

Future research in emergency medicine: explanation or pragmatism? Large or small? Simple or complex?

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BACKGROUND

Recent publications have indicated that there is a crisis in clinical research. The cost of an industry-led clinical trial is now estimated at some US\$100–200 million, within which an average 25% of centres will recruit no patients. The median number of enrolment (entry) criteria in a drug trial is 49, with a median of 158 different trial procedures. The number of data items per patient often runs into thousands, so it is little surprise that the average time to trial completion increased 70% between 1999 and 2006.¹

There seems to be a self-sustaining 'industry' of bureaucracy around research. This system generates huge costs and a mountain of paperwork, which in turn makes the employment of trial managers essential. These costs are passed on to the industry or public funders of medical research. Regulatory rules that are designed for 'pharma' trials of new drugs are also applied to 'investigator-led' trials, even if the drug involved is already in use and has a very well-known safety profile.

Against this background, as our specialty evolves, it is a good time for us to ask how emergency medicine research fits in the complex and competitive world of clinical research. Our specialty is a broad church, with emergency physicians having a legitimate research interest in almost all areas of medicine. We cannot be experts in the science of 'everything', but we can be experts in a particular type of methodology, which can then be applied to many different areas. The question 'What type of primary research is best suited to emergency medicine?' is key to the future development of the academic part of our specialty.

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CURRENT SITUATION

Overall, the clinical trials that are performed in emergency medicine tend to be underpowered. A good example is the analysis of published trials on interventions in head injury.² The authors showed that a sample of 400 patients is needed to show a 10% absolute risk reduction in the chance of death. As the mortality after severe injury is about 20%, an Absolute Risk Reduction ARR of 10% (halving the mortality) would be an impossibly fantastic advance in trauma care—yet almost all of the published trials were smaller than this, so they were not even powered to detect an incredibly large treatment effect. Only one published clinical trial in trauma care had the power to show a clinically meaningful mortality difference—the Corticosteroid Randomization After Significant Head Injury (CRASH) trial of steroids in head injury (powered to show a 1% ARR). The 195 trials that had a sample size below 320 and used a mortality end point were in effect meaningless and illustrate the waste of resources that occurs when undertaking small complex trials. It would surely be better to cooperate and discover a definitive answer to one question rather than to spend time and resources finding inconclusive results for many questions.

WHAT TYPE OF RESEARCH DOES EMERGENCY MEDICINE NEED?

Academic emergency medicine is a relatively young specialty that needs to find a place in the highly competitive marketplace of clinical research. I suggest that there is not one area of research that we can call our own—and most specialist areas of medical research already have large and well-established research groups that will out-compete emergency physicians for grant funding. However, even if we cannot pick a particular topic that defines emergency medicine research, we could identify a methodology that might define

the specialist contribution of emergency medicine to clinical research—the large, pragmatic clinical trial.

The reason that we are producing many underpowered trials may be because the type of trials that are currently produced is not the type of research that our specialty needs. At present, we are undertaking small, complex, 'explanatory' type trials. We have been trained in an academic environment where this type of research is seen as the best way to explain, understand and solve a research question. Explanatory trials tend to be tightly controlled with a large number of entry criteria giving a homogeneous patient group and very well-defined and protocolised intervention and control arms. Explanatory trials are also usually complex and carried out in academic centres. However, the results are then difficult to generalise to the reality of everyday practice—it is not really very useful for me to know whether or not a treatment works under these very controlled circumstances. I want to know whether the treatment works in the altogether messier reality of my daily practice.

Medical training has traditionally been within an academic culture where a more pragmatic approach to clinical trial design is regarded as 'poor science'. Most physicians are educated through a system based on the basic sciences that values explanatory research in which 'Why?' is considered the crucial question. However, emergency medicine is a very practical specialty in which 'What works?' is a more important question than 'Why?'. A more pragmatic paradigm is therefore very well suited to emergency care research.

The difference between a pragmatic and explanatory approach has been long described³; however, it has recently become a 'hot topic' in discussions about clinical trial methodologies, as the problems with the current systems for clinical trials⁴ have become more apparent (eg, an issue of the *Journal of Clinical Epidemiology* in May 2009 was devoted to the topic).⁵ The key difference is that an explanatory trial seeks to optimise the situation to maximise the chances of the treatment showing an effect (asking the question 'Does treatment X work?'). A pragmatic trial seeks to reproduce the situation of the real world of clinical practice (asking the question 'Does treatment X work in real life?'). We know that in the real world there is a lot of variation. Doctors vary in the treatments that they give. Patients vary

in their genetics, age and co-morbidities. Healthcare systems vary; all this affects patient management. All of this variation is normal, natural and cannot be avoided. Pragmatic trials seek to include this variation to increase their external validity (generalisability)—an effectiveness trial to assess the effect of an intervention under the conditions in which it will be used. Explanatory trials seek to reduce variation to increase their internal validity—an efficacy trial to assess the effect of an intervention under ideal conditions. In designing a clinical trial, a decision needs to be made between these approaches. I would argue that emergency physicians should be more interested in effectiveness than efficacy.

A good example of pragmatic trial design in emergency medicine is the development of the CRASH2 trial.⁶ We knew that an anti-fibrinolytic could reduce bleeding after surgery and wanted to study the use of an anti-fibrinolytic in the management of bleeding following injury—needing to randomise 20 000 patients in order to show a 2% difference in mortality. We started by trying to design a trial that had well-defined entry criteria by injury mechanism and physiological and anatomical criteria. However, defining the ‘bleeding patient’ in these terms is difficult without having many criteria and a complex trial. We then asked the question—‘if we proved that there was a benefit from this treatment, how would it be used in practice?’. We then realised that, if effective, emergency physicians would want to give the drug to patients who were bleeding or at significant risk of bleeding following injury. This then defined the simple entry criterion for a large pragmatic clinical trial: ‘patients who the treating clinician thinks are bleeding or at significant risk of bleeding’ were eligible for the trial. Using this pragmatic approach to the trial it does not matter whether physicians make slightly different decisions about which patients are bleeding or at risk of bleeding; in fact, this is a strength of the method, as it reflects the real-world variation between clinicians and increases the generalisability of the trial result. Variation between physicians in the entry criteria will not lead to bias, as randomisation will lead to an even distribution of patients between intervention and control groups. The control arm in the CRASH2 trial uses the typical pragmatic approach of ‘usual care’, without any constraints on what is given as ‘usual care’. The same approach (no constraints) was applied to non-trial treatments.

This sort of approach is an anathema to a traditional way of thinking about medical research. In the traditional approach, it would be seen as very important to make great efforts to standardise entry criteria, control group treatment and non-trial treatment to give a homogeneous study population. However, we know that in the real world there is variation in the way that patients are managed. A pragmatic trial will not try to constrain non-trial treatments, and will in fact welcome variation in the study population, regarding it as a strength not a weakness—as it reflects the variation that occurs in the real world. For laypeople, the best explanation of the difference between explanatory and pragmatic approaches has been suggested as ‘Pragmatic trials are real-world studies “for decision”, whereas explanatory trials are specialised studies “for information”’.⁷

At present, there are relatively few pragmatic trials undertaken. Drug companies support only explanatory trials, as tightly controlled conditions are required by the regulatory authorities. This approach is also more likely to demonstrate a benefit from the drug, keeping shareholders happy. Academics may prefer explanatory trials as they fit with the mindset of medical research, and the tightly controlled conditions are more likely to produce a positive result and hence lead to a publication. In the USA, the FDA has followed the pharma industry lead by requiring a very explanatory approach, labelling pragmatic approaches as ‘poor’ or ‘careless’.⁵ In the past, those in control of the allocation of research grant funding have come from a very ‘explanatory’ background and so have had an inbuilt, if unconscious, bias to feel more positive towards research funding applications that follow the same paradigm. However, the nature of research funding has recently been changing with the growing presence among research funders of organisations such as the National Health Service Health Technology Assessment Programme in the UK and ‘third-party’ funders such as Medicare in the USA. These clinical and healthcare policy decision makers have a need for pragmatic information in order to decide the interventions that should be delivered,⁸ hence they have a much more positive view of pragmatic methodologies.

In any discussion about explanatory and pragmatic approaches, it must be emphasised that the key features of trial design that reduce bias (treatment allocation after trial entry, randomisation,

blinding, intention to treat analysis, etc) are equally important under each approach. It is not necessary to compromise on any of these key aspects of trial design in order to perform a pragmatic trial, so there is no fundamental difference in ‘scientific quality’ between the two. This concept is sometimes difficult for ‘explanatory’ researchers to accept as the pragmatic approach ‘just feels wrong’. However, closer examination shows that none of the sources of variation in a pragmatic trial are necessarily sources of bias and that pragmatic trials can be carried out with just as much intellectual rigour as the explanatory trials.

There is of course no binary distinction between explanatory and pragmatic methods—many trials occupy the shades of grey between the extremes described in table 1. Different research questions require different methodologies, and it is sometimes very appropriate to perform a small complex trial, for example, when demonstrating proof of concept of initial efficacy. A method, the Pragmatic–Explanatory Continuum Indicator Summary (PRECIS),⁹ has been described by an international ‘first rank’ group of trial methodologists to assist in study design. PRECIS contains 10 key domains that identify and quantify the key differences between pragmatic and explanatory approaches, with the results being presented on a ‘radar’ chart. This method is relatively recently published (June 2009), so practical experience is limited; however, it is likely to become the standard by which these methods are assessed.

Many explanatory trials are conducted with end points that do not really affect practice or matter to patients; for example, a trial in acute asthma might commonly use an end point of a change in peak expiratory flow rate, rather than an end point that is important to the patient such as symptom relief, avoidance of admission or mortality. An intervention that improves peak expiratory flow rate in acute asthma may make a good scientific publication, but it will leave clinicians, policy makers and patients thinking ‘so what?’. It could be argued, from a more pragmatic view, that there ought to be three end points in any emergency medicine trial—one related to a *clinically important* end point (mortality, a physiological measurement, etc), one related to a *patient* end point (symptom relief, length of stay, return to work, etc) and one related to *cost effectiveness*.

Clinical trials can be either ‘large and simple’ or ‘small and complex’ (the ‘small

Table 1 Comparison of explanatory and pragmatic approaches

Explanatory trial	Pragmatic trial
Variation reduced as much as possible	Accept variation—embrace variation!
Tight entry criteria (lots of exclusions)	Entry based on broader criteria
Non-trial treatments tightly controlled	No control of non-trial treatment
Smaller sample size (small complex trial)	Large sample size (large simple trial)
Control treatments strictly defined	Control left as 'usual care' at clinician's discretion
Performed in academic centres	Often performed across many centres
Difficulty in generalisation to other patients	Easy to generalise
Overestimates benefit—results never as good when applied to the real world	'Real world' estimate of benefit
Further studies needed to look at other patient groups	Will not identify subgroups who may not benefit or may be harmed
Meaningful economic analysis impossible	Economic analysis can be performed

and simple' are rare and the 'large and complex' are impractical). Explanatory trials tend to be complex, and if small effects are clinically significant (such as a 1% or 2% absolute change in mortality after severe injury), they become 'large and complex', giving rise to practical problems and huge expense. Pragmatic trials are much easier to make relatively simple, so it becomes much easier to contemplate performing a very large trial (eg, the CRASH2 trial successfully randomised 20 000 severely injured patients). Emergency physicians may have difficulty in obtaining funding for the traditional type of clinical trial, as we are competing against very well-organised and established specialities. However, we have the advantages of large numbers of patients and a reasonably cohesive specialty with the goodwill to participate in emergency care research. These advantages could be real strengths in research grant applications if we move to large, simple pragmatic trials that use the power of large numbers to reduce uncertainty.

To perform large simple trials, we need the cooperation of many emergency physicians, especially those outside the traditional 'academic centres'. To get this cooperation, our specialty leaders and training programmes need to dispel the myth that research is for academics. Research may be led by academics, but without the participation and enthusiasm of many emergency physicians, a large clinical trial will not succeed. The motivation will not be a financial reward, as large, simple 'investigator-led' trials will not have the funds to pay on a per-patient basis like pharmaceutical industry research. The reward will also not be publications, as it is impossible for all investigators in a large trial to be authors. The motivation of participants needs to be internal—they need to want to know the

answer to a question that is important to their clinical practice. This must become part of the ethos of our specialty. Participating physicians also need to feel a sense of 'belonging' to the trial, so regular communication and rewards, such as their team's photograph in a newsletter, are very important.

The structure of the trial itself needs to make it easy for the emergency physician to participate—data collection sheets need to be as small as possible (the CRASH2 trial data collection forms were one side of paper at entry and one side of paper for the results). Each piece of data collected is more work for the participating centres, so the design process has to be ruthless in eliminating the 'nice to have' data points so that only the 'must have' data points remain. A complete dataset of a few variables for each patient is much better than attempting to collect many variables for each patient, but ending up with a lot of missing data.

The coordinating centre plays an important role in a large simple trial. They are the 'glue' that holds together the project, using helpfulness, persistence, charm and nagging in the right combination to assist and motivate. It is important that this group takes on much of the regulatory burden of trial administration, as 'no time to fight the bureaucracy' is a common reason for emergency physicians to avoid participation in research. Communication is the key—newsletters, email updates, a good up-to-date website and meetings keep up the profile of the trial. The attendance of senior investigators at local meetings is always well received and usually leads to a surge in recruitment.

Finally, large, simple pragmatic trials are relatively cheap. As an example, the CRASH2 trial was publicly funded for \$8 million, which is only \$400 per subject.

This is an order of magnitude less expensive than the \$120–\$200 million cost of the average pharma industry explanatory trial.

CONCLUSION

There is a current opportunity for emergency medicine researchers to develop a leadership role focused on a specific methodology strongly applicable to our specialty. There is an increasing interest in pragmatic trials, increased funding for clinical research that gives answers to policy makers about real-world problems, a 'gap in the market' caused by a lack of pragmatic researchers and an alignment of the pragmatic paradigm with the mindset of emergency physicians. An organisation of research networks with altruistic behaviour from many emergency physicians (participating in research for the good of their patients and their specialty rather than for personal gain) would give a powerful advantage to emergency medicine research. Such networks could be powerful tools to furnish healthcare providers with pragmatic data and cost-effective end points. We may not be able to compete with the molecular geneticists for traditional 'medical research' funding, but we are in a unique position to use our cohesive organisation and the large numbers of patients passing through our emergency departments to answer questions that are important to the funders of healthcare. To carve out a distinct identity for emergency medicine research, we should develop an academic strategy that fits well with our potential academic strengths and the clinical needs of outpatients by embracing the principles of pragmatic research and large simple trials.

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