Future directions for Surgical Trial Designs in trigeminal neuralgia

Joanna M Zakrzewska MD [1], Clare Relton PhD [2]

[1] Consultant / Honorary Professor

Division of Diagnostic, Surgical and Medical Sciences

Eastman Dental Hospital

UCLH NHS Foundation Trust

256 Gray's Inn Road

London

WC1X 8LD

UK

[2] Senior Research Fellow

School for Health and related Research

University of Sheffield

Regent Court, 30 Regent Street

Sheffield

S1 4DA

UK

c.relton@sheffield.ac.uk

Corresponding author

Joanna M Zakrzewska

Division of Diagnostic, Surgical and Medical Sciences

Eastman Dental Hospital

UCLH NHS Foundation Trust

256 Gray's Inn Road

London

WC1X 8LD

j.zakrzewska@ucl.ac.uk

Tel. 020 3456 1195

Fax 020 3456 1105

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Key points:

1. There is no high quality comparative effectiveness research for surgery versus pharmacological management or for different surgical techniques.
2. High quality evidence (randomised controlled trials) is required to inform routine decision making for patients with TN and their consultants.
3. The design and conduct of surgery trials using the standard design has numerous challenges (patient preferences, clinician preferences, clinically meaningful outcome measures, learning curves for surgical techniques, irreversibility of results)
4. The 'cohort multiple RCT' design is an innovative alternative design that provides both long term observational data and a facility for quick and efficient conduct of multiple trials. Unlike standard trials, patient information and consent replicate that found in routine healthcare wherever possible.
5. Embedding multiple trials within a cohort of patients with a diagnosis of TN would enable the quick and efficient identification and recruitment of patients to trials of a variety of interventions, and help provide the information that patients and clinicians require.

Synopsis

Should patients undergo a surgical intervention as soon as they receive a diagnosis of trigeminal neuralgia (TN), or should they wait until pharmacological treatment fails? Knowing the answer to this question would help inform patient and clinician decision making. To answer this question, randomised controlled trials (RCTs) comparing standard medical pharmacological interventions with surgical treatments are needed. This article describes some of the challenges that have been encountered in surgical trials for TN, and provides some guidance for future trials in this area. One future direction for TN research is to utilise the innovative 'cohort multiple RCT design'. This approach enables multiple trials to be

embedded within a single cohort of patients a diagnosis of TN, providing an efficient and effective approach to the testing of multiple interventions for TN with each other and with usual care.

Introduction – which trials are needed?

Unusually trigeminal neuralgia (TN), a rare disease, can be managed both medically (pharmacologically) and surgically, and there is some evidence of the importance of psychological therapies. So what trials are needed?

1. Comparison of medical vs surgical treatments

Surgical management can yield 100% pain relief for 70% of patients for 10 years [1] [2]. Medical management provides 50% pain relief but becomes less effective over time and as the doses is raised result in poorer tolerability [3] . Many of these patients eventually opt for surgery but best timing of this is still unknown. [4] Although the majority of patients remain on medical management until it fails [5] [6], there is evidence that **patients prefer surgical management** . [7] Zakrzewska et al [8] reviewing 220 patients who had posterior fossa found 73% said they would have preferred earlier surgery.

There is also evidence that **clinicians/ surgeons support early surgery** for classical cases of TN and those with positive imaging [9]. Others suggest that surgical treatments should only be offered after patients become refractory to medical management which is defined by Obermann as failure of two drugs [10]. Di Stefano et al [6] in their cohort of 200 patients on medical management suggest that medications remain highly effective and only 7% in their cohort needed surgery.

However, there is **no rigorous (i.e. randomised controlled trial RCT) evidence to support either an early or delayed surgical management compared to pharmacological management of TN.** The recent Cochrane systematic review on neurosurgical interventions in TN identified just 11 RCTs involving 496 patients, [11] however the majority of these trials were biased. None of the high quality trials compared different surgical techniques with each other or compared surgery with pharmacological management. The three high quality RCTs compared different surgical

techniques with potentially more refined versions of the same technique [11]. There were no RCTs of microvascular decompression MVD, (the most invasive procedure and only non-destructive procedure) but observational data which suggests that it may have the best long term outcomes for pain relief. [12]

Given patient and clinician preferences and the lack of evidence to support surgery or pharmacological management, the most important research question for the TN profession is should patients undergo a surgical intervention as soon as the diagnosis has been made (i.e. very early in the course of the condition), or should they wait until the conservative (pharmacological) treatment has failed? In other words, should they receive surgical treatment that provides something very close to a cure (albeit not necessarily permanent) cure or remain on medication? If early surgery was comparable to (or better than medical management) this information would impact on how patients viewed their options at the time of diagnosis, and provide more flexibility in the decision making process in the early stages.

2. ***Comparison of the different surgical techniques***

There are an emerging number of studies comparing different techniques, however the interpretation of the results of these studies is hampered by differences in the outcomes used and the short duration of outcomes. [13] Future trials should use the same outcomes and also follow up patients for minimum of 5 years. [1]

3. ***New and comparative drug trials***

Drug trials in TN are few and far between and most drugs used to date have been established anti-epileptics. However there is now a potential for a new drug with good efficacy and better tolerability to be evaluated. Phase 2 studies have been completed using a novel design of enriched enrolment randomized withdrawal (EERW) design in which patients are initially screened, and then all are put on the active drug for a set period [14]. After this period only those considered to have been responders are allocated

to the randomised part of the trial where the active drug is compared to a placebo. In this design there is a set time for the trial but non responders are encouraged to drop out.

Moore et al [15] have done a systematic review of all the pain trials using the EERW trial design and suggest that these can play an important role if correctly designed but may be difficult to compare outcomes with classical trials. Comparisons of different drugs are also required and whether single or multiple drugs should be used [12] .

4. ***Addition of psychological therapies*** .

TN has considerable impact on quality of life and patients live in fear of a recurrence of their pain. [16] One small study (n= 15) has shown that spontaneous pain as opposed to pain evoked by a trigger could be driven by emotional factors. [17] There is anecdotal evidence from surgeons and patients that patients are reluctant to touch their faces after surgical treatments in case they trigger an attack, this behaviour is also seen in continuation of medications post-surgery especially after stereotactic radiosurgery surgery (SRS).

In summary there are a number of research questions in the field of TN that require evidence from well design RCTs. This article describes a number of challenges in the design and conduct of trials with a particular emphasis on surgical trials for TN. It will provide some pointers for future trials.

Problems with randomised controlled trials

This section describes the problems with the design, implementation and interpretation of RCTs of interventions to help patients with their health.

1. Recruitment

RCTs often have difficulty recruiting sufficient numbers of patients. Macdonald et al [18], found that less than a third of 114 multicentre, publicly funded UK RCTs recruited their

original target number of patients within the time originally specified. Failure to recruit to target may have implications for the power and generalisability of trial results. The sample populations often do not contain ethnic minorities or other hard to reach groups e.g. elderly so making it difficult to apply to general practise. Trials of medical management in TN are all very small. [19]

Ethical issues

In a systematic review of the literature on barriers to participation in RCTs, Ross [20] et al found that concerns with information and consent were some of the major reasons why both patients and clinicians were unwilling to participate in trials. In routine real world health care, patients are rarely told of treatments that their clinicians cannot with certainty provide nor are patients told their treatment will be decided by chance [21] . On the other hand, in clinical trials providing this type of "full" information before randomisation is regarded as an ethical requirement. The consequence of this “full” information is that patients worry about the uncertainty of treatment outcome especially if there is the possibility that they may be allocated to placebo. It is acknowledged that for clinicians there is a potential conflict of interest between what is good for the current patient and what is good for future patients [22]. These issues are nicely demonstrated in the anecdote in box 1.

Box 1 here

In a recent phase II trial patients were reluctant to be recruited as they had got reasonable control and tolerability on their current drugs and were concerned that the new drug for TN would upset this balance (currently unpublished). Moreover, in general practice patients are often given less information about their treatments than that currently required by some ethics committees who are asked to review intervention trials.

2. Patient preferences

Standard "open" (unblinded) pragmatic trials often compare an intervention with treatment as usual. Where the "standard care" on offer is available outside the trial, however, the only incentive for the patient to participate (apart from altruism) is to receive the new intervention. If a patient is allocated to treatment as usual, he or she may withdraw from the trial (attrition bias) or exhibit disappointment bias when reporting outcomes. [23] Patients with rare diseases are more reluctant to take part in trials for this reason. [24] There may therefore be a treatment effect, which results from patient preferences and not from therapeutic efficacy [25]. This is a major problem in TN were destructive treatments give very different results from non destructive methods or if compared to medical therapies. As surgery is irreversible patients may prefer to delay this yet when asked specifically about timing of MVD the majority in retrospect said they would have wanted surgery earlier. [8]

3. Treatment comparisons

For conditions with many potential treatment options, there are often multiple trials conducted, with each potential treatment being trialled, one at a time, in different populations by different research teams, often with heterogeneous outcomes and heterogeneous trial populations. Thus when treatments need to be compared, they can only be done by indirect methods. The effectiveness of treatments A versus C can be difficult to evaluate if the only trials of treatments are A versus B and B versus C exist. Indirect comparisons—where two interventions are compared through their relative effect versus a common comparator—can succeed, but sometimes result in significant discrepancies compared with the results of head to head randomised trials. [26]. Many competing interventions have thus not been compared or have been compared inaccurately which is a waste of valuable information and money. This is a major problem in TN where there are no RCTs of MVD and the RCTs that have been done compare surgical techniques and use varying outcome measures at varying time points. It has therefore been very difficult to compare not just surgical trials but medical ones for the same condition.

4. Diagnosis

An essential of all trials is an accurate description of the participants using evidence based diagnostic criteria as this will enable clinicians to determine if the patients in the trial are representative of their patients. TN was considered to have very clear diagnostic criteria but it is now emerging that there are several variants and the nomenclature has become confusing with terms such as type 1 and 2 TN or TN with concomitant pain. [27] , [28] There has also been a group of conditions known as the trigeminal autonomic cephalalgias which include four different conditions. Two of them short unilateral neuralgiform headache with conjunctival redness tearing (SUNCT) and short unilateral neuralgiform headache with any autonomic symptom (SUNA) may in fact be yet other variants of TN [29] .

TN and its variants are unusual in that the pain is episodic and there are unpredictable remissions and relapses which makes it even harder to be sure that the end result is due to the intervention rather than the natural history of the disorder.

5. Timing

New medications undergo a specific standardised pathway in order to become registered, but this is not the case for surgical interventions. A surgical intervention passes through many phases of innovation and refining and has a tipping point at which the intervention is no longer an innovation but a routine procedure. The tipping point (when equipoise is lost) is extremely variable and cannot be predicted thus making the accurate timing of RCTs difficult **.** [30] This has generated what has become known as Buxton's law: 'It is always too early [for rigorous evaluation] until suddenly it's too late'. [21]

Thus the newest intervention for TN, SRS was first assessed in an exploratory trial to determine its efficacy and this was done in those patients who would benefit most and by surgeons who had the freedom to develop and refine the intervention. In 2001 a RCT by Flickinger et al [31] of this procedure in a multicenter trial showed that one rather than two isocentre were sufficient to provide pain relief without sensory loss, one of the first refining

studies. This could have been followed by a pragmatic trial which included a very broad population and surgeons with a range of expertise so it represented most closely what occurs in general practice. This approach would have provided information on both the short and long term outcomes of SRS and could have addressed cost effectiveness and quality of life questions if outcomes had been assessed independently. [23] This would have then enabled a standard to be set against which audits could be carried out. Schnurman and Kondziolka [32,33] have suggested an alternative approach to this problem see Box 2

Box 2 here

Schnurman and Kondziolka [33] then applied this to a series of surgical procedures including SRS for TN. They found for this procedure an equal number of initial studies,16 with 1250 patients and 16 cohort studies and therefore estimated that the year to PAS was 10 years , occurring in 2002-3 and years to objective efficacy i.e when accepted by the surgical community was 10-11 years. In comparison endovascular coiling of aneurysms took only 5 years to objective efficacy. These results are also influenced by accessibility and approval of the equipment, the rarity of the disease and the ease with which an RCT can be done. The authors conclude that SRS for TN could be evaluated through an RCT.

6. Funding

Funding is often lacking and estimates of costs of the studies can be difficult to predict due to the multiplicity of factors involved, estimates becomes more complicated if the trials are multicentred .[34] Commercial influences often also come into play and may affect surgeons' involvement. The equipment for SRS is very expensive and in cost evaluations, which also take into account quality –adjusted life years, SRS is the most expensive procedure of all surgical approaches.[35]

7. Choice of comparators

There are many types of comparator available, but not all comparators are suitable for all types of surgery. Many trials compare surgical intervention to watchful waiting or medical treatment and this can be a satisfactory method for chronic conditions. When comparing surgical procedures complications may be very different for the two interventions and this can affect both patient preference and blinding of outcomes e.g. ablative procedures are likely to result in sensory loss whereas decompression of the trigeminal nerve is highly unlikely to lead to sensory loss but can result in hearing loss. When the comparator is a different surgical technique then the same surgeon may be performing both interventions. He/she may be skilled in both but it is equally likely that there is a differential expertise between procedures. This then calls for a different approach that takes into account surgical expertise. [36] However, using expert surgeons may then result in an inability to generalise to all neurosurgeons.

8. Surgeons' equipoise

Equipoise means that there is uncertainty regarding whether the trial treatment will be more beneficial to people than the comparator. Individual surgeons often have preferences for one intervention over another and thus may not be willing to take part in a clinical trial. Career surgeons are selected for traits that include comfort with making important clinical decisions quickly with incomplete information. This quality, required for decisive action during operations, may make it difficult for them to be consciously uncertain which of two treatments is better. Equipoise as to whether a treatment is effective or not is required in the scientific medical community but is not required from individual surgeons unless they have to perform two different types of surgical intervention in the trial. This can be a problem in neurosurgical interventions in TN as some procedures are destructive whereas others aim to preserve sensory function and so neurosurgeons may be reluctant to randomise patients to ablative procedures which they may consider using only in those patients who are not medically fit for major surgery.

9. Interventions

In pharmacological trials the main intervention in most cases is the drug alone, however, surgical interventions are highly complex and include the procedure itself, the surgeon, the surgical team and pre and post operative care . [9, 15, 23, 37]

All surgical interventions have two learning curves, both of which are variable. The first is perfecting the surgical techniques and the second is the personal learning curve of the surgeon. This has been well illustrated when looking at the drop in mortality and complication rates of MVD for TN over the years, mortality was over 1% and now is around 0.2-0.4%. [38]

10. Blinding

Although it is considered important that both patients and health care professionals are blinded to ensure that exaggerated estimates of treatment are not reported.it can lead to patients being unsure of what is the required outcome and opting for an intermediate outcome. [39] However this is much more difficult to do in non pharmacological trials then pharmacological trials**.** [40] In a review of 110 RCTs evaluating treatment of pharmacological and non-pharmacological interventions in patients with hip or knee osteoarthritis it was showed that blinding was more difficult to achieve and unblinding occurred more frequently in non-pharmacological intervention studies. Blinding of surgical procedures of patients/care providers is possible if the methods to blind are common. These include treatments that have the same physical characteristics and the same route of administration, surgical interventions that leave similar scars and post-operative care e.g number of isocentres for delivery of radiation to the trigeminal nerve but difficult to do when a using a frame or not for neuronavigation for delivery of radiofrequency thermocoagulation. [41] Blinding is improved if surgeons who performed the operation have no further contact with the patients. In studies where treatments are radically different e.g surgical versus drug therapy or where control treatments are usual care or waiting list, then blinding of one group becomes impossible. In

some trials it may be easy to blind the patient to the procedure but the subsequent clinical outcomes could result in unblinding e.g different doses of radiation will lead to different complications. There is considerable evidence to show that unblinded outcomes assessment is associated with significantly larger treatment effects than blinded outcomes assessment. [42] When it is suspected that blinding may be problematical it is useful to perform an assessment e.g ask the patients which treatment they think they were given, as to whether the blinding was successful but current methods to do this assessment are far from standardised. [40]

11. Randomisation

The strength of the RCT is that by randomisation, assuming adequate concealment of group allocation, the distribution of any known or unknown prognostic factors at baseline arises purely by chance, thus randomisation is the main method that ensures that allocation bias is eliminated at baseline. [30] It is often possible to randomise in the operating theatre as shown in Erdine et al's trial of pulsed and continuous radiofrequency thermocoagulation for patients with TN. [43] It is essential when analysing the studies to ensure that the patients remain in the groups that they were randomised to at the beginning of the study, i.e use an intention to treat analysis.

12. Outcome measures

Outcomes need to be varied and include clinical, patient reported and economic both in the short and long term. Developing valid reproducible generalisable outcome measures that are then suitable for meta-analysis is complex and requires considerable consensus. Boutron et al [44] have suggested a range of different types of outcome measures which are listed in Box 3 .

BOX 3 here

Different specialties have tried to develop some core outcome measures that will then lend themselves to meta-analysis and in determining the sample size of a study. e.g pain [45], orthopaedics [46]. Often some generic questionnaires are needed in order to compare to other data and the International Association for the Study of Pain (IASP) have suggested a range of measures that should be used in clinical trials of pain patients IMMPACT [45]. Measures using questionnaires need to undergo testing which include its test-retest reliability (reproducibility), responsiveness (ability to detect clinically important change), and validity [47]. The major outcome measure of surgical treatments for TN has been pain relief and there are very few reports of quality of life or other patient important outcomes. [48] The Barrow Neurological Institute (BNI) scoring system [49] (which evaluates pain intensity and numbness) was first used in SRS and has been adopted by several centres. However, this has not undergone psychometric testing and it is not clear how it is administered e.g from the medical notes or with the patient [50] . Reddy et al [51,52] have reported on the use of the BNI and a Visual Analog Scale (VAS) to determine the minimum clinically important difference in pain improvement after an MVD [51] , SRS [52] but the sample sizes were small. To overcome these shortcomings Lee et al [53] developed the Brief Pain Inventory Facial for which they have also estimated the minimum clinically important differences [50] and have applied it pre and post surgery to a group of patients undergoing SRS [54]and MVD. [55]

Poolman et al [46] have highlighted other difficulties in using outcome instruments, these include cultural and linguistic considerations, physical and mental capacity of patients and the statistical methods used to evaluate them. Many outcome measures are in the form of questionnaires which then need to be administered in an independent way to prevent the assessor being blinded by the researcher e.g. patient completing questionnaire in the presence of or help of the researchers.

As. Zarins [47] point out that in many trials the outcome measures are then applied in a modified form which if they have not been tested invalidates them . Poolman et al [46] showed in their review of outcome measures used in orthopaedic RCTs that ten trials (37%)

used modified outcome measures and nine did not describe how the modified instrument was validated and retested. Some questionnaires are generic and can be applied to a wide variety of conditions e.g SF36 but can have little meaning for a specific entity. Thus, a questionnaire that has been validated for one clinical condition is not always valid when applied to a different clinical entity. Pan et al [56] used the SF36 in his cohort of patients but then did not find any other published study that used this tool and so went on to convert his data to the BNI as they could then compare their data. The only validated questionnaires used in TN have been the verbal rating scale of pain, Hospital Anxiety and Depression Scale to measure mood and the Brief Pain Inventory Facial for quality of life.

One of the major difficulties when comparing medical against surgical trials in TN is that for the latter 100% pain relief is expected whereas for dug management it is set at 50% in line with all other pain conditions. Patients' expectations of other outcomes may be different from medical versus surgical treatments.

Future approaches

Some important requirements of future trials are listed in box 4

Box 4 here

There have been various attempts to address the difficulties in designing surgical trials e.g. the formation of the Balliol Colloquium which reports its findings in a series of publications in the Lancet . [30], [37] , [57] have put forward their IDEAL model of the stages in surgical practise as shown in Box 5.

Box 5 here

At all stages of the development of surgical practise it is possible to use RCT designs. Although newer trial designs have been created to address some of the above problems none of these designs either increase the number of patients randomised and/or address the cost/ funding problem with standard trials. More recently, a number of studies

are embedding trials within cohorts as a way of overcoming these problems. These are described below.

Trials within Cohorts

Cohort multiple RCT design: In 2010, Relton et al [58]published their theoretical article describing the 'cohort multiple randomised controlled trial' design. This is an innovative approach to the design and conduct of pragmatic or comparative effectiveness trials – trials which aim to inform routine healthcare decision making [58]. The design aims to address many of the problems associated with standard RCT design which may reduce the generalizability of results, potentially introduce post randomisation selection bias and create a sub-optimal system for producing the information required for healthcare decision making. Since the publication of the theoretical article a number of triallists have started using the design in the UK, Canada, and Netherlands, including both trials with usual care as comparator e.g. trials within the PICNIC cohort study of patients with rectal cancer (conference presentations). Figure 1 and box 6 illustrate how this may be used for TN.

Insert figure 1 here

Insert box 6 here

Figure 1 A 'cohort multiple RCT' approach to TN

The rationale for this approach to informed consent is twofold. Firstly, as the primary motive for patients to enter clinical trials is not altruism, but their own direct benefit as patients. Clinical trial informed consent procedures should, therefore, put the needs of the patient at the centre; that is, patients should not be told about treatments that they might not then receive, nor should they be told that their treatment will be allocated by chance. Secondly, the greater the similarity between patients' experiences in trials and their

experiences in routine care, then the greater the generalisability of the trial results to patients in routine care.

The ‘cohort multiple RCT’ design will not only yield much needed data on long term prognosis of this condition but will allow both surgical and drug treatments and even adjunctive psychological treatments to all be evaluated alongside each other. It will also take into account patients and surgeons preferences, as it will be possible to evaluate the acceptability of different procedures by following up those patients who refuse the offered RCT.

Research using standard RCT designs often struggles to recruit and consequently has to randomly allocate all patients to either group in equal proportions to maximise statistical power within their total sample. The large numbers of patients recruited to the cohort in the cmRCT approach increases the statistical power of any RCTs and enables unequal randomisation. For example, a small number of patients could be randomly selected to be offered an expensive treatment and compared with a larger number of unselected patients. Unequal randomisation thus improves the efficiency of trials of high cost interventions e.g. SRS, compared with equal allocation. These factors strengthen the inferences in the trial, lower treatment costs compared with standard designs (that is, once the cohort is established, it potentially allows for rapid and cheap recruitment of patients for any RCT), and allows significant cost savings for trials of expensive treatments. Furthermore, data on treatment refusers provides information on the acceptability of the treatment and thus the generalisability of the trial results.

RCT within a cohort design: More recently, the cmRCT design has been adapted by the Finnish Degenerative Meniscal Lesion Study (FIDELITY) [59] to be able to incorporate one or more placebo trials of surgery within their cohort of patients with knee pain with meniscus injury. All patients recruited are informed that they may be offered a placebo

intervention at some point. Sihvonen [59] et al describe this as an ‘RCT within-a-cohort’ design.

Conclusion

This article has described some of the challenges encountered in trials and particularly surgical trials for TN, and provides some guidance for future trials. One future direction for TN research is to use designs which embed trials with cohorts such as the innovative ‘cohort multiple RCT design’. This approach enables multiple trials to be embedded within a single cohort of patients with TN, providing an efficient and effective approach to the testing of multiple interventions for TN with each other and with usual care.

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Box 1 Problems of informed consent "a Canadian surgeon participating in a workshop on designing clinical trials. The Canadian surgeon reported explaining a trial to a potential participant and the fact that there was uncertainty about the best treatment. At the end of the discussion the surgeon asked the patient if he had any questions. *"Yes"* said the patient, *"Can you refer me to a surgeon who **does** know what is the best treatment for me?"*

*(*Relton, Clare (2009) *A new design for pragmatic randomised controlled trials: a 'Patient Cohort' RCT of treatment by a homeopath for menopausal hot flushes.* PhD thesis, University of Sheffield. *http://etheses.whiterose.ac.uk/6644/)*

Box 2 : The progressive scholarly acceptance (PSA) method

Aim : use publications to chart progress from innovation to general acceptance

Method :

- Assumes that once there is broad acceptance that an innovation is effective the next series of papers focus on refining the technique.
- The point at which there are more papers on refinement than efficacy or effectiveness becomes the PSA point
- Assess authoring group to see if the procedure was being disseminated and the quality of the publications

Results :

- Refining studies increase efficiency, decrease costs and may have a moderate effect on outcomes
- Initial efficacy studies have a higher impact on patient care.

Box 3 Types of outcome measures

1. “Patient-reported outcomes” (e.g., pain and disabilities), when the patient is the outcome assessor.

2. “Outcomes that do not suppose a contact between patients and outcome assessors” (e.g MRI)

3. “Outcomes that suppose a contact between patients and outcome assessors” (e.g., sensory testing).

4. “Clinical events and therapeutic outcomes that will be determined by the interaction between patients and care providers” (e.g. length of hospitalization, treatment failure, and repeat surgery), in which the care provider is the outcome assessor.

5. “Clinical events and therapeutic outcomes that will be assessed from data on the medical form” (e.g., death, significant complication, short term, long terms).

Box 4 Requirements of future trials

- Use of multi-disciplinary team and a range of different skills e.g methodologists, statisticians, database designers, patients
- Completion of a systematic review not only of clinical material but animal studies
- Clinical trials protocol published before the trial start so they can be modified if necessary
- All trials registered on trial sites such as clinicaltrials.gov prior to their completion so it is transparent that the protocol outcomes are used.
- The results published regardless of whether they are positive or negative. All RCTs should be reporting using the CONSORT

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Box 5 Stages in IDEAL : Innovation, Development, Exploration, Assessment, and Long-term study

- Stages 0 - the initial pre-human work and development
- Stage 1 idea - first time it is used in human beings.
- Stage 2a development - few patients recruited, few surgeons for the intervention
- Stage 2b exploration - early exploratory phase, reports appearing
- Stage 3 assessment - procedure is part of many surgeons' practices
- Stage 4 long term study surveillance – databases set up, long term outcomes, quality assurance

Box 6 The key features of the 'cohort multiple RCT' design

I. All patients with a diagnosis of TN are recruited into a large observational cohort study, all receive treatment as usual (which may include medical or surgical options)

II. Appropriate easily collected outcome measures are chosen and measured at regular intervals for the whole cohort – including description of treatment as usual.

For each randomised control trial in the field of TN e.g. MVD or a new drug

III. All patients who are eligible for the trial are identified from the cohort "NA".

IV. Using randomisation a selection of patients" nA "are identified and then offered trial intervention "nA"

V. The outcomes of those randomly selected "nA" are then compared with the outcomes of those eligible patients not selected (but who were eligible to be selected) "NA- nA"

VI. The information given to patients and the consents sought from patients are as similar as possible to those found in routine care. All cohort patients consent to provide observational data at the outset; however, consent to "try" a particular intervention is sought only from those offered that intervention, thus replicating the patient centred information and consent procedures that exist in routine health care, where clinicians provide patients with the information they need, at the time they need it.