel occlusion and in patients with suspected small vessel occlusion (lacunar infarction); in patients aged 75 and over and in patients aged less than 75; in patients in coma and in those who are drowsy or alert; patients with and without certain features at the time of randomisation (eg atrial fibrillation, visible infarction on CT scan, severe systolic hypertension etc.).

Interim analyses: the data monitoring committee

During the period of recruitment into the study, interim analyses of in-hospital mortality and of any other information that is available on major outcome events (including serious adverse events believed to be due to treatment) will be supplied, in strict confidence, to the chairman of the data monitoring committee, along with any other analyses that the committee may request. In the light of these analyses, the data monitoring committee will advise the chairman of the steering committee if, in their view, the randomised comparisons in IST have provided **both** (i) "proof beyond reasonable doubt"* that for all, or for some, specific types of patient, one particular treatment is clearly indicated or clearly contraindicated in terms of a net difference in mortality, **and** (ii) evidence that might reasonably be expected to influence materially the patient management of the many clinicians who are already aware of the results of the other main trials. The steering committee can then decide whether to modify intake to the study (or to seek extra data). Unless this happens, however, the steering committee, the collaborators, and the central administrative staff (except those who produce the confidential analyses) will remain ignorant of the interim results.

Collaborators, and all others associated with the study, may write through the IST office, Edinburgh to the chairman of the data monitoring committee, drawing attention to any worries they may have about the possibility of particular side-effects, or about particular categories of patient requiring special consideration, or about any other matters that may be relevant.

Planned analyses if IST randomises 20,000 patients

As an example of the appropriate way of analysing a factorial study, just the planned analyses of the effects of aspirin are described: the analyses of heparin would be similar.

	10,000 allocated ASPIRIN		10,000 allocated AVOID ASPIRIN	Apparent mortality reduction (Aspirin vs. Avoid aspirin)
Row 1	A 2500 ASPIRIN & MEDIUM-DOSE HEPARIN	vs.	B 2500 MEDIUM-DOSE HEPARIN	D_1 = Difference in deaths (group B - group A)
Row 2	C 2500 ASPIRIN & LOW-DOSE HEPARIN	vs.	D 2500 LOW-DOSE HEPARIN	D_2 = Difference in deaths (group D - group C)
Row 3	E 5000 ASPIRIN	vs.	F 5000 NIL	D_3 = Difference in deaths (group F - group E)

ASPIRIN versus AVOID ASPIRIN: grand total of mortality difference = $D_1 + D_2 + D_3$

* Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but some members of the committee have expressed sympathy with the view that a difference of at least 3 standard deviations in an interim analysis of a major outcome event may be needed to justify halting, or modifying, such a study prematurely. If this criterion were to be adopted, it would have the practical advantage that the exact number of interim analyses would be of little importance, and so no fixed schedule is proposed[27].

If aspirin did nothing to mortality in **any** row then D1 would differ only randomly from zero, so would D_2 and so would D_3. When three things which differ only randomly from zero are added up, then their total will differ only randomly from zero. Conversely, if the grand total is much more positive than could be ascribed to the play of chance this disproves the idea that aspirin does not reduce mortality at all. The grand total of D_1, D_2 and D_3 involves data from all patients, so examination of it provides as sensitive a test of whether aspirin saves lives as would a direct analysis of a single trial among 20,000 patients (and, this test does not involve any unjustified comparisons between patients in one row and patients in another row*).

7. ORGANISATION

Responsibilities of the medical coordinator in each hospital (after local ethical committee approval has been obtained)

(1) *To ensure that all medical and nursing staff involved in the care of patients with acute stroke are reasonably well informed about the study.* This involves explaining the IST protocol to medical and nursing staff (and, perhaps, to some of those in the emergency room), displaying the wall-chart in several imaginatively chosen places where it is likely to be read, and distributing the regular newsletters and the plastic protocol summaries (which can be carried in the pockets of the medical and nursing staff).

(2) *To seek the collaboration of the hospital CT scanning staff*. To inform them of the study and of the importance of early CT scanning. Active involvement of all members of the CT scanning department is essential; good communication between medical staff, radiologists and radiographers will lead to optimal use of the CT service. This is more likely to be achieved if the CT staff understand, and are involved in, the trial. Medical staff can help CT staff in a number of ways by proper completion of X-ray forms, by giving advance warning of patients who require urgent CT, or who are very ill; ill patients should be sent to the CT scan on a trolley.

(3) *To check the IST log routinely* to ensure that virtually all patients admitted with suspected or definite acute ischaemic stroke do get considered for the trial, and that virtually all patients who are eligible, and willing to participate, do get randomised.

(4) *To make sure that the single-sided discharge forms are completed reasonably promptly* (eg within a month or so of discharge or death in hospital; or, if not, to ensure that they are completed reasonably soon after the reminder to do so arrives).

Responsibilities of the nursing coordinator in each hospital

(1) *To ensure that an IST log is kept of all patients admitted to the hospital for suspected or definite acute ischaemic stroke*, with a note that **either** the patient was entered in IST **or** the main reason(s) for not randomising.

(2) *To ensure that nurses remind medical staff to consider randomising all patients with suspected or definite acute ischaemic stroke into IST.* **Such reminders are of enormous importance**: with them the study will succeed, and will provide reliable evidence about the value of such treatments both for high-risk and for low-risk patients.

(3) *To ensure that the nursing staff remember to give all IST trial treatments* (unless some contraindication develops).

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* The argument remains completely valid even though the sizes of any effects of aspirin on mortality may be somewhat different in different rows, for D_1 involves only the comparison of like with like, so does D_2, and so does D_3. There are no inappropriate direct comparisons of patients in one row with patients in another. This method of analysis of a factorial trial is sometimes referred to as "retrospective stratification"; analogous methods can be used to provide analyses (either of simple two-way trials or of factorial trials) that are retrospectively stratified for age, sex, country, hospital, various patient characteristics, and so on[27]. Although in principle such analyses are preferable, in practice for a trial as large as IST they will give results that are virtually identical to those produced by a simple unstratified analysis (see, for example, the ISIS-2 results[14]).

Responsibilities of the national coordinators

(1) *To maximise collaboration*, and to arrange occasional meetings of collaborators so that any problems or questions can be dealt with.

(2) *To provide both medical and nursing coordinators with information* about the study's progress and to deal with most of the problems and questions that might arise.

(3) *To represent the collaborators' views at the steering committee meetings.*

(4) *To undertake the final six-month follow-up of all randomised patients* to determine whether the patient has died (and the cause of death) and, if alive at six months whether the patient has recovered fully and if he or she needs help in everyday activities. This can be done very cost-effectively (by telephone call or postal questionnaire from the national coordinator's office). **This is very important:** it reduces the work for physicians and nurses in the participating hospital and ensures widespread collaboration. It also ensures that assessment of outcome is performed 'blind' to allocated treatment. N.B. This arrangement does not apply in all countries. See back cover of protocol for the method of final follow-up in your country.

Central coordination: supply of all trial printed materials, data collection and analysis

The IST office in Edinburgh is responsible for providing the printed IST materials (forms, protocols, wall charts etc.). These will be supplied, to each collaborating centre, after any relevant ethics committee approval has been obtained. Patient entry in a hospital can start immediately thereafter. Additional supplies of any printed material can be obtained on request. The IST office is responsible, in collaboration with the national coordinators, for collection of data (including reports of serious adverse events thought to be due to trial treatment) and for data analyses. The IST office also provides an on-call service for any clinical questions about the trial. The Clinical Trial Service Unit in Oxford provides the 24 hour randomisation.

Finance and non-negligent liability

The costs of the IST office, and some of the costs of transnational coordination between European countries, are provided by the UK Medical Research Council (MRC), the European Community and the Clinical Trial Service Unit (Oxford). Funding of some of the preparatory work of the trial has been received from the UK MRC, the UK Stroke Association, Lilly Industries, Sterling Winthrop (USA), Bayer (UK), Sanofi (France), the European Aspirin Foundation and Edinburgh University. The general structure of the study was, however, designed independently of the pharmaceutical companies, who have no representation in its organisation and who will, like the steering committee, remain blind to the results as they accumulate. This arrangement is intended to ensure that no suggestion of lack of objectivity of the findings can be justified. The IST offers no financial support to the collaborating hospitals, other than reimbursement of any minor costs.

The treatments being tested in this study are not new or patentable; indeed no particular formulation or preparation of either agent is specified. Aspirin and heparin are already widely used - albeit haphazardly- by clinicians caring for patients with acute stroke, and such use, in normal clinical practice, is not accompanied by any specific or unusual indemnity arrangements. Provided that: a) local ethical approval is obtained for the study; b) there is no importantly relevant departure from compliance with the protocol, there need be no special or unusual indemnity applied to the use of these agents - in a more systematic way than in normal clinical practice - within the context of this study.

APPENDIX A:

Example of possible consent/information sheet (if required)

As already noted, in the setting of an acute stroke - when patients are likely to be frightened, confused or in coma, and when any appreciable delay may cause some extra deaths - it may not always be considered appropriate to discuss at much length the various options for treatment. In IST therefore, the degree and timing of consent is left entirely to individual doctors to decide for individual patients, in the light of local requirements and advice from any relevant ethics committees. Where some written information is considered useful, the following example (adapted as locally appropriate) may help:

Information sheet to be read by, or to, patient or relative
(and, if so desired, left with the patient or relative afterwards)

ist
International Stroke Trial

INVITATION TO JOIN A STUDY OF STROKE TREATMENT

We would like to explain some of the research we are doing and then ask if you would help with it. Every day, all over the country, many people like you come into hospital who have just had - or nearly had - a stroke. Most strokes are caused by a blood clot blocking a blood vessel that carries blood to one part of the brain. Early treatment to prevent more clots forming could be effective, and improve your chances of recovery, but there could be some risks from side effects such as bleeding. We - and the doctors and nurses in the hundreds of other hospitals involved in this study - hope that these clot preventing treatments will be useful, but we need the help of many thousands of patients like you to find out whether or not they really are. If you decide to take part, then in addition to any standard treatments you need, you may be given small injections of heparin which may prevent clots forming . You may also be given a tablet containing a small dose of aspirin, which could also help prevent clots forming.

The study would not involve complicated tests; we would just send the important details of your progress in hospital to the study centre in Edinburgh, Scotland. The study centre will contact you by post or telephone about six months from now to find out how you are. This information would be used in confidence for medical research purposes only.

Whether or not you are in the study, you will, of course, always be given any treatments that seem definitely good for you - and, if you wanted to withdraw from the study at any time, then you would be free to do so.

If you have any questions before you decide whether to take part or not, then please feel free to ask them.

ISTUK/IL/1

Copies of this consent/information sheet are supplied to all collaborating hospitals in the IST trial folders. Further copies will be sent on request to collaborating hospitals by the national co-ordinating centre.

APPENDIX B:

Example of a letter that can be used (if required) to inform the family doctor of their patient's involvement in IST.

IST study of antithrombotic treatment for acute ischaemic stroke, involving two weeks treatment with oral aspirin, subcutaneous heparin, both or neither

Date: ...../...../.....
Hospital name: .....
Telephone no .....

Dear Colleague

Re:.....
.....
(patient's name, date of birth and address)

Your patient was recently admitted to this hospital with a stroke, and is taking part in a randomised controlled study of the treatment of acute cerebral infarction (the International Stroke Trial). This study of two simple, promising treatments (oral aspirin and subcutaneous heparin) is being conducted in several hundred hospitals worldwide. The hope is, as with the studies in acute **myocardial** infarction, such as ISIS-2, which clearly showed the benefits of antiplatelet and fibrinolytic therapy (Lancet 1988; ii: 349), that it will help us find out how best to treat patients with acute **cerebral** infarction.

Patients entering this study are randomised, and may or may not have received two weeks aspirin, and may or may not have received two weeks subcutaneous heparin injections.

After the two week trial period is completed and/or the patient is discharged from hospital, all aspects of management (treatment of hypertension, high blood cholesterol and other risk factors) are at your discretion. In general, most patients will (unless there is some clear contraindication to its use) benefit from the use of long term low-to-medium dose aspirin to prevent recurrent stroke and other serious vascular events.

The central trial coordinating office will, about six months after the stroke, need to find out about your patient's condition. In order to avoid any distress by attempting to contact families of patients who have died, the trial office may contact you (or your surgery) briefly to confirm that the patient is still, to the best of your knowledge, alive. If the patient is alive the trial office will then contact the patient (or their family or carer) directly by telephone or postal questionnaire. This is an important aspect of the study to determine whether early antithrombotic therapy for stroke can reduce long term disability (and improve quality of life) in stroke survivors.

Should you have any questions about the study, then please feel free to contact me via the hospital switchboard (see above).

Many thanks for your assistance.

Yours sincerely

Signature: .....

Printed Name:.....

ISTUK/GPL/1

Copies of this letter are supplied to all collaborating hospitals in the IST trial folders. Further copies will be sent on request by the national coordinating centre.

APPENDIX C:

Discharge form. Copies of this form, printed on duplicating paper that automatically provides a copy for the patient's clinical notes, are supplied in the IST trial folders. Further copies will be sent to collaborating hospitals by the IST office as they are required, or on request.

INTERNATIONAL STROKE TRIAL - DISCHARGE FORM UK

Please complete form 14 days after randomisation (or at death, discharge/transfer from randomising hospital if sooner)

IDENTIFIERS (Please PRINT and give complete details to help locate patients at six months)

Hospital code no. & name: ☐☐☐ _____

Patient's family name: _____

& all given names: _____

Date of birth: day_____/month_____/year_____

Patient's Telephone No.: (_____) _____

Address: House No. & Street _____

District: _____

Town: _____

Country (& post code): _____

GP Name & address: _____

_____

_____

GP telephone No.: (_____) _____

office use ☐☐ ☐☐☐ ☐☐☐☐☐

OR patient sticker can be used to provide some details (but please write in any other details not shown on sticker)

DATE OF RANDOMISATION: Day_____Month_____/Year_____

ASPIRIN (Please tick ✓ one box on EACH line, whether or not allocated aspirin)

YES	NO	
☐	☐	Given for14 days (or until death, discharge/transfer if sooner). Ignore one or two missed doses
☐	☐	Discharged on long term aspirin or other antiplatelet therapy

LOW-DOSE SUBCUTANEOUS HEPARIN (Please tick ✓ one box on EACH line, whether or not allocated low-dose sc heparin)

YES	NO	
☐	☐	Given for 14 days (or until death, discharge/transfer if sooner). Ignore one or two missed doses

MEDIUM-DOSE SUBCUTANEOUS HEPARIN (Please tick ✓ one box on EACH line, whether or not allocated medium-dose sc heparin)

YES	NO	
☐	☐	Given for 14 days (or until death, discharge/transfer if sooner). Ignore one or two missed doses

NON-TRIAL TREATMENTS FOR STROKE IN RANDOMISING HOSPITAL (Please tick ✓ one YES/NO box for EACH treatment)

YES	NO		YES	NO	
☐	☐	Non-trial aspirin or other antiplatelet	☐	☐	High-dose steroids (e.g. dexamethasone)
☐	☐	Non-trial subcutaneous heparin	☐	☐	Calcium antagonists
☐	☐	Intravenous heparin	☐	☐	Haemodilution
☐	☐	Oral anticoagulants	☐	☐	Glycerol
☐	☐	Thrombolysis	☐	☐	Carotid endarterectomy

NOW COMPLETE NEXT COLUMN

POSSIBLE SIDE-EFFECTS OF TRIAL TREATMENTS (Please tick ✓ one box on EACH line and give date of FIRST event)

YES	NO	Day/Month/Year	
☐	☐	__/__/__	Major non-cerebral haemorrhage (ie fatal or requiring transfusion); specify: _____
☐	☐	__/__/__	Other side effects; specify: _____

FINAL DIAGNOSIS OF INITIAL (RANDOMISING) EVENT (Please tick ✓ ONE box on EACH line)

office use ☐☐ ☐☐ ☐☐ ☐☐ ☐☐ ☐☐

YES	NO	
☐	☐	Definite or probable ischaemic stroke (CT/ autopsy excludes haemorrhage)
☐	☐	Definite or probable haemorrhagic stroke (CT/ autopsy confirmed)
☐	☐	Definite stroke, type uncertain (no CT or autopsy performed)
☐	☐	Initial event was not a stroke. Specify diagnosis (eg cerebral tumour) _____

MAIN EVENTS (FATAL OR NOT) WITHIN 14 DAYS OF RANDOMISATION (or before death,first discharge /transfer if sooner)

(Please tick ✓ one box on EACH line and give date any **FIRST** event occurred)

office use ☐☐ ☐☐ ☐☐ ☐☐ ☐☐ ☐☐

YES	NO	Day/Month/Year	
☐	☐	__/__/__	Recurrent stroke; definitely or probably ischaemic (CT or autopsy excludes haemorrhage)
☐	☐	__/__/__	Recurrent stroke; definitely or probably haemorrhagic (CT or autopsy confirmed)
☐	☐	__/__/__	Recurrent stroke; type not known (no CT or autopsy)
☐	☐	__/__/__	Pulmonary embolism confirmed by lung scan,angiogram or autopsy
☐	☐	__/__/__	**First discharge/transfer alive** from randomising hospital to (tick ✓ ONE box only):

☐ Own home ☐ Relatives home ☐ Residential care ☐ Nursing home ☐ Other hospital

☐ ☐ __/__/__ **Death in hospital** and likely **primary** cause (tick ✓ only ONE box)

☐ Neurological damage from initial stroke	☐ Coronary heart disease
☐ Recurrent stroke: ischaemic or unknown	☐ Pulmonary embolism
☐ Recurrent stroke: haemorrhage	☐ Other vascular (or unknown); specify: _____
☐ Pneumonia	☐ Non-vascular; specify: _____

PERSON COMPLETING FORM (PLEASE PRINT) _____ **Date** _____/_____/_____ ***Thank you***

Please check that one YES/NO box has been ticked on EACH line and check that the DATES of events are reported and then return form to:
IST, Neurosciences Trials Unit, Western General Hospital, Edinburgh EH4 2XU, SCOTLAND (or Fax (44) 31 332 5150)

ISTUK/D/1

APPENDIX D:

Example of a final follow-up form to be completed at six months: this will, in most countries, be completed by the National Coordinator. It assesses disability and handicap. This method has been validated against the Barthel Scale and the Oxford Handicap Scale, and can be administered by telephone (or, in a modified form, by postal questionnaire)[30]. The National Coordinator will usually contact the patient directly, but see back cover of the protocol for the arrangement for follow-up in your country.

ist
International Stroke Trial

INTERNATIONAL STROKE TRIAL - SIX MONTH FOLLOW-UP FORM (UK)

office use ☐☐ ☐☐☐ ☐☐☐☐☐

National Coordinator: Please complete this form at six months after randomisation (or when the patient dies if sooner) for all randomised patients, whether or not they received allocated treatment and **EVEN IF** the final diagnosis of the initial event leading to randomisation is not stroke.

Randomising hospital name: _____ Hospital code no. ☐☐☐

Patient's family name: _____

And all given names: _____

Date of birth: day_____/month_____/year_____

Follow-up method: (Tick ✓ one box only)

Telephone Questionnaire ☐ Postal Questionnaire ☐
If YES to either, please attach questionnaire to this form

Clinic visit ☐
Other ☐
specify: _____

IS THE PATIENT DEAD OR ALIVE?

DEAD ☐ ALIVE ☐ NOT KNOWN ☐ If NOT KNOWN, date LAST KNOWN TO BE ALIVE: day_____/month_____/year_____

If DEAD, date of death; day_____/month_____/year_____

and likely PRIMARY cause if known (tick ✓ only ONE box)

- ☐ Neurological damage from initial stroke
- ☐ Recurrent stroke (ischaemic or unknown)
- ☐ Recurrent stroke (haemorrhagic)
- ☐ Pneumonia
- ☐ Coronary heart disease
- ☐ Pulmonary embolism
- ☐ Other vascular or unknown; specify: _____
- ☐ Non-vascular; specify: _____

CT scans etc)

IF ALIVE AT SIX MONTHS (Tick ✓ ONE box on **EACH** line)

YES	NO	
☐	☐	The patient considers he/she has made a **COMPLETE** recovery from the stroke
☐	☐	The patient has needed help from another person to perform everyday activities within the last two weeks (eg bathing or feeding or walking or dressing or use of the toilet)

USUAL RESIDENCE AT SIX MONTHS (Please tick ✓ one box only)

☐ own home ☐ relatives home ☐ residential home ☐ nursing home ☐ other hospital

CURRENT MEDICATION (Tick ✓ ONE box on **EACH** line)

YES	NO	
☐	☐	Antiplatelet therapy
☐	☐	Oral anticoagulants

PERSON COMPLETING FORM (PLEASE PRINT) _____ **Date of follow-up** _____/_____/_____

Thank you

Please return the top copy of this form by post to the IST Office, Neurosciences Trials Unit, Western General Hospital, Edinburgh EH4 2XU by post, or by Fax -44 -31-332-5150

ISTUK/FU/1

APPENDIX E:

Card to notify IST national coordinator of any deaths which occur AFTER the IST discharge form has been completed, but LESS than SIX months after randomisation.

Among patients randomised in the IST, about ten percent can be expected to die within two weeks of randomisation; any such deaths which occur in the randomising hospital should be recorded on the discharge form (Appendix C), which is completed at 14 days after randomisation or at discharge/transfer if sooner.

We would be very grateful if you could complete and return this card for any patient who you discover has died **AFTER** the discharge form was completed (and returned), but **LESS THAN** six months after randomisation. This will a) enable the accumulating mortality data to be kept up-to-date and thus improve the monitoring of the safety and efficacy of treatment, b) simplify follow-up procedures for your national coordinator and for the IST office in Edinburgh

IST International Stroke Trial office use ☐☐ ☐☐☐ ☐☐☐☐☐

Please complete and return this card for any patients who dies **AFTER** you have completed (and returned) the IST discharge form but **LESS THAN** six months after randomisation. To maintain confidentiality, please put this card in one of the pre-addressed envelopes provided in the IST trial packs. No Stamp is required.

Patient's family name: _____

All given names: _____

Date of Birth: day _____ /month _____ /year _____

Randomised in IST at Hospital: code number ☐☐☐ (name of hospital) _____

Date randomised: day _____ /month _____ /year _____

Date of death: day _____ /month _____ /year _____

Cause of death: _____

Return to the IST National Coordinator in the pre-addressed envelope supplied in the IST trial pack *THANK YOU*

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For 24-hour randomisation, telephone 0865-240972

Acute Stroke?

CONSIDER FOR:

If not randomised, record main reason in IST log

IST International Stroke Trial

Eligibility

- **All patients, mild, moderate or severe deficit, with acute stroke,** unless previously entered in IST.
- **≤ 48 hours since onset of symptoms first noticed** (NB Randomise as promptly as possible: if not eligible immediately on admission, reassess a **few** hours later).
- **No known intracranial haemorrhage**
  CT scanning to exclude haemorrhage before randomisation is **strongly recommended**. If the patient is comatose, CT scanning is **mandatory**. If a CT scan is not immediately available and the clinician considers intracranial haemorrhage unlikely then randomise and perform a CT scan **as soon as possible** thereafter.
- **Doctor's opinion - no CLEAR indication for: aspirin or subcutaneous heparin**
  (NB patients who are already on long term aspirin or who have had a few doses of heparin can still be randomised).
- **Doctor's opinion - no CLEAR contraindications to: aspirin or subcutaneous heparin**
  Reasons for not entering patients in the trial are specified not by the protocol, but by the responsible physician, and **might** include:
  - **either** only a small likelihood of worthwhile benefit
    - symptoms considered likely to resolve **completely** within the **next few hours**
    - patient dependent on others for everyday activities (to dress, wash, bathe, eat, walk, or use toilet) prior to the onset of the present stroke
  - **or** a high risk of adverse effects of treatment, such as:
    - known hypersensitivity to aspirin or heparin
    - history of **currently** active peptic ulceration **or recent** gastrointestinal bleeding
    - patient already on longterm oral anticoagulants

Telephone randomisation

- Any consent required for IST should have been sought.
- Prepare for telephone questions using the randomisation notepad.
- Ring 24 hour randomisation service **0865-240972**.
- When questions on randomisation pad have all been answered, a treatment allocation will be given for: 'aspirin' or 'avoid aspirin' and 'low-dose heparin' or 'medium-dose heparin' or 'avoid heparin'.
- Send top page of note pad to your hospital's IST medical coordinator.

Treatment

- **Aspirin allocations**

  Aspirin: if able to swallow, give 300 mg aspirin by mouth daily for 14 days (or until discharge home/transfer to another hospital if sooner). If unable to swallow give: EITHER one 300 mg aspirin tablet, crushed or dissolved via nasogastric tube daily; OR one 300 mg aspirin suppository per rectum daily; OR 100 mg of the lysine salt of aspirin intravenously, dissolved in 100 ml saline, administered over 60 minutes daily, for 14 days (or until discharge home/transfer to another hospital if sooner).
  Avoid aspirin: stop any prescription for regular aspirin. Avoid aspirin for 14 days. Use paracetamol if required for analgesia.

- **Heparin allocations**

  Low-dose heparin: 5,000 units unfractionated calcium heparin twice daily subcutaneously for 14 days (or until discharge home/transfer to another hospital if sooner).
  Medium-dose heparin: 12,500 units unfractionated calcium heparin twice daily subcutaneously for 14 days (or until discharge home/transfer to another hospital if sooner)
  Avoid heparin: stop any prescription for regular heparin. Avoid heparin and other anticoagulants for 14 days.

- All other management as considered appropriate by the responsible physicians **with no extra tests or special monitoring**.

Complete discharge form

- At 14 days, discharge home, transfer to another hospital or death (whichever occurs first). Complete the single-sided discharge form from the case notes, and return it to the IST office, Edinburgh.

Final Follow-up

- Final follow-up data at six months will be obtained by the IST office contacting the patient directly. If you discover that a patient has died after you have completed (and returned) the discharge form, please inform the IST office, using one of the cards provided.

For 24 hour randomisation telephone 0865-240972

IST Hospital Medical Coordinator:

IST Hospital Nursing Coordinator: