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Clinical research is a priority for emergency medicine but how do we make it happen, and do it well?

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In this issue, Keijzers et al present a survey of emergency physicians from the Australasian College for Emergency Medicine (ACEM) researcher database, aiming to inform a strategic research agenda specific to multi-centre clinical research. However the majority of respondents had postgraduate degrees and/or academic titles, so the results are likely to reflect the pet topics of researchers and must not be assumed to represent the needs of clinicians and patients. The views of our academic workforce are important, but there is a risk that failing to engage clinicians and the main clinical problems they face will lead to their further disenfranchisement from the research endeavour and make multi-centre clinical trials even harder to do.

The stakes are high for our patients, hospitals and the health system

Research provides the foundation for everything we do in medicine. Bedside clinical research, where patients are prospectively enrolled in studies including those which compare diagnostic and/or therapeutic strategies, is particularly important for guiding clinical management. Large multi-centre clinical trials are the most important way to obtain robust, generalisable results to guide our decision-making processes. Well-designed trials not only improve patient outcomes, but save money too. This is particularly so when trials are collaborative, publicly-funded and not subject to commercial interference.

Whether emergency physicians embrace bedside clinical research as a professional group will determine whether we continue our development as a strong clinical specialty, or become a rapid triage service following the agendas of other specialty groups. This is not about “protecting turf”, but rather it is critically important for our patients. Specialist groups tend to design studies to further their own interests, and their interpretation of data can be subject to strong biases. As one commentator has observed, there are good reasons to beware of these “single issue fanatics”. Of course, we ourselves are not immune to such bias. One solution is to foster strong interdisciplinary research collaborations that include a range of clinical perspectives, including those of our patients and their carers. Studies can then be designed from the beginning to answer the right questions. However, real collaborations are built from the ground up, not superimposed from above. We need to establish an environment
that encourages collaborative research and puts clinicians and their patients in the driving seat.

**Big problems, but no easy solution**

Across most if not all clinical disciplines, we face serious problems with the research we do. Many if not most studies are underpowered and/or severely biased, so the majority of “evidence” on which we base our daily practice is probably false.\(^3\)-\(^6\) When studies are clearly negative, an "important message" is often looked for somewhere amongst secondary outcomes and post-hoc analyses or, even worse, studies are dressed up as positive ones.\(^7\)-\(^8\) This continues to occurs even in major journals, despite years of work attempting to increase the quality of clinical trial reporting.\(^9\) The impact of potential biases are often overlooked or underemphasised and conflicts of interest abound throughout the research endeavour and subsequent clinical guideline development.\(^10\),\(^11\) It is little wonder that many clinicians take their academic colleagues with a pinch of salt!

This state of affairs is driven by systemic rather than individual failures. Academic performance assessment and research funding are based on numbers of publications and self-promotion, research grants never cover the true cost of research, and the lions share of funding flows to large institutions, empowering the few rather than the many. Even more important is the fact that research is simply not considered a core business in many if not most hospitals, so it can be nearly impossible to do high quality clinical research. Most hospital research groups depend on industry-sponsored trials to maintain their research infrastructure and with shrinking research budgets our universities encourage this; as the old saying goes, never stand between an academic and a pot of cash!

During clinical training most doctors receive, at best, superficial training in research methods. Many do not understand how flimsy the evidence often is for what we do, or the degree to which we are being manipulated by industry and “special interests”, and how we may be causing avoidable harm to our patients and the health system that serves them on a daily basis.\(^6\),\(^12\)
As a result of all these factors, clinical trials are notoriously hard to do, and certainly hard to do well. In addition, there remains a divide between clinical work and academia. Clinician researchers are rare animals indeed.

*The emergency medicine environment presents additional challenges*

Bedside research in the emergency medicine environment presents additional, unique challenges. Most patients are undifferentiated, with problems rather than diagnoses. Patients present with a broad spectrum of conditions, making it difficult to maintain study awareness and identify triggers for enrolment if the people of interest are only a small fraction of those we treat. Competing clinical pressures can be problematic and compounded by a dismissive attitude towards emergency research by hospital administrators and senior clinical staff. This attitude “feeds down” to junior medical staff.

There has been a call for emergency medicine as a specialty to address these unique challenges by focussing more on large multicenter trials using very simple methodology and pragmatic outcomes, requiring minimal work from enrolling clinicians.\(^\text{13}\) While there is definitely a role for this type of research, we still need to do clinical trials that collect more comprehensive data and also basic mechanistic studies, both of which help to explain clinical outcomes and generate new hypotheses. This again requires clinician researchers who bring together science and the understanding of disease processes and treatments, with an awareness of the real world clinical situation.

A number of groups have developed approaches to ED research that overcome many of these difficulties. However, one approach does not fit all clinical conditions and environments. We believe that a common factor in all successful multi-centre studies is that there has to be some sort of buy-in from the clinicians who are at the coalface, so that they see the value in balancing research with immediate clinical priorities. This is often difficult because the research may not directly affect the patient they are caring for. Examples of multi-centre ED studies we have successfully completed as National Health and Medical Research Council (NHMRC) Fellows and/or which are ongoing include the Australian Snakebite Project (ASP) including the ASP-FFP trial,\(^\text{14}\) the Emergency Department Anaphylaxis Study (EDA),\(^\text{15}\) the Redback AntiVENom (RAVE) trials I
and II, and the ongoing Primary Spontaneous Pneumothorax (PSP) Trial. The unique characteristics of these studies, practical difficulties and solutions that we have engineered are summarised in Table 1.

_Do we as a specialty (in Australia) really “get it”?_

Unfortunately, the answer to this question may be “no”. Although a number of Australasian emergency departments have done a range of studies, much research has tended to follow a “scattergun” approach rather than a cohesive long-term plan. This is perhaps largely due to the old Regulation 4.10 demand for every trainee to do a small project, without established research networks to guide them in a strategic way. We have only a handful of college fellows that can stand up on the international stage as respected experts in specific disease processes and/or secure large research grants. Few of our departments are actively participating in multi-centre studies in a way that the medical and nursing staff on the floor are always thinking “is there a clinical study available that could help this patient or future patients with the same problem?” We tend to adopt changes in practice based on the recommendations of various specialties that are themselves subject to commercial manipulation and conflicts of interest.

There is an urgent need for trainees to be properly schooled in good research methods, critical thinking and the scientific basis of medicine. Recent changes to regulation 4.10 are a good start, but more is needed so that clinical research excellence becomes embedded within all of our major emergency medicine training networks in Australasia.

_A simple plan?_

We propose a plan to address these problems (Table 2). Its foundations are clinical engagement, resource sharing, educational initiatives and real collaboration. Real, or “natural” collaboration starts from the ground up so that every participant obtains what they need, rather than dancing to tune of others, and successful approaches may vary according to local politics and/or clinical demands. For example, some departments may decide that recruiting patients into clinical trials is an expected clinical role for all staff, whereas others may decide to separate clinical and research workloads by providing extended-hours research nurse support. Therefore, we think that the key is to pursue overall
goals and principles, rather than prescribing the precise methods by which these goals are achieved. Excellent communication between all stakeholders, a free exchange of ideas and independence from commercial interests will be essential.

Some modest changes in how we measure the performance of individuals and departments is needed, along with a commitment by ACEM to improve how we educate and assess our trainees and how we accredit hospitals for training. But, most of all, we all have to understand, spread the word and demonstrate that the integration of high quality bedside clinical research into daily practice in our emergency departments is essential for patient welfare, and a cornerstone for cost-effective management of our hospitals and the health system as a whole. Government and the NHMRC will not come to our rescue. We have to do this ourselves.
5. Shun-Shin MJ, Francis DP. Why even more clinical research studies may be false: effect of asymmetrical handling of clinically unexpected values. PLoS One 2013;8:e65323.
7. Freemantle N. Interpreting the results of secondary end points and subgroup analyses in clinical trials: should we lock the crazy aunt in the attic? BMJ 2001;322:989-91.


Table 1. Examples of problems encountered when conducting multicentre studies.

<table>
<thead>
<tr>
<th>Design</th>
<th>Main difficulties</th>
<th>Key strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASP</td>
<td>Prospective, observational study of snakebites, with sample (blood) collection at multiple time points.</td>
<td>Identifying cases early and triggering recruitment across very large number site including small rural hospitals, patient followup and data collection.</td>
</tr>
<tr>
<td>ASP-FFP</td>
<td>RCT (open label) comparing FFP to no FFP for treating venom-induced consumption coagulopathy.</td>
<td>As for ASP, plus very small number of eligible cases at any individual hospital, and added workload of RCT.</td>
</tr>
<tr>
<td>RAVE I</td>
<td>RCT (double blind) of intramuscular vs. intravenous route of administration for redback spider antivenom.</td>
<td>Identifying cases early and triggering study, added workload of RCT. Patient follow up and data collection.</td>
</tr>
<tr>
<td>RAVE II</td>
<td>RCT (double blind) placebo-controlled trial to determine effectiveness of intravenous redback spider antivenom.</td>
<td>As for RAVE-I, plus practice changes triggered by RAVE-I. Randomisation across multiple sites with limited on-site support and therefore potential for protocol violations</td>
</tr>
<tr>
<td>EDA-I</td>
<td>Prospective study of anaphylactic mediators and adrenaline pharmacokinetics.</td>
<td>Large number of data elements and frequent blood sampling.</td>
</tr>
<tr>
<td>EDA-II</td>
<td>Study of gene activation in anaphylaxis.</td>
<td>Complex laboratory procedures</td>
</tr>
<tr>
<td>PSP</td>
<td>RCT (open label) comparing intervention with doing nothing for the treatment of large primary spontaneous pneumothoraces.</td>
<td>Uncommon presentation, large number of exclusion criteria. Resistance to change.</td>
</tr>
<tr>
<td>Goal</td>
<td>Structural changes required</td>
<td>Some things that will help</td>
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<tr>
<td>Clinical engagement</td>
<td>Improved clinical research training.</td>
<td>Reviewing ACEM training, assessment and department accreditation processes with a specific focus on bedside clinical research</td>
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<td></td>
<td>Protected clinical research time for ED clinicians, with clinical research support in EDs to enable a balance between immediate clinical priorities and clinical research.</td>
<td>ACEM accreditation of departments to include criteria for (i) appropriate protected time and support for bedside clinical research and (ii) satisfactory clinical research outputs that are required to maintain accreditation.</td>
</tr>
<tr>
<td>Resource sharing and collaboration</td>
<td>Improved access to specialised resources such as expertise in ED trial planning and logistics, expertise in specific diseases, and research laboratories.</td>
<td>Forming regional and national ED research alliances to share existing resources, minimise duplication of efforts and seek collaborative funding opportunities as they arise.</td>
</tr>
<tr>
<td></td>
<td>Systematic approach to developing trial protocols, engaging clinicians from all sites that are likely to participate</td>
<td>Developing standard operating procedures within research alliances.</td>
</tr>
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<td></td>
<td>Focus on measuring and rewarding collaborative research outputs by clinical researchers, and downplay the importance of numbers of publications by individual staff members</td>
<td>Making collaborative clinical research outputs a major component of ACEM accreditation criteria for training hospitals. This should focus on effective participation in collaborative (non-commercial) clinical trials and research alliances, including confirmation of numbers of patients enrolled, quality and completeness of data collected, and the quality of site research governance processes.</td>
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</tbody>
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