Health Research Authority

FROM:	**NATIONAL RESEARCH ETHICS ADVISORS' PANEL**

To:	**NRES REC Chairs/RECs**

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Title of document:	**Conflict of Interests/Competing Interests.**

Short Description:

This document sets out a number of principles and possible solutions that might be applied by RECs when considering how conflicts of interests/competing interests should be managed.

Background

The terms ‘conflict of interests’ and ‘competing interests’ are often loosely defined and used interchangeably in the literature and by RECs. A conflict of interests (CoI) has been defined as:

> “…a set of conditions in which professional judgment concerning a primary interest (such as patients' welfare or the validity of research) tends to be unduly influenced by a secondary interest (such as financial gain).”[1]

Competing interests are currently defined by the journal Nature as:

> “…those of any kind that could undermine the objectivity, integrity or perceived value of a publication through their potential influence on behavior or content or from perception of such potential influence.”[2]

The Panel prefer the term "competing interests" for those interests that, whilst in tension with the proper conduct of the research, simply need to be acknowledged and managed appropriately to minimise their impact. They recommend that the use of the terms "conflicting interests" or "conflict of interests" should be used solely for those situations where the competing interests are sufficiently serious as to be incompatible with the individual subject to the conflict taking part in the proposed research due to the *undue* influence exerted. However, RECs should always take care in their use of these terms to ensure that applications are not given an unfavourable opinion inappropriately as a result of any confusion between them.

It is acknowledged that all researchers will be exposed to a number of competing interests in the normal course of their work. Some of these interests will be ‘intangible’ and implicit in the role of being a ‘researcher’ such as the legitimate interest in wishing to successfully complete and publish the study, desire for career advancement or the simple need to retain one's job. Other competing interests will be ‘tangible’ i.e. financial in nature and could include a chief investigator owning a patent for a device under study[3] or engaging in research on behalf of a pharmaceutical company from which the investigator has received, or will receive, either direct or indirect remuneration. In addition, health care professionals engaging in research face potential conflicts between their duty of care to their patient and their duty to other patients and also the wider community partly realised through the conduct of research.

Society has a vested interest in the integrity of research and researchers. Unfettered and unmanaged conflicts of interests may threaten the integrity of the research enterprise through interference with the principle of objectivity essential for the advancement of knowledge and may lead to a reduction in public support for, and inclination to take part in, research.

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[1] Thompson DF. Understanding financial conflicts of interest. N Engl J Med1993; 329:573–576 - http://www.interessenkonflikte.de/x1993Thompson.pdf

[2] Nature – Competing Interests Policy: http://www.nature.com/clinicalpractice/policies/competing_interest.html

[3] See “Ethical Review of Medical Device Studies – Financial Interest of Chief Investigator” NRES OMEA No.38 19/04/2011 for more information and guidance on this issue.

Given that competing interests can never be completely removed (and, it may be argued, provide beneficial and necessary incentives to conduct research) it is important that they are disclosed and appropriately managed in order to mitigate their potential for harm. Whilst RECs should be particularly alert to both declared and undeclared financial interests, there will be other 'intangible' interests that may also need to be identified and managed.

A useful rule of thumb in considering whether a conflict of interest is one which should be declared and appropriately managed is that used by the BMJ:

> "We are restricting ourselves to asking directly about competing financial interests, but you might want to disclose another sort of competing interest that would embarrass you if it became generally known after publication."[4]

Finally, whilst not the focus of this guidance, it should be acknowledged that both RECs and REC members may also be subject to competing interests which could unduly influence their judgment and thus it is important that all members are aware of this possibility and declare any such interests in line with SOPs so that they may be managed appropriately and transparently.

Recommendations

Where a REC identifies a potential competing interest, financial or otherwise, it should not automatically lead to an unfavourable opinion being given in the absence of any other substantial ethical issues that would require such an opinion.

In such cases, the competing interests should be discussed with the investigators and sponsor in order to arrive at a satisfactory plan in order to manage any potential conflict. Where appropriate, a provisional opinion should be given in which the sponsor and chief investigator are requested to set out how the competing interest would be managed as part of their response to the committee's opinion.

Principles to be considered

In considering the management of competing interests the National Research Ethics Advisors' panel recommend that consideration be given to the following principles:

- **Transparency**
- **Sharing of responsibilities with (independent) others**
- **Divesting responsibility of the research to (independent) others**
- **Independent trial management/monitoring**
- **Access to unbiased information for participants**
- **Freedom of Publication – all parties should be free to publish (negative) data**

Questions the REC might raise

[4] http://resources.bmj.com/bmj/authors/checklists-forms/competing-interests

REC Questions	Possible Solutions
Do researchers have possible competing interests that might jeopardize duties of care? **Tangible:** Payments Commercial reward e.g. Holding shares **Intangible:** Professional reward Curiosity/quest for knowledge Pressure to publish **If they do, have they satisfactorily explained how they will handle them?**	• Transparency (does the Chief Investigator recognise and declare CoI) • Sharing of responsibilities with (independent) others • Divesting responsibility of the research to (independent) others • Independent trial management/monitoring • Access to unbiased information for participants • Freedom of publication – all parties should be free to publish (negative) data
Does the research design address potential conflicts of interests?	Ensure scientific review has looked specifically at contentious or sensitive areas.
Will control of the data rest in inappropriate hands (those with particular interests)? **Will the study be rewritten once data collected to suit other interests?** **Do the researchers have freedom to publish (even negative) results?**	It helps to clarify before the study starts how results will be made publically available and analysed Study should be registered on a publically accessible database. Publish the protocol Agree a plan on how results will be published Agree ownership of, access to, and rights over the data to ensure that publication policy does not unreasonably restrict access to results Encourage researcher to make research dataset publically available Agree a reporting method e.g. standard designs such as the “CONSORT” agreement (http://www.consort-statement.org/consort-statement/)
Have countervailing voices been heard and incorporated?	Include participant/patient involvement in the design of the study

What proposals could a REC make?

The following steps might be taken in order to mitigate the competing interest (N.B. these measures should be applied in a proportionate manner in accordance with the seriousness of the competing interest):

- The investigator's financial interests/other competing interests should be publically declared and described in the participant information sheet
- Independent (or shared) management of the research. Responsibility for participant recruitment and enrolment, the informed-consent process, analysis of the study data, and the subsequent reporting to the sponsor could be devolved to an independent third party
- Independent (or shared) monitoring of the research
- Encourage researchers to make their research datasets publically available to allow independent validation of results
- Where the source of the researcher's competing interests derives solely from their relationship with a particular research site then consideration might be given to changing the research site(s) involved the study
- Divestiture of significant financial interests
- Ending of relationships that create actual or potential conflicts
- Disqualification of the researcher from part, or all, of the research project

Existing guidance:

NRES

NRES OMEA No.38, 19/04/2011

"Ethical Review of Medical Device Studies – Financial Interest of Chief Investigator"[5]

Background

It has recently been brought to the attention of NRES that some RECS are giving unfavourable opinions in respect of medical device studies and reporting, as the main reason, the fact that the Chief Investigator has a financial interest in the device.

It is, of course, legitimate for the REC to consider such a potential conflict of interest during the ethical review process. However, the nature of device invention and development is that, if a clinician has an idea, patents it and manages to get a company to take it forward for manufacture, then that clinician is almost certainly going to be the CI for the clinical investigations required, especially in proof of concept studies and the

[5] http://www.nres.npsa.nhs.uk/home/hra-extranet/operational-email-alerts/?entryid61=131026&p=2

pivotal clinical investigation for CE Marking. It will therefore be necessary to permit clinical investigations in these circumstances. The following advice has been developed with the assistance of members the MHRA Medical Devices Collaboration Group.

Issues for RECs

Whilst a potential conflict of interest is an issue for the REC to consider, what is important is whether the conflict of interest has been declared and appropriately recognised. The REC will also need ensure that the CI's financial involvement in the invention and development of the device is made clear to potential study participants. It is primarily the employer's responsibility to manage the Intellectual Property and Conflict of Interest issues. However, the REC may also wish to consider including, as a condition of any approval that, not only should the NHS organisation give permission, but the employer should also have in place appropriate arrangements to manage the conflict of interest.

Whilst large companies may have the resources to limit their choice of CI to an individual with no potential conflict of interest, in SME's, this may not be feasible. Irrespective of the size of the company, transparency and independent oversight may be considered key issues and these may be tackled through study design and by arrangements for study monitoring.

In such circumstances, the REC should consider whether the study design could be strengthened to include the use of an independent observer for site data collection, the use of patient reported outcome measures (PROMS) alongside clinical rating systems and the use of objective measures such as imaging or biological markers. A multicentre study design involving at least one independent investigator is strongly recommended especially for a pivotal clinical investigation, as a single centre may be subject to provider or intensity bias, and the results are more generalisable.

As an example, such features have been included in study designs where designer/surgeons were involved in clinical investigations of novel orthopaedic implant devices. Study sites were subject to thorough monitoring and source data validation in line with ISO 14155. Study designs are invariably multicentre, often with an independent observer to read all the study radiographs to minimise both bias and inter-observer errors.

Additional data monitoring could also be carried out, but in general, study sites should already be being monitored by the Sponsor in line with ISO 14155 to the level where the detection of possible fraud would be likely. For high-risk devices and single centre studies, it is suggested that the use of an independent data monitoring committee to review SAEs etc may be useful, depending on the Sponsor's study governance procedures.

NRES SOPs (Version 5.0 September 2011)

> "5.30 Guidance from NRES is that the following changes should normally be regarded as substantial:
>
> A change to the payments, benefits or incentives to be received by participants or researchers in connection with taking part in the study, or any other change giving rise to a possible conflict of interest on the part of any investigator/collaborator"

The Medicines for Human Use (Clinical Trials) Regulations 2004 [6]

Ethics committee opinion

15.

(5) In preparing its opinion, the committee shall consider, in particular, the following matters

(k) the amounts, and, where appropriate, the arrangements, for rewarding or compensating investigators and subjects;

SCHEDULE 3

PART 1 - APPLICATION FOR ETHICS COMMITTEE OPINION

1. An application document including the following information or, in each case, an explanation of why that information is not being provided—

(g) the financial arrangements for the trial, in particular—
(i) sources of funding for the trial and information on financial or other interests of the applicant relevant to the trial,
(ii) the arrangements for remuneration of, or re-imbursement of expenses incurred by, subjects,
(iii) any provision for compensation in the event of injury or death attributable to the trial,
(iv) details of any insurance or indemnity to cover the liability of the sponsor and investigator, and
(v) summary details of any financial arrangements between—
(aa) the sponsor or person funding the trial and the investigator, and
(bb) the sponsor or person funding the trial and the owner or occupier of the trial site;

(l) details of any relationship between subject and investigator which may be relevant for the purposes of an ethical opinion;
(q) any agreement on—
(i) the access by the investigator or his team to the data produced by the trial, and
(ii) the policy for publication of that data;

(s) details relating to the chief investigator and each investigator, including—
(i) experience in conducting research, and
(ii) any potential conflicts of interest; and
(t) details of any proposed trial site and its suitability for conducting the trial.

General Medical Council

Good practice in research: Honesty and integrity[7]

21. You must conduct research honestly. If you are concerned about the quality or integrity of the research, including allegations of fraud or misconduct, you must follow the

[6] http://www.legislation.gov.uk/uksi/2004/1031/pdfs/uksi_20041031_en.pdf

[7] http://www.gmc-uk.org/guidance/ethical_guidance/6005.asp

guidance in paragraph 19 on raising concerns. You must report evidence of financial or scientific fraud, or other breaches of this guidance, to an appropriate person in your employing or contracting body, and where appropriate to the GMC or other statutory regulatory bodies.

22. You must be open and honest with participants and members of the research team, including non-medical staff, when sharing information about a research project. You must answer questions honestly and as fully as possible.

23. You must make clear, accurate and legible records of research results, as soon as possible after the data are collected. You must keep records for the appropriate period15 to allow adequate time for review, further research and audit, or to help resolve any concerns about the data or research project.

24. You must report research results accurately, objectively, promptly and in a way that can be clearly understood.16 You must make sure that research reports are properly attributed and do not contain false or misleading data. Whenever possible, you should publish research results, including adverse findings, through peer-reviewed journals.17

25. You should make research findings available to those who might benefit. You should make reasonable efforts to inform participants of the outcome of the research, or make the information publicly available if it is not practical to inform participants directly.

Avoiding conflicts of interest[8]

26 You must be open and honest in all financial and commercial matters relating to your research and its funding.

27 You must not allow your judgement about a research project to be influenced, or be seen to be influenced, at any stage, by financial, personal, political or other external interests. You must identify any actual or potential conflicts of interest that arise, and declare them as soon as possible to the research ethics committee, other appropriate bodies, and the participants, in line with the policy of your employing or contracting body.

Royal College of Physicians

Guidelines on the practice of ethics committees in medical research with human participants 2007 (Fourth edition)[9]

10.1 Any pecuniary relationship of an investigator with a sponsoring company has ethical implications and should be declared to the REC, with details of both the amount and nature (money, gifts, travel etc) of payments to investigators. Such relationships constitute a conflict of interest.

10.2 Similarly, payments to departments and to institutions by a pharmaceutical company or contract research organisation should be declared.

[8] http://www.gmc-uk.org/guidance/ethical_guidance/6006.asp

[9] http://bookshop.rcplondon.ac.uk/contents/pub232-e0da0967-8bed-4ac3-a12f-b05ad6a6c873.pdf

10.3 Even where ethically permissible economic arrangements exist, safeguards are needed to protect against the appearance of impropriety. Clinical investigators should therefore disclose any ancillary ties to companies whose products they are investigating, such as participation in educational activities or in other projects supported by the company or any other conflicts of interest.

UK Research Integrity Office (UKRIO)[10]

3.6.1 Organisations and researchers must recognise that conflicts of interest (i.e. personal or institutional considerations, including but not limited to financial matters) can inappropriately affect research. Conflicts of interest must be identified, declared and addressed in order to avoid poor practice in research or potential misconduct.

3.6.2 When addressing a conflict of interest, it must be decided whether it is of a type and severity that poses a risk of fatally compromising the validity or integrity of the research, in which case researchers and organisations should not proceed with the research, or whether it can be adequately addressed through declarations and/or special safeguards relating to the conduct and reporting of the research.

3.6.3 Organisations should have a clearly written and accessible policy for addressing conflicts of interest, including guidance for researchers on how to identify, declare and address conflicts of interest, and should disseminate and explain the policy to researchers. Organisations should ensure that researchers understand the importance of recognising, disclosing and addressing conflicts of interest in the conduct and reporting of research.

3.6.4 Organisations should comply with the requirements of their policy for addressing conflicts of interest, as well as any external requirements relating to conflicts of interest, such as those of funding bodies. Heads of organisations and other senior staff should be aware of potential or actual conflicts of interest at the institutional level and disclose them when they arise so that they can be addressed.

3.6.5 Researchers should comply with their organisation's policy for addressing conflicts of interest, as well as any external requirements relating to conflicts of interest, such as those of funding bodies. This should include declaring any potential or actual conflicts of interest relating to their research to: their manager or other appropriate person as identified by their organisation; any ethics committee which reviews their research; and when reporting their findings at meetings or in publications. Conflicts of interest should be disclosed as soon as researchers become aware of them.

3.6.6 Researchers should agree to abide by any direction given by their organisation or any relevant ethics committee in relation to a conflict of interest.

[10] http://www.ukrio.org/what-we-do/code-of-practice-for-research/live-document-code-of-practice-for-research/3-0-standards-for-organisations-and-researchers/3-6-conflicts-of-interest/

Faculty of Pharmaceutical Medicine of the Royal Colleges of Physicians of the United Kingdom

Competing Interests[11]

Pharmaceutical physicians, in whatever role they find themselves, be it regulatory, marketing, research, academia or otherwise, must declare all potential competing interests. Competing interests cover anything that might influence the making of balanced, unbiased judgements of importance to patients or research subjects. This includes potential competing interests in dealings with professional colleagues, scientific journals and the general public.

Document Control

Change Record

Version Status	Date of Change	Reason for Change
V1.2	13/02/2012	To reflect changes following NREAP review at meeting held on 2011/11/09

[11] http://www.fpm.org.uk/FPM_-_Guiding_Principles_for_Pharmaceutical_Physicians.pdf