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Conducting Clinical Trials

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EVIDENCE BASED MEDICINE

Sackett has defined evidence based medicine (EBM) as "the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients. The practice of EBM means integrating individual clinical expertise with the best available external clinical evidence from systematic research." (1). Sources of external clinical evidence include clinical research (of which randomized controlled trials are only a part), research from basic science, and research which synthesises expert opinion. A hierarchy has been proposed (Table 1) for use in evaluating this evidence.

Table 1. Hierarchies of evidence defined by Eccles et al. (2)

Category of Evidence
Ia: evidence from meta-analysis of randomised controlled trials
Ib: evidence from at least one randomised controlled trial
IIa: evidence from at least one controlled study without randomisation
III: evidence from non-experimental discriptive studies; such as comparative studies, correlation studies and case-control studies
IV: evidence from expert committee reports or opinions and/or clinical experience of respected authorities

Since more weight is placed on the results of the randomized controlled trial (RCT) than on expert opinion, it follows that a basic understanding of clinical research is relevant to all clinicians who wish to practice EBM. Does it also follow that all clinicians should undertake research? Research is expensive in time, and often also in other resources. Our patients are our most precious resource. The world literature has been flooded with reports of studies varying from excellent to un-interpretable. Separating the meaningful from the meaningless and synthesizing these data into useful information has become a major challenge. In fact, a whole industry has arisen around systematic reviews of clinical studies (Box 1). Unfortunately, systematic reviews (with or without meta-analysis) can only be as good as the trials they review.

THE VARIABLE QUALITY OF PUBLISHED RESEARCH

A persistent problem with the interpretation of the results of research relates to the variable quality of the research. This may seem surprising, at least in respect of peer reviewed journals. However, the assumption that the process of editorial peer review ensures adequate quality in either the conduct or the reporting of research seems to be unfounded. In 1983, Bailar and Patterson identified that part of the problem of poor quality in published research was a lack of empirical research into the peer review and editorial processes at the heart of medical literature, and called for studies to be done on these processes (3). Editors at JAMA responded by convening a conference at which the results of such research could be presented. By 2002 nearly 200 papers per year dealt with this subject. However, in an editorial on the fourth such conference Rennie quoted the following comment made after the third conference and indicated that it still applied.

". . . there are scarcely any bars to eventual publication. There seems to be no study too fragmented, no hypothesis too trivial, no literature citation too biased or too egotistical, no design too warped, no methodology too bungled, no presentation of

Box 1. Some organisations which provide evidence based reviews and guidelines in relation to healthcare.

The Cochrane Library Britain (http://www.cochrane.org/docs/descrip.htm) is coordinated by the Cochrane Collaboration (an international not-for-profit contains the following (regularly updated) evidence based healthcare databases.

- Cochrane Database of Systematic Reviews (CTSR);
- Database of Abstracts and Reviews of Effectiveness (DARE);
- Cochrane Central Register of Controlled Trials (Central-CCTR);
- NHS Economic Evaluation Database (NHSEED);
- Cochrane Database of Methoodological Reviews (CDMR).

The Cochrane library organisation) and the UK's National Health Service Centre for Reviews and Dissemination (below)

The National Health Service Centre for Reviews and Dissemination (CRD), University of York, UK (http://www.york.ac.uk/inst/crd/index.htm), was established in 1994 to promote the use of research based information. The centre for reviews and dissemination has three databases:

- Database of abstracts, of reviews of effectiveness (DARE);
- NHS economic evaluation database (NHSEED);
- Health technology assessment database (HTA).

Agency for Healthcare Research and Quality (AHRQ), USA (http://www.ahrq.gov/), is described on its webpage as "the Nation's lead Federal agency for research on health care quality, costs, outcomes, and patient safety". This agency has various functions including the establishment of evidence based practice centres whose role is to produce reports on particular aspects of practice or technology.

National Institute of Health and Clinical Excellence (NICE), Britain (http://www.nice.org.uk/page.aspx?o=home), is described on its webpage as "the independent organisation responsible for providing national guidance on the promotion of good health and the prevention and treatment of ill health." It provides guidelines and systematic reviews on a wide range of clinical topics, and numerous appraisals of medical technology.

results too inaccurate, too obscure, and too contradictory, no analysis too self-serving, no argument too circular, no conclusions too trifling or too unjustified, and no grammar and syntax too offensive for a paper to end up in print" (4).

Some of the deficiencies which have repeatedly been identified in clinical trials, even those reported in major journals are:

- Inadequate review of the literature in relation to the study
- inadequate formulation of hypotheses;
- inadequate blinding;
- incorrect statistical analyses;
- inadequate discussion of limitations;
- ghost or guest authorship;
- publication bias (positive results are more likely to be published than negative);
- fraud (e.g., data that have simply been fabricated).

It can be seen that the pressing need in research is not more volume, it is better quality. We should be focusing the use of our time and resource, particularly our patient resource, on high quality, important research. This requires expertise which can only be obtained by experience or through training. It follows that the primary responsibility for research should be assumed only by those with reasonable experience in this activity, but a contribution to research can be made and is needed from all clinicians.

QUANTITATIVE AND QUALITATIVE RESEARCH

It is often said that research is about finding the answer to an answerable question. This is true for clinical trials but it is not true of all research. Medicine is based on phenomenological or observational research. This is one example of qualitative research, the importance of which is being recognized increasingly in recent years (5). Qualitative research tends to be inductive and one of its roles is to develop hypotheses. Quantitative research is generally about testing these hypotheses. In addressing a particular question for research, the best method is the one best suited to answering the question, and this is not always an RCT. Runciman (6) [and others (7,8)] think EBM should include qualitative data (9).

This paper, will concentrate on quantitative clinical trials and will four aspects of these trials:

- the process of research;
- compliance with regulatory requirements for research;
- reporting research (i.e., writing the paper);
- inspirational aspects of research.

THE PROCESS OF RESEARCH

Literature Review

This is the first step. Research is about adding to the existing body of knowledge. It is a waste of time and resource, and unethical, to expose patients to the risks and inconvenience of research in relation to question that have already been answered.

The literature review needs to be systematic and comprehensive. It needs to summarise what is known on the subject, identify what is not known and justify the primary hypothesis of the study.

Formulation of the Research Question

The generation of an accurate, testable, primary hypothesis is possibly the most important step in the development of a research protocol. I recently spent two hours in a meeting, involving some of the most prestigious researchers in the country, in which the discussion was entirely focused on refining a primary hypothesis. Closely linked to the primary hypothesis is a defined primary outcome variable. Put simply, it is essential to define the question you intend to answer, and to define how you are going to answer it.

Definition of Population

Inferential statistics utilise samples to infer information about populations. The population might be all patients in New Zealand, all patients admitted to Auckland Hospital in 2005, or all patients between the ages of 70 and 71 who bank with the Auckland Savings Bank. The results of the study will only apply to that population. In general, a high degree of selectivity in defining the research population increases the chance of showing a difference between intervention and placebo but reduces the degree to which the results can be extrapolated to wider groups of patients. Recruitment is always difficult, so inclusion and exclusion criteria need to be considered carefully.

Definition of Sampling Strategy

To make valid inferences from a sample about a population, it is essential that the sample is taken in an appropriate way. There are various techniques of sampling, depending on the objective of the study, but usually a random selection of subjects from the population will be used. The method of making this selection needs to be clear and explicit.

Allocation Between Groups

Typically, the clinical trial will involve randomisation of patients to an intervention or a control situation. Randomisation needs to be rigorous and explicit. The methods by which randomisation is achieved need to be clearly spelled out.

Patient Information Sheets

These are important and tend to be inadequately developed. They should be written clearly in simple language. They should be explicit about possible risks. The protocol should explain who will get consent. Some authorities require the formal signed consent to be obtained by a doctor. A combination of provision of information by a nurse and final confirmation and form signing by a doctor works well.

Sample Size Estimation

This is a black art, but very important. Most researchers will need advice. Sample size estimation is more about understanding the implications of the sample size than about getting an absolute answer to the question of how many patients should be studied.

A Protocol

A fully developed protocol is essential for a successful research project (Table 2). Protocols tend to be well done with company sponsored research but are often neglected in smaller projects. The protocol should define every aspect of the study. It is a tool for the conduct of the study and for the subsequent write up of the results. There is an increasing trend towards registering protocols at the time the study begins. For the FDA and industry research this has becoming particularly important.

Table 2. Check list for evaluating the quality of a clinical trial, modified from Huwiler-Muntener et al. (10) following the items in the Consort Statement (11) (indicated by a +). This check list can be used as a template for writing a protocol or a paper.

Section	Item	Consort
Title	1. Does the title identify the study as a randomized controlled trial?	+
	2. Is the trial identified as prospective and blinded?	
	3. Does the title give a balanced indication of the significant findings of the trial?	
Abstract	4. Is the abstract presented in a structured format?	+
	5. Are the key methods described?	
	6. Are as many data as possible included in the abstract?	
	7. Is there a balanced conclusion indicating the significant findings of the trial?	
	8. Are all parts of the abstract strictly in concordance with the same parts of the main body of the paper? No new or different claims or material should appear in the abstract.	
Introduction	9. Is there a brief summary of a systematic review of the relevant literature?	+
	10. Are deficiencies in current knowledge identified?	
	11. Is the importance of the study explained?	
	12. Are the objective stated?	+
	13. Is the hypothesized stated?	+
Methods	14. Is the study population described?	+
	15. Are start and end dates of data collection stated?	
	16. Is Ethics Committee approval indicated (and the specific committee identified)?	
	17. Is the process of informed consent explained	+
	18. Are inclusion and exclusion criteria described?	+
	19. Are the interventions described?	+
	20. Are the outcome measures described?	+
	21. Is the primary outcome specified?	+

Table 2. Continued

Section	Item	Consort
Title	21. Is the primary outcome specified?	+
	22. Is a minimum important difference for the primary outcome reported?	+
	23. Are power calculations described?	+
	24. Is the rationale for the statistical analyses explained?	+
	25. Are the methods for statistical analyses described?	+
	26. Are stopping rules described?	+
	27. Were any interim analyses carried out?	
	28. Was a safety monitoring committee used?	
	29. Is the unit of randomization described?	+
	30. Is the method used to generate the allocation schedule described?	+
	31. Is the method of allocation concealment described?	+
	32. Is the timing of assignment described?	+
	33. Is the method to separate those generating the allocation sequence from those assigning participants to groups described?	+
	34. Are the mechanisms of blinding described?	+
Results	35. Is the number of eligible patients reported?	+
	36. Is the number of randomized patients reported for each comparison group?	+
	37. Are prognostic variables by treatment and control group described?	+
	38. Have confounding influences been considered (note; these should not be the subject of statistical testing)?	
	39. Is the number of patients receiving intervention as allocated reported for each comparison group?	+
	40. Is the number of patients analyzed reported for each comparison group?	+
	41. Are withdrawals and dropouts described for each comparison group?	+
	42. Are protocol deviations described for each comparison group?	+
	43. Is the estimated effect of the intervention on primary and secondary outcomes stated, including a point estimate and measure of precision (confidence interval)?	+
	44. Are the results stated in absolute numbers?	+
	45. Are summary data and inferential statistics presented in sufficient detail to permit alternative analyses and replication?	+
Discussion	46. Are the key findings summarised?	
	47. Are these findings related to the literature?	
	48. Are the limitations of the study explained?	
	49. Are the strengths of the study outlined?	
	50. Is the significance of the findings explained?	
	51. Are possibilities for future work outlined?	

Forms

Data should be collected on pre-designed case record forms (CRFs). Most clinical trials should include adverse event reporting. A predefined grading system and specific forms for adverse events are needed.

COMPLIANCE

Table 3 lists compliance requirements typical of a current clinical study. There is a great deal of time and work in meeting these regulatory requirements. Research must be conducted strictly with ethics committee approval and involvement, but the Ethics Committee is in fact the researcher's friend, and should be seen as a source of advice in the face of difficulty. If in doubt about any aspect of the research ask the Ethics Committee.

Table 3. Some compliance requirements for clinical studies

Item
1. Compliance with good clinical practice guidelines (see Box 2)
2. Ethics committee approval
3. Written, informed consent from all participants
4. Consultation with Maori (probably Pacific Island populations should also be consulted)
5. Contractual agreement with host hospital
6. Contractual agreement with sponsor, whether a funding agency or company
7. Reporting requirements
a. To ethics committee
b. To funding organisations
c. To patients at the end of the study
8. Retention of data (typically 10 or 15 years)
9. Compliance with security requirements for document storage
10. Compliance with privacy requirements for all aspects for the research
11. Compliance with confidentiality requirements for industry sponsored research

Box 2. Illustration definition of good clinical practices.

Good Clinical Practices (or GCP) means the practices prescribed by the New Zealand Regulatory Guidelines for Medicines Volume 3 "Interim: Good Clinical Research Practice Guidelines", the good clinical practices prescribed by the "Code of Federal Regulations" and the ICH
Guidelines as adopted by the FDA for Good Clinical Practice, and in the event of any inconsistency between any of these guidelines or practice prescribing the higher standard of practice will apply.

WRITING THE PAPER

The scientific report of a research project should follow a highly structured format (Box 3 and Table 2). Writing a scientific paper becomes much easier once one realises what should and should not be included. In writing a paper it is important to keep material in its correct section. It is a very common mistake to put discussion into the methods and results sections or to include new results into a discussion section. This is confusing and should be avoided. Each journal has its own guidelines for authors, and these should be followed explicitly. Reviewers are busy researchers, who give their time free – make sure the paper has been carefully proofed and internally reviewed before sending it to the journal. It is disrespectful to submit shoddy work.

Box 3 Brief outline of a paper reporting a randomised clinical trial.

Abstract. The abstract is usually written last, which is appropriate, but it is actually the most important part of the paper in today's electronic era. The abstract is the only part of most papers that gets read. It is also the part most readily downloaded during literature searches. The emphasis should be on a brief description of the methods and on presentation of as many data as possible in the space allowed. No materials should
appear in the abstract that is not in the paper.
Introduction. This should be a brief synopsis of the relevant literature identified in a systematic survery. Neither the introduction nor the discussion is meant to contain a full literature review. What is needed is a list of recent key references, a summary of what is known and what is not known and an explanation of why the gaps in knowledge are important. It is basically a justification for your research project.
Methods. The writer should explain precisely what has been done in sufficient detail for another researcher to repeat the study if necessary.
Results. The results should indicate, in summary form, the key findings. Enough detail should be given for the reader to repeat the statistical analyses or at least verify in broad terms that the data support the conclusion. Graphical and tablet presentation of data is very helpful.
Discussion. The discussion should focus on the research, not on the subject of the research (although a few comments on the latter are acceptable—perhaps one short paragraph). The key findings and conclusions should be clearly stated in a balanced way.

INSPIRATIONAL ASPECTS OF RESEARCH

This outline might suggest that the primary requirement of research is a recipe. Nothing could be further from the truth. However, despite the fact that every project is unique and represents its own challenges, there are a large number of issues that need to be considered and dealt with on a routine basis. In this paper, I have tried to give an overview of some of the more important aspects of any research project.

Ultimately, however, good research arises out of an inquiring mind. A good research project is underpinned by a good question. Researchers are sceptics who question everything. Typically they differ from good teachers, who tend to be clearer at expounding currently accepted knowledge. The researcher, by contrast, doubts the validity of currently accepted knowledge, and questions it. This in itself is only the first step, but it is a key defining characteristic of the good researcher. The fascination with knowledge and the thrill of the pursuit of new information is what drives research.

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Pericardial Suction Blood–What Are We Doing About It?

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INTRODUCTION

In August 2004 we introduced the Dideco 903 Avant hard-shell membrane oxygenator (Mirandola, Italy) into our practice that incorporates a cardiotomy reservoir integral to the venous reservoir that enables pericardial suction blood (PSB) to be separated from the circulation and sequestered.

METHODS

Following ethics committee approval, a prospective audit of the treatment of PSB was conducted on 58 adult patients undergoing elective cardiopulmonary bypass (CPB) at Auckland City Hospital. A sheet was filled out for each procedure to include patient demographics, whether unprocessed PSB was reinfused and reason for reinfusion, use of the blood cell processor, and perioperative hematology, blood product transfusion and blood loss.

RESULTS

Pericardial suction blood was reinfused unprocessed in 28% of patients (group R) and sequestered and not returned in 72% (group S). The reason for reinfusion of PSB unprocessed in Group R was "excessive volume" in all cases.

While the age and weight of patients both groups were similar (62.8 yrs vs. 65.5 yrs and 81.5 Kg vs. 76.8 Kg) the case mix and CPB times were different. The operating room (OR) discard suction was variably used regardless of whether PSB was sequestered or reinfused.

Table 1. Discarded OR suction and sequestered PSB volumes.

	Group R	Group S	*p*
Mean OR discard suction (ml)	545	439	ns
Mean OR discard equated units	0.86	0.35	0.02
Mean sequestered PSB discarded	249	125	ns
Mean sequestered PSB equated units discarded	1.7	0.4	ns

Where blood was not processed ($n = 45$), in 53% no processor disposables were used. A cell processor reservoir plus aspiration line was used and wasted in 13% of cases, the majority of these being CABG where there was insufficient PSB volume to process.

BLOOD PRODUCT USE

Table 2. Blood product use.

	RBCs	Plts	FFP	Cyro	Donor Exp
Group S	1.4	0.36	0.5	0.05	3.8
Group R	2.5	1.4	1.9	0.18	11.8
p	ns	ns	ns	ns	0.02

There was no difference post operative chest drainage (24 hour) between Group R and Group S (770ml and 716ml respectively).

CONCLUSION

These limited data show the Avant 903 cardiotomy to enabled improved avoidance of reinfusion of cardiotomy blood with an open system (72% vs. 4% for the year prior to its introduction). Discarded blood in group R yielded a significantly greater red cell mass (and hence equated units of blood) than group S and this should have been directed to a blood processor. While there is level 1 evidence that PSB contains deleterious elements there is currently no strong evidence on the impact of avoidance of reinfusion of PSB on patient outcome. Further prospective clinical trials are warranted.