Bath, Philip M.W. and Brainin, Michael and Brown, Chloe and Campbell, Bruce and Davis, Stephen M. and Donnan, Geoffrey A. and Ford, Gary A. and Hacke, Werner and Iglesias, Cynthia and Lees, Kennedy R. and Pugh, Stacey S. and Saver, Jeffrey L. and Schellinger, Peter D. and Truelsen, Thomas (2014) Testing devices for the prevention and treatment of stroke and its complications. International Journal of Stroke, 9 (6). pp. 683-695. ISSN 1747-4949

TESTING DEVICES FOR THE PREVENTION AND TREATMENT OF STROKE AND ITS COMPLICATIONS

Philip M Bath,[1] Michael Brainin,[2] Chloe Brown,[3] Bruce Campbell,[4] Stephen M Davis,[4] Geoffrey A Donnan,[5] Gary A Ford,[6] Werner Hacke,[7] Cynthia Iglesias,[8] Kennedy R Lees,[9] Stacey S Pugh,[10] Jeff L Saver,[11] Peter D Schellinger,[12] Thomas Truelsen [13]

Stroke Trials Unit,[1] Division of Clinical Neuroscience, University of Nottingham, Nottingham, UK
Department of Clinical Neurosciences and Preventive Medicine,[2] Danube University Krems, Krems, Austria
Covidien,[3] ev3 Europe, Paris, France
Melbourne Brain Centre @ Royal Melbourne Hospital,[4] University of Melbourne, Melbourne, Australia
Florey Institute of Neuroscience and Mental Health, University of Melbourne,[5] Melbourne, Australia
Stroke Research Group,[6] University of Newcastle, Newcastle, UK
Department of Neurology,[7] Ruprecht-Karls-University Heidelberg, Heidelberg, Germany
Department of Health Sciences,[8] University of York, York, UK
University Department of Medicine & Therapeutics,[9] University of Glasgow, Glasgow, UK
Neurovascular,[10] Vascular Therapies, Covidien, Irvine, USA
Geffen School of Medicine at UCLA,[11] UCLA Comprehensive Stroke Center, Los Angeles, USA
Chefarzt der Neurologischen Klinik und Geriatrie,[12] Johannes Wesling Klinikum Minden, Minden, Germany
H Lundbeck,[13] Copenhagen, Denmark

Correspondence to:
Professor Philip Bath
Stroke Trials Unit
Division of Clinical Neuroscience
University of Nottingham
City Hospital campus

Nottingham NG5 1PB UK

Tel: 0115 823 1765

Fax: 0115 823 1767

Email: philip.bath@nottingham.ac.uk

Introduction

Stroke is common and devastating for both patients and carers. Although there are multiple strategies for preventing recurrence (e.g. antithrombotics, blood pressure and lipid lowering, carotid endarterectomy),(1-4) those for acute treatment (e.g. thrombolysis, aspirin, hemicraniectomy (5-7)) and rehabilitation (8) remain more limited. The majority of existing stroke interventions are pharmacological and many are derived from research initially conducted in patient populations accrued to test hypotheses concerning ischaemic heart disease. An emerging range of devices are now being tested as acute and preventive interventions in stroke populations.

The following review results from a workshop held in London May 2013 on devices for the treatment and prevention of stroke. The meeting was organised by the Industry Roundtable of the European Stroke Organisation (www.eso-stroke.org). The aims were to explore the increasing development of devices as interventions in stroke, populations including ongoing trials, methodological issues, health economics, regulation, challenges and implementation of results. The workshop follows on from a previous European Stroke Organisation (ESO)-managed one in 2011 on acute stroke outcomes and statistical analysis.(9-11)

Hype or hope?

The rate of new pharmacological developments is falling reflecting that 'quick and easy' wins have been realised whilst many other novel agents have failed. Device assessment is now filling the gap in development and yet insufficient high quality clinical evaluation may lead to the use of interventions that are ineffective, or even hazardous.(12) A number of examples exist whereby early uncontrolled studies led to unregulated use of devices before properly designed trials were performed and reported, these including thrombectomy (for hyperacute reperfusion (13)), venous compression stockings (for acute and subacute prevention against deep vein thrombosis (14, 15)), and renal denervation (for the treatment of resistant hypertension, and therefore prevention of stroke (16-18)). Fortunately, well designed randomised trials have been completed or are underway for these and other devices.

Completed and ongoing trials

The types of devices relevant to the treatment or prevention of stroke and its complications are numerous in number, aim, trial size, whether led commercially or academically, and by size of company if commercial. Broadly, devices for stroke can be defined as those for:

1. Treating hyperacute and acute stroke to reduce neuronal loss, e.g. reperfusion, neuroprotection, hypothermia
2. Treating specific stroke impairments during rehabilitation, e.g. dysphagia, limb weakness
3. Preventing complications following acute stroke, e.g. deep vein thrombosis
4. Promoting brain plasticity, e.g. transcranial magnetic stimulation
5. Preventing stroke recurrence, e.g. for patent foramen ovale (PFO), atrial fibrillation

These targets mirror, significantly, pharmacological and surgical interventions for stroke treatment and prevention. Table 1 lists devices and their associated trials ordered by the aim of the intervention; the list gives examples and is not intended to be comprehensive whether by clinical target, device, or developing organisation.

Studies of devices in stroke are a relatively new phenomenon and a significant number have suffered from problems in their design, e.g. based on a registry or single treatment arm, i.e. no comparator); statistically underpowered, i.e. too small; inappropriate patient selection; poor site selection, i.e. unskilled operators; delayed time to treatment; testing older devices; and inappropriate choice of outcome. Few device evaluation studies in stroke have used randomisation, or utilised blinding or sham procedures. Inadequate or inappropriate study designs have led to unpersuasive results and so to limited device sales or, in the extreme, business failure for a number of companies.

A key problem is that it often appears superficially 'obvious' that a device-based intervention should work (e.g. stent opening of an arterial stenosis should be expected to improve outcome) and yet RCTs often turn up unexpected results. Examples include: stent treatment of a stenosed internal carotid artery is not superior (and may often be inferior) to carotid endarterectomy,(19-21) stenting of stenosed intracranial large arteries is inferior to best medical therapy,(22) and closure of patent foramen ovale may not reduce strokes secondary to paradoxical embolism.(23-25) Consistent explanations are that the procedural risk outweighs the 'obvious' benefit,

or that the intervention is applied too late or to a poorly defined patient group. The results of failed trials with older devices cannot necessarily be extrapolated to newer methodologies. Hence, all devices need to demonstrate feasibility of use and tolerability in early registry or phase II/pilot studies, and show safety and efficacy in one or more phase III/pivotal RCTs.

Sequence of trials

The classic drug development pathway encompasses: preclinical/proof of mechanism studies; phase I human healthy volunteer studies; pilot/proof of concept/phase IIa/b trials in the target patient population; pivotal/proof of mechanism/phase III safety and efficacy trials; and phase IV/post-marketing surveillance studies/registries.(26) Although all preclinical and phase I-III studies should incorporate a randomised controlled trial (RCT) design, many do not. Following phase III, licensing authorisation is received from regulators, and other bodies (e.g. Institute for Quality and Efficiency in Health Care [IQWiG] in Germany, National Institute for Health and Care Excellence [NICE] in England & Wales) decide on the 'value' of the intervention and its reimbursement. Because of the complexities of doing RCTs, it has been suggested that some phases of development might use data from concurrent non-randomised control patients, or data from trial archives (see below).

Historically, devices have followed a different development route comprising: engineering, preclinical and safety studies in models; pilot studies in a few patients, prospective case series; and safety and feasibility studies (which may be randomised). In the European Union (EU), a Conformity European (CE) mark is then sought (involving conformity testing and then declaration), this indicating that the product complies with EU legislation. Marketing of the device may follow award of the CE mark. Negotiations about reimbursement again involves bodies such as IQWiG and NICE. Until recently, this system did not require evidence that the device was efficacious.

This system is now being refined so that devices that require invasive procedures or implantation will need definitive evidence of safety and efficacy and, hence, the need for RCTs. Furthermore, before licensing, these trials should demonstrate improved clinical outcomes, not just a positive effect on the biological target, such as recanalisation for mechanical thrombectomy in phase II/pilot designs. Although it has been suggested that small companies do not have the financial resource to perform phase III/pivotal trials, in reality such funding could be available from venture capital

or partnership with larger life science companies; either way, organisations need to provide adequate information on safety and efficacy whatever their size. In addition, trials can be done in the context of commissioned healthcare whereby the device or procedure is only funded for patients enrolled into the trial (whether active or control) at selected sites. In the UK, this approach is termed 'commissioning through evaluation', and the approach is likely to be used for the testing of PFO and left atrial appendage closure. A similar approach in the Netherlands is aiding recruitment into the MR CLEAN thrombectomy trial.

Trial designs

Most phase II and III trials in acute stroke or stroke prevention are *parallel-group* in design and so compare the active treatment(s) with control. A refinement is where the randomisation defines when to start the intervention: the active groups receives it immediately and the control group has the intervention later (so-called *randomised start* trials); in this design, all patients have the potential to benefit from the intervention and the approach confirms disease modification if the control group differs from the experimental group at the end of the parallel-group phase. In some circumstances, it may be possible to use a *cross-over* design whereby both randomised groups receive the treatment and control, but in a different order. Cross-over trials are highly efficient statistically but are largely only relevant where time-to-treatment is not important, during phase II/pilot dose assessment where the treatment effect is likely to be short-term, or where it is desirable that both groups receive treatment eventually, e.g. for ethical reasons. Although cross-over trials of pharmacological interventions are common at phase I/II,(27) their use with devices is rarely used.(28, 29)

Patient selection

Inclusion and exclusion criteria are determined by the aim of the trial. Inappropriate choice of these criteria, and having too many exclusion criteria, can contribute to the failure of a trial.

1. *Time window:* Interventions work best when used at the most appropriate time. Using existing treatments as an example, the efficacy of intravenous thrombolysis for reducing poor functional outcome declines rapidly over a few hours after stroke onset;(5) aspirin should be given within 48 hours to prevent early recurrence;(6) and hemicraniectomy needs to be performed within 48 hours to benefit patients

with malignant middle cerebral artery ischaemic stroke.(7) Equally, hazards may be maximised by treating at the wrong time, e.g. by delaying intravenous thrombolysis beyond 6 hours. The same issues will apply to devices. For example, faster intra-arterial revascularisation is likely to lead to an improved outcome.(30, 31) Equally, it may also be important to delay treatment with some devices; for example, dysphagia can improve rapidly so recruiting patients too early would mean the trial was diluted with those who were going to get better anyway.

2. *Stroke severity:* Patients with mild stroke (e.g. assessed using the National Institutes of Health Stroke Scale) usually have a good outcome, and those with severe stroke usually a poor outcome. Hence recruiting patients with very mild or severe patients will dilute the trial with patients who are less likely to respond significantly to the intervention.
3. *Recurrence risk:* The aim of prevention trials is to reduce, or delay, the occurrence of further vascular or stroke events. If patients are recruited with a low risk of recurrence (e.g. assessed using the ABCD2 score (32)) then they will, again, dilute out the trial. It is important to note that the statistical power of a prevention trial is driven more by the number of events (which depends on the risk of recurrence) than the size of the trial.
4. *Age:* Having a minimum age for recruitment, e.g. >50, will help increase stroke recurrence rates in prevention trials. However, maximum ages for recruitment are ageist and neglect the fact that the absolute benefit of an intervention may be greatest in older people.
5. *Image selection:* Recent phase III/pivotal trials of mechanical thrombectomy have been neutral and did not uniformly utilise advanced imaging for patient selection. Effective reperfusion depends on salvage of vulnerable, hypoperfused tissue in the ischemic penumbra. Moreover, reperfusion of large cores is known to be hazardous with a high risk of symptomatic haemorrhagic transformation. Advanced multimodal imaging will also identify the relevant occluded artery and avoid unnecessary catheter angiography. Both MRI perfusion-diffusion mismatch and CT perfusion-mismatch can identify penumbral presence and extent in real time using computer programs. The first trials such as EPITHET and MR RESCUE,(33, 34) although neutral, provide some support for the concept that delayed reperfusion can salvage tissue in the ischemic penumbra with improved clinical outcomes. Ongoing trials (table) are therefore testing the hypothesis that patients who have already received intravenous rt-PA and who have MRI or CT evidence for mismatch

and an occluded vessel, will benefit from subsequent clot retrieval using a modern mechanical device.

6. *Inclusion criteria:* Specific inclusion criteria relevant to the device will also be needed, e.g. presence of leg weakness if testing a device for preventing deep vein thrombosis, atrial fibrillation if testing a device for occluding the left atrial appendage, and dysphagia if testing a device for treating this stroke complication.

Comparators

When developing a new intervention it is vital to test it, where possible, against control in the setting of best medical practice. In the absence of such comparative controlled data, it is difficult to interpret the results of trials that compare two active, but unproven, interventions. However, where there already is an intervention that is known to be effective, then the new potential treatment needs to be tested against this so that patients are not denied treatment. An example is the comparison of carotid artery stenting/angioplasty (CAS) with carotid artery endarterectomy, an intervention that is already known to be effective.(4) Unfortunately, CAS was not shown to be consistently as effective.(21, 35-38) Either way, comparators should not be selected on the basis that they favour the study's financial sponsor, a form of *funding bias*.

Blinding and sham-placebos

Trials should, ideally, be placebo-controlled to minimise participant, investigator and observer *ascertainment bias*. Empirical studies have shown that studies that are not double-blind may enhance apparent treatment effects by a relative 17%.(39) If patients know they are in the control group, they may feel disappointed and be less willing to report improvement. Equally investigators may treat patients differently depending on which treatment groups they are randomised to, leading to *performance (or co-intervention) bias*.

Although many pharmacological interventions can be placebo-controlled, finding a suitable and relevant sham for patients randomised to control in a device trial varies by the type of intervention:

1. Sham double-blind treatment. Certain device treatments lend themselves to treatment that is double-blind, particularly those involving only a minimally invasive procedure and electrical or magnetic stimulation (e.g. neuromuscular

electrical stimulation, transcranial direct current stimulation, transcranial magnetic stimulation, and pharyngeal electrical stimulation). Here, the stimulator can be programmed to deliver treatment according to a randomisation code, i.e. participants randomised to control receive all other parts of the intervention without the stimulation itself. This approach was successfully implemented in the transcranial laser therapy program (NEST I-III).(40-42)

2. Sham single-blind treatment. Rather than the device control unit being programmed to give active or sham treatment according to the randomisation code, the operator controls whether the stimulator is turned on or off. The participant remains blinded to treatment assignment.
3. Open-label treatment. Trials of highly invasive procedures such as catheter and stent insertion are difficult to mask since it is usually considered unethical to insert a device and then not deliver any treatment. Such a procedure would expose the patient to the risk of the procedure (e.g. haematoma, infection) and general anaesthetic without any potential for benefit. As a result, patients randomised to active treatment have the procedure and those randomised to control do not have any of the procedure. Examples of open-label trials include endovascular treatment for middle cerebral artery occlusion, comparison of carotid artery stenting with endarterectomy for stroke prevention, and pneumatic leg compression sleeves for prevention of deep vein thrombosis (table 1).(21, 35-37)(13, 34, 43)

Although efficacy trials should, where possible, utilise sham double-blind treatment, studies assessing effectiveness (efficacy in the real world) may, if necessary, be open-label so as to measure the treatment effect cost-effectively when the device is delivered in 'real-world' routine practice.

Outcome blinding

A key source of bias in any trial is *detection bias* where there are systematic differences occur in the measurement of outcomes between treatment groups. Hence all trials must have outcomes assessed by a person/system that is blinded to treatment. Importantly, this applies to double-blind studies almost as much as single-blind and open-label trials, not least because active treatment, whether drug or device based, may be detectable by the patient or operator. Although detection bias is less likely with 'hard' outcomes such as death, blinding of outcome assessors is especially important for assessment of 'soft' or subjective outcomes, such as magnitude of post-intervention pain when testing a nerve stimulator.

Trials of acute stroke that measure functional outcome are challenging to blind thoroughly if either the patient or the interviewer may have learned treatment assignment. Answers to structured interviews may still be influenced and summaries prepared by an investigator can subtly influence scoring. An approach that is being used in the NIH-funded CLEAR-III surgery trial in intraventricular haemorrhage is central adjudication by independent observers of an outcome assessment interview conducted with the patient and recorded to digital video. In this interview, a local investigator explores functional outcome and probes for evidence to support the responses but leaves interpretation to a committee of experienced raters. Technical aspects of the web-based management of the video recordings and any necessary translation have been solved. A similar approach is being used in the EuroHYP-1 trial of endovascular or surface cooling in hyper-acute stroke. The combined use of both double-blind treatment and outcome blinding is referred to as *triple-blinding*.

In stroke prevention trials, *referral bias* is an issue when independent outcome adjudication committees are employed. Although the adjudication committee independently reviews candidate outcome stroke or TIA events, the universe of events the committee sees is determined by the ascertainment procedures used by the local sites. Local investigators may be more likely to work-up and refer atypical events based on treatment arm assignment. Referral bias can be mitigated by the use of structured interviews with positive symptoms automatically triggering referral to the adjudication committee regardless of local investigator judgment of the event.

Outcomes and analysis

The primary outcome should reflect the aim and phase of the trial, i.e. assessment of mechanism of action, proof of principle or efficacy, and phase II/pilot versus III/pivotal. For example a phase II trial assessing the treatment of dysphagia is likely to focus on return of swallowing. In contrast, phase III trials of acute thrombectomy are likely to use the modified Rankin Scale as the primary outcome, and assess other secondary measures such as disability, mood, cognition, and quality of life, as recommended by the ESO.(9, 10) Vascular prevention trials usually measure stroke recurrence, or major adverse cardiovascular events (MACE, the composite of non-fatal stroke/myocardial infarction and vascular death). Either way, outcomes should not be selected on the basis that they favour the study's financial sponsor, a form of *funding bias*. In general, trials should not have more than one primary outcome; however,

when two are more primary outcomes are deemed to be required,(44) the European Medicines Agency provide guidance on the design and analysis of such studies.(45)

It is vital to optimise the analysis of outcomes to maximise statistical power. In general, ordinal or continuous scales should not be dichotomised since this significantly reduces power. ESO recommends the use of ordinal logistic or multiple linear regression when analysing the mRS.(11) A new technique in vascular prevention trials is to ordinalise stroke recurrence although this approach remains experimental at present (46) and has yet to be used in a device trial.

Choosing the best sites

The efficacy of most devices will depend significantly on the skills and experience of the interventionist or operator. (This situation is analogous to surgical interventions where surgeons are trained in a specific operation and then need to perform this regularly to remain skilled and in practice.) In almost all cases, operators will need training (proctorship), which may need visits to other sites that are already doing the procedure. Hence, device companies will need to invest in training both prior to, and during, the study. Ultimately, it is easy to nullify a real treatment effect by having an intervention tested by poorly skilled practitioners. Often it is desirable to have a certification committee that evaluates a practitioner's experience and recent cases and approves participation based on an appropriate performance threshold, and also monitors practitioner performance during trial conduct. For new interventions that have not been widely adopted in practice prior to the trial, a "roll-in" phase is often advisable, during which consecutive patients receive the device treatment, allowing operators to ascend the learning curve and achieve full competency prior to start of randomisation at each site.

Equally sites that have an experienced research team who are used to delivering trials will provide more accurate, timely and reliable data. Hence, trials should choose sites that are experienced in both delivering the device procedure and clinical research. Such sites will, usually, be managing large numbers of patients with stroke and will have modern facilities including a stroke unit and access to advanced imaging; they will also usually have an evidence-based approach to stroke care with guidelines addressing most routine clinical practice, e.g. for the management of blood pressure, lipids and glucose. Nevertheless, it is important to check that large centres are

randomising a significant minority of their patients (say >10%) so that the resulting trials are generalisable and do not suffer from selection bias.

Supervision of trials

It is vital that all multicentre (and probably the majority of single centre) clinical trials have appropriate oversight in the form of a Trial Steering Committee (TSC) and independent Data Monitoring Committee (DMC).(47) The TSC should include independent members, as already demanded by many government and charity funders of academic studies. Additionally, studies should be peer-reviewed by independent assessors at the design stage; although most academic studies will have peer-review as part of their funding process, this is often missing in commercial studies, especially if the company is small and does not have its own internal peer-review system. The presence of independent members in the development and oversight of trials is likely to make studies more relevant to patients, and reduce design flaws that lead to bias and raise ethical issues.

Trial committees should have guaranteed access to all raw trial data at conclusion of the trial, or if the trial stops early due to collapse of the sponsoring organisation; this will ensure timely, accurate and ethical scientific reporting. Examples exist where bankruptcy of the sponsor has compromised proper termination of a trial according to Good Clinical Practice rules, these preventing full data access and delaying or even preventing publication of the results. Through foresight, data have been recovered, albeit relying on goodwill of third parties who put scientific and ethical responsibility over monetary concerns. Ideally, finance for all trials would be guaranteed through protection of the funding through a third party but as a minimum data access should be guaranteed in case a company does go into liquidation.

Combining device and pharmacological interventions

Combining pharmacological and device interventions may provide new treatment opportunities for patients with stroke.(48) Scenarios of combining an unproven device and drug interventions can be summarised as follows:

1. Drug is licensed, device is unlicensed: so untreated drug comparator group is not acceptable:
    a. Device vs Drug; or
    b. Device + Drug vs Drug

2. Both drug and device are unlicensed: so untreated comparator group(s) is acceptable:
    a. Device vs Drug vs Control
    b. Device + Drug vs Device vs Drug vs Control (factorial trial)
    c. Device vs Control, with Device further randomised to Drug vs Placebo

Using the example of intravenous thrombolysis (which is licensed), devices could be used after bridging therapy with alteplase; in patients receiving rt-PA within the clinical time window, but who have the dual target of persisting large artery occlusion and a large penumbra; as first line treatment in patients who are outside the approved time-window for thrombolysis; or in patients with large occlusions where alteplase may have a low recanalisation rate. Previous trials have demonstrated that it is feasible to combine testing alteplase both in the approved time window and beyond, while allocating patients to device interventions.(31, 49)

Development of combination treatments is, however, challenging for several reasons including (i) regulatory differences between devices and drugs, (ii) how to allocate adverse events to the examined treatments, (iii) how to determine the number of patients needed to show treatment effect in trials with several treatment arms, and (iv) whether clinical equipoise will be maintained during the period of patient enrolment:

1. In the US there are two distinct regulatory paths for new device versus pharmaceutical drug/biologic product. The *FDA 510(k) clearance* process requires comparison of the new device to one or more similar legally marketed devices, with the aim of demonstrating that the device is substantially equivalent: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/default.htm (downloaded 26/10/13). An *approval* of a medical device (only required for innovative/high-risk devices) relies on scientific evidence showing that the device is safe and efficacious for its intended use(s); this typically requires a substantial amount of scientific data, similar to that required for studies of new pharmaceutical drugs. These regulatory differences between new devices and pharmacological products can impact on the expectations of an ideal trial design.
2. Identification and reporting of safety data from patients treated with two treatments is complex as both the drug and the device may cause similar adverse

events, e.g. bleeding. Evaluation of the most likely cause of an event is best performed by an independent adjudicator and/or Data Monitoring Committee; the situation is easier if there is a parallel control group being randomised to mono-therapy or standard medical practice within the same trial since this can provide background serious adverse event data.

3. Unless a factorial design is used, statistical comparison of several treatments will need more patients to demonstrate a significant clinical effect between the various randomised groups. It may be possible to identify sub-groups of patients where the treatment effect is expected to be particularly high (for example by using MR patient selection and enrichment) although this will increase the number of patients to be screened, slow recruitment, and narrow the final indication.
4. Achieving unselected patient enrolment into acute stroke trials may be a particular challenge. For example, it was already apparent in 2007 that the use of non-randomised endovascular procedures in patients with large vessel occlusion hampered the recruitment of patients into randomised controlled studies in acute ischaemic stroke.(50) Recently, lack of clinical equipoise has been claimed to be a leading cause of slow recruitment in the IMS-3 and MR RESCUE studies.(12, 31, 34). Such low recruitment rates in large volume centres are one of the biggest obstacles for generalisability of the data. Trials combining pharmacological and device interventions are at risk of experiencing selection bias during patient recruitment which could jeopardise finding treatment benefits and assessing safety in a clinically representative patient population. However, given the low recanalisation rate with IV rt-PA in patients with a large proximal artery occlusion, such a design (standard licensed therapy +/- add-on therapy in patients with large vessel occlusion and large penumbra, has been the basis for ongoing trials such as EXTEND-IA. Early time window trials such as THERAPY do not necessarily look for penumbral lesion, but require fast treatment on top of standard rt-PA with proven vessel occlusion.
5. Patients with a contraindication for rt-PA such as active anticoagulation, recent major surgery or trauma may require a different approach irrespective of the time window. Even in patients who arrive early, a randomisation between intervention and BMT without rt-PA is advisable, while for later comers some penumbral imaging would be recommendable.

Health economics

Economic evaluation analyses are recognised as the back-bone of health technology

assessment processes, the remit of which is to issue recommendations regarding reimbursement decisions. Guidelines to how to conduct economic evaluations have not distinguished between different types of health technologies, i.e. pharmaceuticals, medical devices, or diagnostics. There are three overall methods for assessing the value for money of any medical device: cost-effectiveness, cost-utility, and cost-benefit, analyses.

Economic evaluation analyses assess the value for money of alternative competitive courses of action in terms of both the health benefits and costs associated with their use. The choice of outcome to measure health benefits determines the type of economic evaluation to be conducted. So, in cost-effectiveness analysis health benefits are measured in '*natural units*', i.e. clinical outcomes such as survival, improvements in mobility range, pain reductions. Cost-utility analysis allows the comparison of the value for money of health technologies with different indications through the use of '*composite measures*'. These are measures of health benefit that consider the impact on mortality and morbidity, e.g. healthy-years equivalent (HYE) and quality adjusted life years (QALYs). Finally, quantification of health benefits in monetary terms is at the core of cost-benefit analyses; this makes it both the most flexible and most challenging method of economic evaluation.

The advantages of conducting economic evaluation analyses alongside clinical studies have been extensively discussed. A key advantage is the generation of economic evidence/data as early as possible in the development process of medical devices, e.g. in pre-launch studies. This requires collecting additional data documenting information on: (i) key resource use; (ii) generic preference based health related quality of life outcomes, e.g., the EuroQol 5D (EQ-5D); and (iii) unit costs.

Whilst there are a number of national and international guidelines to conduct economic evaluations, the precise analysis plan will need to reflect the unique characteristics of the technologies and health conditions under evaluation as well as the type of data available (individual patient level versus summary data). In addition, economic evaluations often require the implementation of complex statistical methods to estimate mean health benefit and costs associated with the alternative treatments. Consequently, when designing, implementing and interpreting the results from these studies it is advisable to seek input from experienced health economists and statisticians from the very start of the project.

For example, NICE now has two different programmes for device evaluation: (i) the Technology Appraisal Programme uses 'cost-utility' analysis to assess the value for money of medicals devices whose provision is likely to both vary geographically and be cost incurring; and (ii) the Medical Technologies Evaluation Programme uses 'cost-consequences' analysis – a partial method of economic evaluation in which health benefit is measured using clinical outcomes and where no incremental analysis is conducted. The latter approach is relevant for evaluating medical devices that are likely to be cost saving. To inform its recommendations regarding the reimbursement of medical devices, NICE requires estimates of health benefit and resource consumption to support manufacturers/sponsors value claims on their products.

Pooling trial data

Individual phase III efficacy trials should be of sufficient size to detect clinically worthwhile efficacy. Financial and practical limitations may prompt statistical sample size/power calculations that are excessively liberal in their expectations of treatment effect. As a result, many trials are too small and even if large enough to detect a reasonable treatment effect, will lack adequate statistical power to examine effects in subgroups. It is then desirable to combine data from two or more trials in a meta-analysis/systematic review. Analysis plans for the pooled analysis should be designed prospectively and without knowledge of the individual trial results. This has been successfully done in the joined analysis of the European hemicraniectomy trials, where patient characteristics for inclusion and the endpoints were consented before the individual trial outcome result were known.(7) A similar approach will be used in the STTC analysis of alteplase, for which the analysis plan was written before the IST-3 trial results were known.(51) In the case of recanalisation devices, a future pooled individual data analysis should be designed now for the just planned or early recruiting large RCTs, also implementing quality markers and minimum quality requirements to design a reliable per protocol population.

Many systematic reviews based on summary (group) data have been published on pharmacological and rehabilitation interventions of relevance to stroke - see the Cochrane Database of Systematic Reviews: http://www.thecochranelibrary.com/ (downloaded 26/10/13). However, the gold-standard for systematic reviews is to use individual patient data (52) which, in addition to allowing refinement of the treatment's effect size, better allows analyses to be performed in subgroups of

patients; they also facilitate covariate-adjusted analyses so that interactions between treatment and baseline variables can be assessed, e.g. for time to treatment. Example systematic reviews based on individual patient data include intravenous thrombolysis, aspirin, hemicraniectomy, antiplatelets and occupational therapy.(5-8, 53) Calls have now been made for systematic reviews based on individual patient data of device trials, e.g. closure of patent foramen ovale.(54) Such synthesis of data across several trials will usually require collaboration between two or more device institutions, whether commercial and/or academic. Ideally, such collaborations should be set up prospectively so that trial inclusion/exclusion criteria and outcomes are chosen *a priori* and are not data driven; this has been done successfully for intravenous thrombolysis (5) with an update expected shortly.(51)

At the STAIR-8 conference in 2013, there were informal indications that a trial that simultaneously tests multiple similar devices may be considered by regulatory authorities in circumstances where it could be demonstrated that the devices under test share a common mechanism and other features, provided that various caveats about homogeneity and sample size for individual devices were satisfied.(55) A prospective pooling project for endovascular treatment of acute stroke has been proposed. Unlike the other VISTA registries, the endovascular one will collect both active and control data. A similar individual patient data meta-analysis is ongoing for trials of pharyngeal electrical stimulation in the treatment of post-stroke dysphagia (Bath, personal communication).

Archiving trial data

The Virtual International Stroke Trials Archive (VISTA) was established to solve the ethical and scientific need for trial data to contribute maximally to development of the clinical field. Numerous trials had 'failed' and yet had collected invaluable data about stroke care and outcomes, data that may assist in the planning of new trials, permit hypothesis generation, or answer ancillary questions about other aspects of stroke care. VISTA is a not-for-profit collaboration of senior trial investigators across various themes (acute, rehabilitation, prevention, imaging, endovascular, haemorrhage), with the original datasets from 74 trials including over 60,000 patients and leading to more then 56 peer-reviewed publications.(56, 57) To protect the intellectual property of the contributing sponsors and investigators, VISTA analyses do not revisit the effects of the treatment that was studied in the original trial. However, treatments received as standard of care can be studied. It has contributed to the development of more

sensitive outcome measures for early phase stroke trials and to publication of essential data on intra-class correlations for use in cluster randomised trials. VISTA can also act as a conduit to original investigators and data, and thus enable industry to meet their ethical obligation to place data in the public domain while releasing them from handling repeated requests for data or analyses. They are also freed from the financial and scientific costs involved in oversight of the intellectual property, statistical and publication issues that would arise. A related archive holding cardiovascular and cognitive data operates under the same principles, and holds data from over 170,000 patients (www.VICCTA.org).

Other archives have more specific aims for the use of data. For example, the 'Optimising Analysis of Stroke Trials-acute' archive gathered together individual patient data from >50 trials with the aim, using an empirical approach, of identifying what were the most efficient statistical approaches for analysing trials.(58-61) Similar projects are now ongoing assessing how the analysis of vascular prevention ('Optimising Analysis-prevention'),(46) and cognition and dementia ('Optimising Analysis-cognition') trials may be improved. Commercial and academic institutions are encouraged to share their data with collaborative data archiving groups such as VISTA and Optimising Analysis.

Other challenges with device trials

Device trials are not immune to the generic problems of any development of a new intervention. The most basic problem is that a device may simply not achieve the intended biological effect, as seen with the NeuroThera Laser System where early safety and efficacy (40, 41) were not replicated in a later and larger trial.(42) Similarly, the early promising results of endovascular treatment for acute ischaemic stroke (13) have not been repeated in three recent trials (31, 43, 62) although these were testing older devices with relatively poor recanalisation rates, involved late treatment windows and only one attempted to assess penumbral selection. Other, larger and more refined studies are ongoing or planned.

Recruitment estimates, both in total numbers of participants and enrolment period, may be over-optimistic and can slip due to excess estimates of recruitment by investigators, bureaucratic issues that delay approvals, competition between trials, and inadequate funding.

Industry-Academia collaboration

There is much advantage in having companies, academics and clinicians collaborating closely in the development of new devices for stroke. A number of different models have worked or been proposed for drug development in the past, and all are relevant to device development:

1. Industry-led and sponsored trials. These trials are sponsored and funded by the company, and are intended to contribute to licensing application and approval of the device. The data are owned by the company. Ideally, Academia contributes to the design of trials (to ensure relevance to patients and stroke management, e.g. by external review of protocols) and their analysis and interpretation.
2. Investigator-initiated trials. Investigators suggest trials to industry which funds them (at least in part, perhaps through the provision of devices), possibly with parallel government/charity funding. The trial is sponsored by a healthcare institution or university which then own the data.
3. Investigator-designed trials with government or charity funding. These are usually done independently of industry. The trial funder or participating sites need to buy the device on the open market and the data are owned by the sponsoring institution.

In each case it is vital that investigators, industry and regulators communicate and coordinate at the design phase, as recommended in STAIR-7.(48)

Case studies

1. Mechanical thrombectomy

The central role for intravenous thrombolysis in the treatment of hyperacute ischaemic stroke is well rehearsed.(5) By extension, local intra-arterial treatment might be more effective and the highest profile development of a family of devices relates to such treatment. Intra-arterial therapy includes local administration of a lytic agent via an intra-arterial catheter, piercing and retracting the clot with a 'corkscrew-like' device, entrapment and removal of the clot with a retrievable stent, and aspiration of the clot with a suction device. The latter three approaches are examples of mechanical thrombectomy, lead to removal of the clot, and restore perfusion. An appropriate development sequence for mechanical thrombectomy should have included the following stages:

1. Small case series demonstrating the feasibility and early safety of the device. This phase has been completed for some devices.
2. Phase II: Randomised or historical control safety and explanatory phase utilising assessment of mechanisms of action (effect on reperfusion), with comparison of device A versus control. This phase has been completed for some devices.
3. Phase III: Safety and efficacy phase, i.e. comparison of device A versus control. The first generation of trials in this phase showed neutral results and second generation trials testing new thrombectomy technology are ongoing.
4. Phase IV: Safety and effectiveness in routine use, utilising a registry of use of device A, or head-to-head comparison of two efficacious devices, i.e. device A versus device B. Some studies have been performed in-spite of item 3 not being completed.

Unfortunately, the development of thrombectomy devices has been disorganised and illogical in several respects. First, some recent trials have compared different devices (e.g. Solitaire Flow Restorer or Trevo Retriever versus Merci Retriever (63, 64)) without knowledge of whether the individual devices themselves work when compared with no intervention. Second, other recent trials have included a mixed group of interventions, albeit mostly using first generation devices, so that it is difficult to assess which, if any, are potentially of benefit.(31, 34, 65) Third, trials did not select appropriate patients or intervene fast enough.(66)

Last, and unusually for the development of a new intervention, both commercial and academic trials of thrombectomy have run in parallel. Usually, patent protection and availability of the novel intervention has limited initial testing to the company(s) developing the intervention and it is only later that academic trials start, perhaps testing the intervention in a larger and/or more diverse group of patients, and using a more pragmatic design. The presence of academic trials early in the development lifecycle of thrombectomy reflects an initial lack of willingness of companies to do randomised trials, in part for financial reasons but primarily because regulators did not require this for devices. The pragmatic design of some of the existing academic trials led to a mixed focus on intra-arterial fibrinolysis and mechanical thrombectomy, rather than an explanatory interrogation solely of devices.(31, 65) A number of medium or large trials are ongoing or planned, both commercial and academic (table 1); it can be argued that at this early-to-medium stage in the development of

thrombectomy, trials run by companies, with academic input, will be as useful as studies run solely by academic consortia.

The result of the above is that at present guidelines limit thrombectomy to level B, class IIa and healthcare funders are considering whether to pay for the procedure.(67) The confused development of thrombectomy has led to multiple commentaries that are variously positive, neutral and negative about the procedure.(12, 68)

2. Prevention of deep vein thrombosis (DVT)

DVT is a common complication of stroke leading to significant morbidity (through post phlebitic limb) and mortality (through pulmonary embolism). Graduated compression stockings (GCS) are effective in patients undergoing surgery (69) but their role was unclear in patients with recent stroke.(70) Two large trials compared the role of GCS: CLOTS-1 (n=2518, 64 sites) found that there was no difference in the rate of proximal DVT between patients randomised to thigh-length GCS versus no GCS,(15) whilst CLOTS-2 (n=3114, 112 sites) reported that proximal DVT was more common in patients randomised to below-knee GCS than with thigh-length GCS.(71) The neutral CLOTS-1 trial led to an immediate reduction in the routine use of GCS.(72)

Although static compression was ineffective, intermittent pneumatic compression (IPC) might be of benefit.(69) The CLOTS-3 trial (n=2876, 94 sites) found that IPC significantly reduced DVT;(73) surprisingly, the risk of all-cause mortality was also reduced in patients randomised to IPC.

All three CLOTS trials benefitted from academic and industry collaboration. Whilst the trials received government funding and were coordinated from a university (Edinburgh), the interventions (GCS, IPC) were provided free-of-charge by a company (Covidien). Several lessons arise from this development sequence: first, that data on device effectiveness needs to be obtained in the relevant patient population and not extrapolated from very different patient groups; second, that where one device fails another may work; and last, that the model of academic-led, government-funded, industry-supported trials may be effective for other device evaluation studies.

Summary

We are entering a challenging but exciting period when many new interventions may appear for stroke based on the use of devices. Hopefully these will lead to improved outcomes at a cost that can be afforded in most parts of the world. Nevertheless, it is vital that lessons are learnt from failures in the development of pharmacological interventions (and from some early device studies), including inadequate pre-clinical testing, suboptimal trial design and analysis, and underpowered studies. The device industry is far more disparate than that seen for pharmaceuticals; companies are very variable in size and experience in stroke, and are developing interventions across a wide range of stroke treatment and prevention. It is vital that companies work together where sales and marketing are not involved, including in understanding basic stroke mechanisms, prospective systematic reviews, and education of physicians. Where possible, industry and academics should also work closely together to ensure trials are designed to be relevant to patient care and outcomes. Additionally, regulation of the device industry lags behind that for pharmaceuticals, and it is critical that new interventions are shown to be safe and effective rather than just feasible. Phase IV post-marketing surveillance studies will also be needed to ensure that devices are safe when used in the 'real-world' and to pick up uncommon adverse events.

Declarations

This paper results from a workshop organised by the European Stroke Organisation (ESO) on devices for stroke, and held in May 2013 in London UK.

PB is Chair of the ESO Industry Roundtable, Chief Investigator of the STEPS trial and OAST/OA-prevention and OA-cognition collaborations, chair of the data monitoring committees for the AVERT, EuroHYP and ReNeuron trials, and a member of the VISTA Executive. MB is President of ESO. CB is International Market Development Manager at Covidien. Covidien manufactures numerous devices of potential relevance to stroke including neurovascular stent catheters (for thrombectomy) and intermittent pneumatic compression sleeves (for DVT prevention). GAD is the Director of the Florey Institute of Neuroscience and Mental Health, Melbourne, Australia and Past President of the World Stroke Organization (WSO), and Co-Chair of EXTEND-IA trial. SMD is Director of the Melbourne Brain Centre at the Royal Melbourne Hospital, University of Melbourne and President of the World Stroke Organization, and Co-Chair of EXTEND-IA trial/ GF is Director of the UK NIHR Stroke research network. WH is founding President of ESO, honorary President of ESO, Chair of the steering

committees of ECASS-1/2/3/4 and member of the steering committee of SWIFT PRIME. CI is Senior Research Fellow at the University of York. KL is ESO President Elect, chairman of the VISTA and VICCTA collaborations, chairman of the data monitoring committees for the DIAS, Grifols plasmin and NEST-3 trials, a member of committees for the REVASCAT and SITS-OPEN trials, and of the STAIR-VIII group. SCP is Vice President, Clinical Affairs, of Covidien Neurovascular. TT is a Senior Specialist at H Lundbeck, a company developing an intravenous thrombolytic agent.

TABLE 1. Completed, ongoing and planned trials of devices for the prevention and treatment of stroke and its complications. The list of devices, companies and trials is designed to give an impression of recent and current activities, and is not meant to be comprehensive. Additional detailed information is available from: http://www.whichmedicaldevice.com (downloaded 26/10/13).

Stroke phase	Aim	Mechanism	Company(s)	Academia	Device	Studies/Trials
Acute stroke	Reperfusion	Thrombectomy, intra-arterial catheter/stent	Codman Concentric Covidien DePuy Synthes/Codman EV3 MindFrame Penumbra Reverse Medical Revive Stryker	Saarland University University of California University of Glasgow	EKOS Merci Penumbra Restore Revive Solitaire	ESCAPE EXTEND-IA IMS-3 (31) MERCI (13) MR-RESCUE (34) PISTE POSITIVE PRIISM ReFlow REVASCAT RIVER-3/4 SWIFT (63) SWIFT PRIME SYNTHESIS (65) THERAPY THRACE TREVO (64)
		Ultrasound enhanced thrombolysis	Cerevast	Texas-Houston Medical School		CLOTBUST (74) CLOTBUST-ER
		Partial abdominal aortic occlusion	CoAxia		NeuroFlo	SENTIS (75)
		Sphenopalatine ganglion (SPG) stimulation	BrainsGate			ImPACT-1 (76) ImPACT-24B
	Neuro-protection	Hypothermia-surface cooling	BARD/Medivance EMCOOLS	University Heidelberg	Arctic Sun RhinoChill	EuroHYP-1 HAIS-SE

			Seiratherm		Tempedy	iCOOL-1
		Hypothermia - endovascular cooling	Innercool ZOLL		Celcius control Thermogard XP	EuroHYP-1 HAIS-SE ICTuS-L (49) ICTUS-2/3 (77) ReCCLAIM-1/2 (78)
		Transcranial near-infrared laser	PhotoThera		NTS	NEST-1/2/3 (40-42) StELLAR
	Perconditioning	Limb ischaemia		University of Nottingham		ReCAST
Treatment of complications	Dysphagia	Feeding tubes		University of Edinburgh		FOOD-2 (79)
		NMES	VitalStim	University of Florida	Cutaneous stimulator	ANSRS Carnaby (80)
		EPS	Phagenesis	University of Manchester	Nasogastric tube	STEPS (81-83)
		tDCS	Phoresor	Harvard Medical School University Hospital Mont-Godinne		iSWAT Kumar (84)
Prevention of complications	Nocturnal supine position	Avoid supine position		Chang Gung Hospital	ZZoma positional device	
	Deep vein thrombosis	Graduated compression stockings	Tyco/Covidien	University of Edinburgh	Thigh/mid-length stockings	CLOTS-1/2 (71, 85)
		Intermittant pneumatic compression of leg veins	Kendall/Covidien	University of Edinburgh	Pneumatic sleeves	CLOTS-3 (73)
Rehabilitation	Limb recovery	Robot, exoskeleton		Chang Gung Hospital Thomas More Kempen Veterans Affairs	Mit-Manus/InMotion2	ARTHE IRCCS San Raffaelel RT

						SRT3
		rTMS	Nexstim	Hadassah Medical Organisation Nationwide Shildren's Hospital University of Minnisota		ContraStim rTMS tmstroke
		Sensory enhancement	AMES			AMES
		tDCS		Charite University Beth Israel Deaconess Medical Center Spaulding Rehabilitation Hospital University di Verona University Hamburg-Eppendorf University Hospital Inselspital		GT-1-tDCS RECOMBINE STIMBOX Tdcs TDCS+OT TraGAT
		Vagus nerve stimulation	MicroTransponder		Vivistim	
		Vibration and mirror		Hadassah Medical Organization		VibMirror
	Limb spasticity	FES		University of Pittsburgh	Ness H200	FES
	Gait	Treadmill		Tan Tock Seng Hospital		VASST
	Neglect	rTMS		Hôpitaux de Paris		NEGLECT
	Shoulder pain	Microstimulator	Bioness Inc		BBPM	BBPM
Prevention	Cardio-embolic stroke	Cardiac rhythm monitoring to detect AF	Biotronik	University of California University of Valencia	Cardionet Reveal XT	CMACS CRYPTONITE IMPACT

		Left atrial occlusion	AGA Medical Corp Boston Scientific St Jude Medical		AMPLATZER Plug WATCHMAN	ACP EVOLVE PLAATO PROTECT AF (86, 87) PREVAIL (88)
	Paradoxical embolism	Patent foramen ovale (PFO)	Gore NMT MEdical St Jude Medical	Hillerod Hospital Hôpitaux de Paris	Starflex Amplatzer HELEX Septal Occluder	CLOSE CLOSURE (25) DEFENSE-PFO PC-trial (23) REDUCE (54) RESPECT (24)
	Carotid artery stenosis	Stent & embolism protection devices	Boston Scientific Mircus Endovascular Corp EV3 Gore Invatec RX Acculink	NINDS Vienna General Hospital	FilterWire Mo.Ma NexStent Pharos stent Protégé SpiderFX	ARMOUR CABERNET CREATE CREATE PAS CREST VISSIT
	Hypertension	Iliac arteriovenous fistula	ROX Medical	Royal College Surgeons Ireland	ROX Coupler	ROX Control HTN (RH02)
		Carotid baroreflex stimulation	CVRx		Barostim neo Rheos IPG	Bakris (89) Hoppe (90)
		Renal artery denervation (chemical, radiofrequency, ultrasound)	Boston Scientific Cardiosonic Kona Medical Medtronic ReCor Medical St Jude Medical Terumo Vessix		Iberis Paradise Tivus	EnligHTN-3 SYMPLICITY HTN-1/2 (18)

FES: functional electrical stimulation; NINDS: National Institutes of Neurological Diseases & Stroke; NMES: neuromuscular electrical stimulation; PES: pharyngeal electrical stimulation; rTMS: repetitive transcranial magnetic stimulation; tDCS: transcranial direct current stimulation
Sources of information: Device companies, Internet Stroke Center, publications, personal files

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