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RM04/JH18: Testing Treatments On Animals: Relevance To Humans

The NHS R&D Methodology Programme has been established to guide researchers, research commissioners and service commissioners on appropriate methods for research and analysis.

The Programme wishes to invite proposals for studies into the validity, for interventions in humans, of the results of studies of different treatment effectiveness in animals. This work should be based on secondary sources (published articles and other documents).

Up to £40,000 has been made available for this project, and the work should be completed within 8 months. The closing date for applications is 12pm Friday 24th September 2004.

Application forms for this single round process can be obtained from http://pcpoh.bham.ac.uk/publichealth/nccrm/invitations.htm, or by contacting Nathalie Maillard (N.C.Maillard@bham.ac.uk, phone: 0121 414 2634).

FURTHER PARTICULARS

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BACKGROUND

Animals are frequently used in basic science experiments aimed at understanding the mechanisms of disease. Animals are sometimes also used to evaluate the effectiveness and safety of interventions, and it is with this use of animals that this call for proposals is concerned. Purely by way of example, hypotensive resuscitation has been compared to normotensive resuscitation in the exsanguinated mouse. In this case, therapeutic approaches have been compared by causing haemorrhage, and randomising the mice to one or other treatment strategy. Meta-analysis of these randomised controlled trials (RCTs) yields the conclusion that hypotensive resuscitation is better – more mice survive[1]. But are these results applicable to humans and, if so, are they universally applicable or only in specific clinical contexts?

There are two basic reasons why the results of an animal experiment might not apply to humans:

I Inter-species differences.
II Failure to adequately replicate human pathology or treatment conditions in the animal study.

For example, failure of replacing denuded cartilage in animals and humans may result either from differences in joint biology between species, or from failure to mimic human joint disease in the animal, eg artificially removing cartilage from the animal joint poorly mimics the relevant aspects of the human disease process. In the case of neutralising sepsis using monoclonal antibodies, it transpired that the results in animals were different when endotoxin was injected as opposed to when sepsis was induced by the introduction of bacteria. The null result in human trials did not reflect interspecies differences, but differences in the models used.

A number of approaches can be used to ameliorate the influence of interspecies differences. One method is to repeat an experiment across many different species – if a treatment works in sheep, pigs and mice, then why not in humans? Another, is to minimise 'genetic distance', say by using primates – approaches to using vaccines against HIV in humans are sometimes tested on SIV (Simian Immunosuppressive Virus) in chimpanzees. Yet another method is to use an animal which is more challenging in some way. For example, maintaining blood in the fluid state is one of the challenges with artificial heart valves, and the sheep has been used as an animal model, precisely because its blood is more prone to clot than human blood.

The acid test of an animal experiment is human experience, or, at least experience in a different genus of animal. There are many anecdotes which bear witness of the relevance (or lack of relevance) of animal experiments to human effectiveness and safety.

WORK REQUIRED

This call for proposals seeks to commission a scoping study to search for concordance or disconcordance between animal and human experiments in therapy.

We ask the research community to suggest imaginative solutions to this issue, but we can suggest two broad approaches:

1. A systematic search of the primary literature and/or documents held in private and public laboratories for instances where both human and animal experiments have been carried out.

2. Searches for systematic reviews of the same intervention in both humans and animals.

In collaboration with colleagues in Birmingham (Dr Luciano Mignini and Dr Khalid Khan), we have attempted the second approach. The above example of treatment of septicaemia is one of the few examples found. While pursuing our enquiries a further systematic was published[2]. It therefore appears that this line of enquiry has been exhausted and Method 1 above offers the best prospects of success. However, if investigators can think of other approaches to the problem, they are strongly encouraged to suggest these.

We are aware that certain animal experiments will not have been replicated in humans precisely <u>because</u> they produced discouraging results, but Pound et al[2] and the Birmingham group found instances where both human and animal experiments had taken place, even when animal experiments produced null or negative results. In some cases the animal and human trials took place concurrently! Moreover, it is possible that the veterinary field will produce insights by comparing results in one type of animal with another, or even the same animal under different circumstances, eg animals artificially infected, intoxicated or invenomated versus the same species with naturally acquired disease or poisoning.

The results of this comparison may also be confounded by any systematic differences in methodology between animal and human experience and differences may also arise from 'co-intervention'. For example, the first heart transplants were carried out in the dog, to test 'proof of first principle' rather than to measure survival – the costs of co-intervention in human

studies (intensive care, immuno-suppressive therapy etc), limited the applicability of animal experiments to long term outcomes in humans. Concordance and discordance must therefore be assessed in light of the context of the various types of study.

The successful applicants will be expected to submit a draft of their findings after 6 months, so that the potential for further work can be assessed (see below).

FURTHER WORK

Further funds may be made available at the end of the 6 months, dependant on the results of the scoping study. Should a range of examples of both human and animal experiments be collected, further work may include:

- Comparison of examples of concordance and discordance, to see if any general rules can be adduced to help inform the decision of the relevance of animal experiments to human treatment.

- Development of an approach to classification of comparisons between human and animal results as concordant or discordant.

MONEY AND TIMESCALE

Up to £40,000 has been made available for this project, over the course of 12 – 18 months. This includes overheads (at a maximum of 40%).

As stated above, the successful applicants will be expected to submit a draft of their findings after 6 months, so that the potential for further work can be assessed.

HOW TO APPLY

This is a single round tendering process.

Applications are solicited from anywhere in the European Union and from academic or commercial organisations, or collaborations between the two.

Application forms and Evaluation Criteria can be downloaded from **http://pcpoh.bham.ac.uk/publichealth/nccrm/invitations.htm**

Applications, consisting of 1 signed copy and 1 electronic version (on disc or CD), and marked clearly with "TENDER" and the title of the project should be sent to:

Ms Judith Harris
Programme Manager, NCCRM
Public Health Building
University of Birmingham
Edgbaston
Birminghan
B15 2TT

Applications must be received by 12pm Friday 24th September 2004.

Please ensure that the paper and electronic versions are identical. If any discrepancies are noted, the paper copy will be taken as the definitive version, and this may slow the progress of your application.

For scientific/project enquiries, please contact either Programme Director, Professor Richard Lilford (Phone: 0121 414 2226, or email r.j.Lilford@bham.ac.uk).

For enquiries relating to the application process, please contact the Programme Manager, Ms Judith Harris (Phone: 0121 414 7833, or email j.harris.20@bham.ac.uk).

Reference List

1. Roberts I, Kwan I, Evans P, Haig S. Does animal experimentation inform human healthcare? Observations from a systematic review of international animal experiments on fluid resuscitation. *BMJ* 2002;**324**:474-6.

2. Pound P, Ebrahim S, Sandercock P, Bracken MB, Roberts I. Where is the evidence that animal research benefits humans? *BMJ* 2004;**328**:514-7.