Module 11

Non-Compliance and Misconduct in Scientific Research

Introduction:

Trust and honesty are amongst the most important values that must be embraced in the conduct of research. Internationally, RECs attempt to encourage ethical research and to ensure participant protection. However, even with the existence of well functioning RECs participant protection can be compromised by individual researchers who evade the system of ethical review or by researchers who deviate from protocols that have already been reviewed by RECs. In the field of research, strong reliance is therefore placed on investigators and their teams to ensure that scientific fraud does not occur. Compliance with GCP and other regulations is encouraged.

Inaccurate statements may be produced in research due to justifiable mistakes, careless errors or overinterpretation of results. However, inaccuracy is regarded as fraudulent when there is intentional misrepresentation of data.

Investigator Non-Compliance and Research Misconduct:

Regulations in the United States distinguish between investigator non-compliance and research misconduct.

Investigator Non-Compliance:

1. Serious Non-Compliance

   - Research conducted without REC approval or without appropriate informed consent
   - Significant modifications to REC approved research without approval
   - Other instances as determined by the REC

2. Continuing Non-Compliance

   - PI makes the same mistake repeatedly especially after the REC has brought these problems to his/her attention
   - PI has multiple problems with multiple projects
   - Anything the REC considers to be “continuing”
Research Misconduct

Various definitions have been advanced. The Office of Science and Technology Policy (OSTP) was implemented in the United States in 2005 and defines research misconduct as follows:

**Fabrication** - making up data or results and recording or reporting the "data"

**Falsification** - manipulating research materials, equipment or processes or changing or omitting data or results such that the data is not accurately reflected in the research records.

**Plagiarism** - appropriating another person's ideas, processes, results or words without giving appropriate credit.

Other practices that that seriously deviate from those commonly accepted within the scientific community

Much of the responsibility that arises after non-compliance or misconduct have occurred rests with the institution and REC.

In the United States and where research is bound by a Federal Wide Assurance (FWA) research non-compliance must be reported to the Office for Human Research Protection (OHRP). Research misconduct must be referred to the Office for Research Integrity (ORI).

Research misconduct and non-compliance may affect

1. the **conduct of research** and
2. the **publication of research findings**

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**The Extremes of Scientific Fraud !!!!!!!!**

Prof W. E. Underwood was head of the Surgery Department at the University of Witwatersrand, South Africa.

He conducted the first ever experiment in open heart surgery on a doberman pinscher Trixie in the 1950s. She died on the operating table. 1 year later a journalist contacted the professor to enquire about the health of the dog. He told her that she was as good as new. He got a look a like dog and painted in the white markings and got the journalist to take an “after” picture.

However, the professor was unpopular and his colleagues exposed his deception forcing him to resign and spend the rest of his years as a mine doctor in Zambia.
The Bezwoda Case (Weiss, 2000)

Werner Bezwoda was professor of Haematology and Oncology at the University of Witwatersrand, South Africa since 1992. In 1995 he announced that high-dose chemotherapy with bone-marrow transplantation increased survival in patients with metastatic breast cancer. In May 1999, he presented the results of a second trial on high dose therapy at the American Society of Oncology meeting. Again he concluded that women receiving high dose treatment had longer survival rates than women on normal dose therapy. Four other papers presented at that conference by other scientists failed to show a benefit.

A team approved by the United States (US) National Cancer Institute visited South Africa in 2000 to audit Bezwoda’s results in preparation for the conduct of large-scale confirmatory trials in the United States (Farham, 2000).

Findings:

1. Bezwoda presented data on 154 patients at the conference – only 151 patients were listed in the enrolment register. Records for 58 patients were produced.
2. There were discrepancies in eligibility of patients including age, tumour category and number of axillary nodes involved. Only 20 of the 58 patients met eligibility criteria.
3. The presentation indicated that 36% of the study population were white women. Only 7% were actually white. The majority of patients were black women.
4. There were discrepancies in dosages of drugs used. Patients in the control group had not been given the treatment specified in the presentation.
5. Deaths in the high dose treatment group were under stated.

As a result of the above findings, the study was invalidated (Weiss, 2000).

On 31 January 2000, Peter Cleaton Jones – Chairperson of the REC at Wits, received a letter from Bezwoda in which he acknowledged scientific misconduct.

In a letter to the president of the American Society of Clinical Oncologists on 4 February 2000, Peter Cleaton-Jones indicated that: …there have been serious ethical violations as well as misconduct and…the study is discredited and must not be used as a basis for further trials. (Farham, 2000).
Bezwoda claimed that he had not submitted his protocol to the REC at Wits as he regarded the study as being retrospective.

The Poisson Case Study (Weijer, 1995)

Like Bezwoda, Dr Poisson was also involved in a breast cancer study at St Luc Hospital, Montreal, Canada between 1977 and 1990. This was the largest and most prestigious breast cancer study in the world where two different modalities of therapy were being compared – radical mastectomy as opposed to lumpectomy. Due to the dilemma created in patients by the radical mastectomy study arm, recruitment was slow. His site, however, recruited 19% of all patients on the study. As a result, attention was drawn to his site. A number of violations were detected at his site: falsifying data, pressurising patients to participate, subjecting patients to unnecessary risk by placing them on cardiotoxic chemotherapy regimens even though he was aware of pre-existing cardiac disease in these patients. He had falsified data on 99 of the 1511 patients he had enrolled at his site. After results of this study were published in an international journal, all sites had to be re-audited and results re-published excluding his results. Fortunately, this did not impact on the overall results of the study.

Commentary on Bezwoda and Poisson

While these appear to be two isolated cases of research fraud, the extent of harm caused has far reaching consequences. Firstly there is the actual maleficence exhibited towards patients directly involved in the trial. In the second place, there is a level of maleficence towards potential patients who would have been recruited into larger trials to confirm Bezwoda’s initial findings. In both the Poisson and Bezwoda cases, data presented was initially included in the body of knowledge used by other clinicians, surgeons and oncologists in choosing a treatment modality for cancer patients based on evidence based medicine principles. Both studies had been published in international journals.

Furthermore, the erosion in public trust caused by these two events is immeasurable. One of the major reasons patients participate in research is based on the relationship of trust between doctor and patient. Commenting on this a gynaecologist based in Kenya had the following to say:

*I would like to emphasize that most patients consent to nearly anything if asked by a trusted authority – in this case a medical person who is supposed to know what is best for the patient.* (Temmerman, 1992).

Researchers are under enormous pressure to conduct research and produce results. Often, their careers are linked to grants which depend on an ability to convince a sufficiently large number of participants to enroll in research projects. There is also a need to publish in order to apply for promotion and apply for continued financial support. Research, as such, is conducted not only to produce generalizable knowledge but also to earn a salary and career advancement. It is therefore not surprising when researchers look for “short cuts to attractive answers” and this clouds the investigator’s judgement about what is and is not appropriate.
What both these cases demonstrate is that in the absence of researcher integrity and trustworthiness, even well functioning RECs cannot protect participants. In the absence of RECs, the individual researcher and his or her integrity remain a crucial factor. (Altman, 1985).

It is claimed that “the primary virtue in health care is integrity” (Beauchamp, 2001). Moral integrity entails living and acting in accordance with moral and ethical norms. The central element of this virtue is the consistent application of a set of values. Integrity demands a willingness to make sacrifices in order to defend these values. Integrity demands the acknowledgement that there are more important goals and values than the promotion of self interest (Gilligan 1997). It is evident that both investigators had not established a certain moral threshold beyond which they were not willing to compromise their values and principles. Both cases demonstrate a serious lack of integrity.

Prior to 1966, each individual investigator bore responsibility for protecting the rights of human subjects participating in research (Taub, 1986). The advent of RECs from 1966 onwards transferred a greater share of this responsibility from individual investigators to the committees. Responsibility shifted from a virtue based system of protection to a principle based system of REC protection. As early as 1969, Jonas described the researcher as “an interested party (with vested interests, indeed, not purely in the public good, but in the scientific enterprise as such, in “his” project, and even in his career)” and this makes him also “suspect”. This precarious and conflicted position of the researcher “calls for particular controls by the research community and by public authority” (Jonas, 1969). Such controls generally mitigate the problem but do not eliminate the problem completely.

"A Hippocratic Oath" for Scientists

Publication and Ethics

Publication & Authorship

The International Committee of Medical Journal Editors (ICMJE) has developed guidelines for authorship. Please see weblink for details.

http://www.icmje.org/

Authorship requires participation in

1. Conception & design and/or analysis & data interpretation AND
2. Drafting or revising article AND
3. Final approval of version to be published

All authors must be able to take public responsibility for content

If a person does not meet the above criteria, s/he can be acknowledged for advice, critical review of study proposal, data collection, participation in clinical trial, technical help, financial & material support.

The covering letter that accompanies a paper to a journal should indicate:
• Prior duplicate publication or partial submission elsewhere
• Conflict of interest
• That the article was read & approved by all authors
• Ethics approval & ethics clearance number
• Clinical trial registration number – WHO & ICJME (1 July 2005)
• Lancet – requires a summary of previous studies

**Publication can be retracted ……**

*If reviewers and editors deem research to be dishonest ….*

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Hwang Cloning Study

*Science 2005*

Woo Suk Hwang, a South Korean scientist, claimed to have created patient specific embryonic stem cells by replacing an oocyte nucleus with one taken from a skin cell. Hwang admitted to fabricating data which appeared in his article in Science in 2005 in which he claimed to have developed 11 embryonic stem cell lines using somatic cell nuclear transfer (SCNT) techniques. Further investigation at Seoul University found that the DNA in the cell lines did not match the DNA of the human subjects used in the research project.

Publication can be retracted…

if colleagues inform journals of dishonest research...

*Jon Sudbo, a Norwegian researcher, fabricated data in his article on oral cancer and non steroidal anti-inflammatory (NSAIDS). This article was published in the Lancet in 2006.*

The retraction in the Lancet read as follows:

“we have received confirmation ……that the paper published by Jon Sudbo and colleagues in the Lancet contains fabricated data. This article supercedes our earlier expression of concern and we now retract this article in full.”

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Research is expensive!!

Finally research & development costs are high. It costs in the region of **$800 million over 10-12 years to develop 1 product.**

Dishonesty in research is unethical, harms participants and the scientific endeavour, but also wastes resources and funding.
Do the Punishments fit the Crime (article)