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Obtaining Regulatory Approval for Multicentre Randomised Controlled Trials:

Experiences in the STICH II trial.

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Abstract

Background and Purpose

Centres wishing to participate in international multicentre randomised controlled surgical trials such as STICH II (Surgical Trial in Lobar Intracerebral Haemorrhage) have to go through a number of regulatory hurdles. These depend on the nature of the study. In surgical studies there is a need to obtain ethical approval and individual hospital approval including fully executing contracts between the host organisation and each institution. Firsthand experience has been gained in STICH II by guiding over eighty hospitals through this process in over twenty different countries worldwide.

Methods

This paper examines the administrative challenges of setting up the STICH II trial which include the time that it has taken for each hospital to obtain ethical approval, sign the study agreement and become a fully registered site. The aim of this paper is to inform potential triallists planning multinational surgical trials about the potential delays and difficulties that may be encountered in the hope that it will encourage the medical research community to simplify administrative systems. We also hope to influence trial funders to build in 'start up periods' for new studies so that they can get up and running in a realistic time frame. The difficulties which were faced will be highlighted so that the organisers of other randomised controlled surgical trials can be aware of these delays.

Conclusion

From the experiences in this trial, it can be concluded that delays will be experienced in obtaining ethical approval and in agreeing on site contracts.

Obtaining Regulatory Approval for Multicentre Randomised Controlled Trials:

Experiences in the STICH II trial.

Background

Randomised controlled trials are designed to establish whether various treatments are clinically efficacious. The sample size for a trial is chosen to provide sufficient power to test the hypothesis. Usually the size of the sample is such that it is not possible to recruit all the patients from one centre within a realistic time period. It is therefore necessary to undertake a multicentre randomised controlled trial in these circumstances. If possible, such trials are often restricted to one country. The advantages of this include funding, unified regulatory issues, good communication between hospitals, ease of site visits, no translating errors and no language barriers or time differences. However, sometimes it can still take too long to recruit sufficient patients, and there is also a danger that the outcome of the trial can be considered biased to patients in one geographical region. It is sometimes therefore necessary to undertake an international multicentre study.

Centres wishing to participate in international multicentre randomised controlled surgical trials such as STICH II (Surgical Trial in Lobar Intracerebral Haemorrhage) have to go through a number of regulatory hurdles. These depend on the nature of the study. In drug studies they will include obtaining competent authority or equivalent approval in each country. Even in surgical studies there is a need to obtain ethical approval and individual hospital approval including fully executing contracts between the host organisation and each institution. Firsthand experience has been gained in STICH II by guiding over eighty hospitals through this process in over twenty different countries worldwide. STICH II is an ongoing international multicentre randomised parallel group trial comparing early craniotomy to evacuate the haematoma with initial conservative treatment. Patients for whom the treating neurosurgeon is in equipoise about the benefits of early craniotomy are eligible for the trial. The objectives of the STICH II study are to establish whether a policy of earlier

surgical evacuation of haematomas in selected patients with spontaneous lobar ICH will improve outcome compared to a policy of initial conservative treatment.¹ The trial will also help to better define the indications for early surgery. This will overcome two of the criticisms of the original STICH trial which were: timing was too late and sometimes location was too deep.²

This paper examines the administrative challenges of setting up the STICH II trial which include the time that it has taken for each hospital to obtain ethical approval, sign the study agreement and become a fully registered site. The aim of this paper is to inform potential triallists planning multinational surgical trials about the potential delays and difficulties that may be encountered in the hope that it will encourage the medical research community to simplify administrative systems. We also hope to influence trial funders to build in 'start up periods' for new studies so that they can get up and running in a realistic time frame. The difficulties which were faced will be highlighted so that the organisers of other randomised controlled surgical trials can be aware of these delays.

Results

Table 1 below contains a list of countries and how many centres we have participating in STICH II in each of those countries. The complete registration process for STICH II, including completing an application form, obtaining ethical approval, agreeing on the contract and the site becoming registered has been split into separate parts. The first part measured was the time it took from receiving the application form to a centre obtaining ethical approval. Also measured was the time from obtaining ethical approval to signing and returning the STICH II site agreement. This then allowed an average for each country to be ascertained (shown in Figure 1). Also available in table1 are the minimum and maximum number of days that it took a country to complete the entire registration process for the STICH II study. Please note that it states zero days for Pakistan for obtaining ethics. This is because their application form and ethical approval arrived on the same day.

Table 1

Break down of registration process.

Country	Number of Sites	Average number of days from receiving application form to obtaining ethics	Average number of days from receiving ethics to becoming registered	Average number of days for centre to complete full registration process	Minimum number of days for country to complete full registration process	Maximum number of days for country to complete full registration process
Armenia	1	58	57	115	115	115
Australia	1	148	229	377	377	377
Austria	1	172	110	282	282	282
Canada	1	383	9	392	392	392
China	1	120	36	156	156	156
Czech Republic	4	85	126	210	142	361
Egypt	1	60	149	209	209	209
Georgia	1	62	161	223	223	223
Germany	17	175	153	320	67	1504
Greece	3	131	53	183	31	237
Hungary	2	77	137	214	140	287
India	8	97	86	184	44	325
Israel	1	98	123	221	221	221
Italy	1	131	26	157	157	157
Latvia	2	58	53	111	51	170
Lithuania	1	48	21	69	69	69
Macedonia	1	103	93	196	196	196
Mexico	2	214	59	273	267	278
Nepal	1	54	49	103	103	103
Norway	1	161	158	319	319	319
Pakistan	1	0	58	58	58	58
Poland	2	99	117	216	116	315
Romania	1	53	56	109	109	109
Russia	1	40	91	131	131	131
Saudi Arabia	1	260	95	355	355	355
Spain	4	127	163	290	172	535
The Netherlands	1	475	185	660	660	660
Turkey	1	85	85	170	170	170
UK	16	197	150	347	79	884
USA	9	194	147	341	111	513

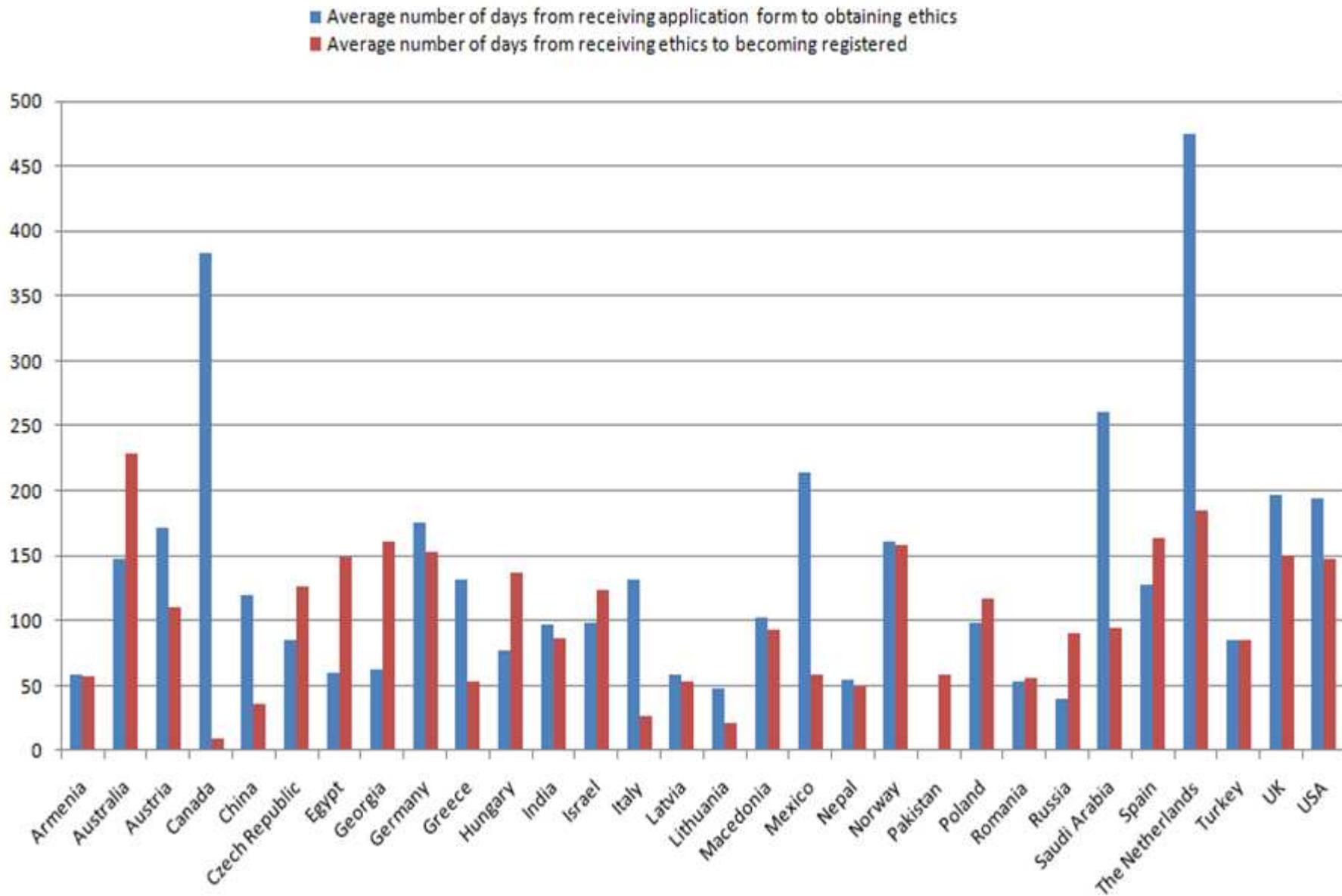


Figure 1

Graph comparing time to obtain ethical approval and time to complete contract signing.

Discussion

Obtaining Ethics Approval

As can be seen from table 1, there is a wide variation between countries in the time taken to obtain ethical approval. These differences have occurred for a variety of reasons. It is important to note that STICH II is not a pharmaceutical study. No devices are used and the two treatments under test are already practiced routinely. The protocol describes the randomisation process and the data collection requirements. The only additional procedure required is one extra CT done at 5 days and this is standard practice in most hospitals anyway. Many centres have misunderstood these aspects of the trial design and therefore ethical approval has taken longer to obtain whilst explaining this issue.

The process of obtaining ethical approval is not standardised between countries or even within a country; this also causes great variation in the time it takes for hospitals to obtain approval. This is despite the 'Harmonisation' process agreed in Helsinki.³ Also, the frequency of ethical committee meetings can cause serious delays in approval being granted; some committees meet monthly, some quarterly and others only twice a year.⁴

As well as ethical committees not meeting very often, in some countries they charge a fee for undertaking the review. Some sites in STICH II have asked us to pay this charge for them, however, our funding does not provide for such costs. The STICH Team has therefore had to stipulate that in countries where this is a requirement, the local investigators cover the payment initially and then recover the cost from the per patient payments once they start to recruit patients; this may therefore have deterred some hospitals from taking part.

If a consultant is new to research, the time it takes to obtain ethical approval is undoubtedly longer. This is because they are not familiar with the complex process and so require a lot of assistance.

In the UK, the process is slow, the average number of days taken to obtain ethical approval is 197. Most of the UK sites participating in STICH II went through on the old COREC system where they needed to obtain separate Ethical Committee approval and Research and Development approval at each site.⁵ This added a lot of time onto the process. It is

hoped that the new National Institute for Health Research Coordinated System for Gaining NHS Permission (CSP) system may speed up the process of local approval for UK sites in the future.

The nature of this study in acutely ill patients is such that the majority of patients are unable to provide consent themselves. The interpretation of recent changes in legislature in some countries with regards to whether consent/assent can be provided by someone else has caused many problems in getting ethical approval, particularly in Lithuanian centres. In some centres, if a patient is unable to consent themselves into the trial then they are not allowed to participate. This has caused problems with recruitment; we have tried to solve this by holding a meeting in Lithuania and inviting members of the government and members of ethical committees, to discuss this issue. Our hope is that there will be a reassessment with regards to unconscious patients which will allow their relatives to provide consent for them to enter into the trial or some other procedure will be put in place so that research can be undertaken on these patients. Nevertheless, some countries, in their interpretations of the regulations, just do not allow for these patients to be included in surgical trials whatever happens.

Despite many problems working against obtaining ethical approval, it is good to know that if two or more hospitals in the same city wish to participate, they can generally use the same ethical approval where the committee is the same. This greatly increases the speed at which the second and subsequent hospital can obtain approval. They must still inform the ethical committee but the process is greatly speeded up.

Tripartite Agreements/Contracts

STICH II is an academic study at Newcastle University (i.e. not commercially sponsored) and therefore requires sponsorship from the local NHS Trust (Newcastle upon Tyne Hospitals NHS Foundation Trust). A tripartite contract was therefore required to be drawn up between the University, NHS Trust and the prospective participating centres. Once each hospital obtains ethical approval the contract therefore needs to be personalised and signed. Many problems have however been experienced during this process.

Issues about Intellectual property arise many times. Essentially, 'Intellectual Property' is the phrase that describes the rights of the STICH II trial team to protect any results that are collected.⁶ Some centres from academic backgrounds however have also wanted to protect their own intellectual property. This means that they often want to insert into the STICH II agreement complicated paragraphs that would allow them to publish their personal results. This however is a problem because it could lead to the integrity of the trial being threatened if any centre published their results prior to the full study results being published. This can be resolved by indicating that the initial paper will be a joint publication but allowing a site to publish their own results after this or at a set time after failure to publish the joint results. Attempting to estimate the length of time that it would take to obtain publication of the final complete trial results is problematic because of the number of unknowns, e.g. how many journals will need to review the paper before it is accepted, how long will the reviewer take and then once the paper is accepted how long to publication.

The issue of insurance has also been raised many times when trying to finalise the contract for some hospitals. This main concern is about insurance to cover design of the trial and also the difference between medical care and research.

With regards to medical negligence, it has been agreed that there can be no breach in the duty of care of a patient so long as the doctor acted in accordance with a responsible body of medical opinion. This is known as the 'Bolam test', which is a test used to determine the standard of care owed to a patient by doctors.⁷ Patients who are included in the STICH II trial receive the same level of care as someone who refused to enter the trial.⁸ Thus, there is no difference between the standard of medical care in or out of the clinical trial. These insurance issues have occurred, particularly with American and Israeli sites. Many hospitals in these countries have sadly not been able to take part because their legal advisors expect the co-ordinating site (in this case, Newcastle), to provide adequate insurance for their patients. All we ask is that the participating hospital has adequate insurance in place as a routine to cover their doctors for the normal care of these patients. This problem is also often

experienced if the hospital has misunderstood the nature of the trial and believes it to be a pharmaceutical trial.

The design of the STICH II trial is also indemnified by the Newcastle upon Tyne NHS Foundation Trust. This ensures that a patient cannot claim against the investigators for design of the trial itself. However, in a study such as STICH II this is extremely unlikely as it is an MRC funded study and is simply comparing two already widely practiced methods of treatment. Furthermore, if there is a dispute with this issue, it clearly states in the STICH II contract that English Law applies. Some centres have had a problem with this. It is usually solved by agreeing to remain silent on the issue.

When negotiating clauses in the contract we always aim to maintain an equitable approach. The original contracts drawn up in 2006 stated that the only laws that applied were the laws of England and Wales. We came to the compromise we now have whereby any claims against another institution have to be made according to the law of their country but any claims against our university/hospital have to be made according to our laws. This was felt to be a fair and even-handed approach to a UK funded study. Also given the nature of the organisation employing those who designed the study, where there is no study drug and where the treating clinician remains responsible for the treatment of the patient at all times, this situation is highly unlikely to arise.

Around twenty hospitals which were progressing through the registration process have unfortunately had to stop participating. This is because the agreements could not be settled. Ethical approval may have already been obtained but if the legal departments could not agree on the wording of the contract, progression unfortunately stopped. So, although the clinicians are in agreement, the administrators are not.

Issues about the destinations of per patient payments have also delayed the contract agreement process. For the STICH II trial it is essential that the per patient payments for this MRC funded trial are not paid to individuals. If a research account is not available, as in a number of cases, one therefore needs to be opened. This is because money from a public source such as the MRC cannot be transferred into a personal account; it is solely for

research and the only way to ensure that this money is used for the correct purposes is to ensure a research account is being used.

We have tried to improve the time it takes to resolve contractual issues in STICH II. We requested that our institution assign a properly trained and qualified member of staff to assist us. Medical research staff are not qualified to resolve legal matters and therefore this seemed a sensible course of action. We have also appointed lead people in each country with centres for STICH II. This is because if hospitals experience any difficulties they have a point of call to go to locally. This helps to speed up the process as documents have already been translated and communication can be easy and with no language barriers.

Conclusion

From the data table and graph shown earlier it is possible to conclude that only 40% of sites obtained ethical approval more quickly than they had agreed on the contract. This seems to indicate that there are many barriers which must be resolved with ethical committees. These delays are severely disabling research. This conclusion comes six years after all EU member states implemented the Clinical Trials Directive. This highlights that it has not been a complete success. The Clinical Trials Directive was introduced to try and create a harmonised framework for clinical research and improve ethical reviews. However, all EU countries that have adopted this, have interpreted it in different ways.⁹ This has led to fragmentation and division. Essentially this is making it harder to include patients into research. In the STICH II trial, it could take up to 400 days to obtain ethical approval. The extraordinary length of time that it is taking to pass through the ethical committee process is shortening the time remaining available to carry out the research.

From the experiences in this trial, it can be concluded that delays will be experienced in obtaining ethical approval and in agreeing on site contracts. This problem has been recognised in a recent article in the British Medical Journal.¹⁰ These delays are occurring even after following the developed and revised CONSORT (CONsolidated Standards of Reporting Trials) Statement. This was designed to help authors improve reporting of two-parallel design RCTs by using a checklist and flow diagram.¹¹ Health care organisations and

universities need to give much more support to researchers so that more time can be spent on the research and less time spent on the bureaucratic affairs.

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