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The ethics of Human Infection Challenge Studies

Hugh Davies, member of the UK ad hoc committee reviewing SARS COV2 studies

https://jme.bmj.com/content/49/5/322

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Part 1

Principles (ethical and otherwise) underpinning Human Infection Challenge Studies

Some history

Interest in these studies has grown in recent years as they are now seen as a means to address the global infectious disease burden.

One of the very early examples was Edward Jenner's vaccination of James Phipps.

and that caused a stir!

https://pubmed.ncbi.nlm.nih.gov/17329392/

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Some general points

(what does ethical research look like?)

http://www.reviewingresearch.com/principles-underpinning-good-research-2/

The ethical concern?

Infecting a volunteer for the benefit of others rightly causes concern, perhaps exceeding the expected level of research risk (“minimal ”).

As there is clearly no benefit to the volunteer, it seems to contravene a central tenet of medicine – “First do no harm”

There should be an unambiguous, justified research question and purpose.

These are its proposed **benefits** which are balanced against its possible **harms,** a central purpose for review.

NOTE: In these studies, these benefits do not accrue to the participant.

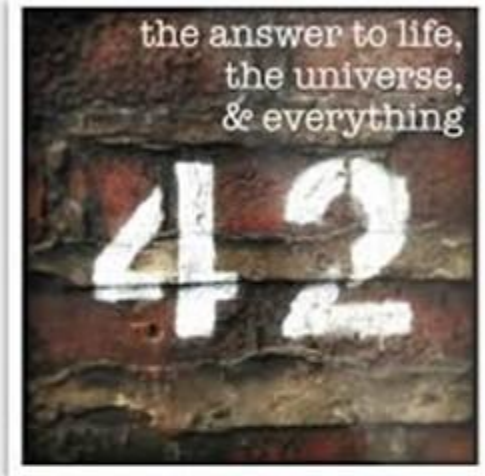
The study should be built on what is known already.

Many have suffered when studies have been conducted, ignoring what we know already.

Research must be built on a systematic, proportionate review of published literature, confirmed if necessary, by independent expert review.

The study should be able to provide meaningful results.

The research questions and purpose should have relevance to all with fair interest (e.g. participants, patients, professionals, public and politicians) while the method should then be able to provide answers of value.



Given current controversy around HICs this is, again, of particular importance.

Broad consultation with these groups is the ideal.

The method should be able to provide valid data and answers to the research question.

We should be able to trust answers or have an estimate of their statistical validity/ trustworthiness for the research to have any value.

The research team should be equipped to complete the study.

The work should be conducted by those with necessary knowledge, skills and attitudes with appropriate monitoring and accountability.

Tools to hand to help evaluate the research (team)

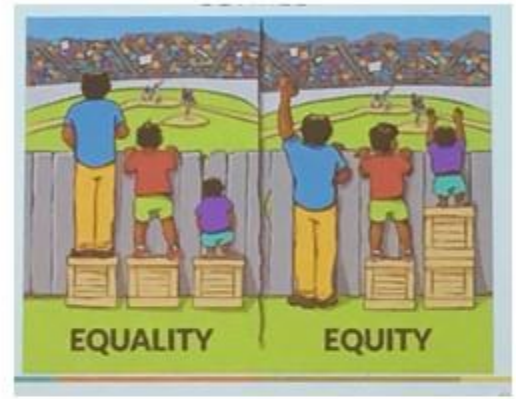
Click here to move on

The research should incorporate public, patient and participant views from its inception.

We should see research as a partnership in which all with legitimate interest (participants, patients, professionals, public and politicians) have fair voice.

Few don't have an interest in research!

Participants should be selected fairly.



The benefits and burdens of research should be shared across the community.

The sample selected must be able to provide valid answers to a relevant research question.

Those known to be at possible risk must be excluded.

Participants should be recruited fairly.

There must be an open and honest invitation, with the opportunity to say “no” (with a few, justified, exceptions)

There should be fair balance of benefits and harms for all with an interest in the study.

This is at the centre of design and review. Assessment should be realistic (evidence based as far as possible), inclusive and proportionate.

It’s important to recognise “One size won't fit all”, depending on the nature of the “challenge agent”

Participants should be offered a fair choice (informed consent).

Consent procedures should ensure the potential participants are able to make up their own minds, given time and appropriate information.

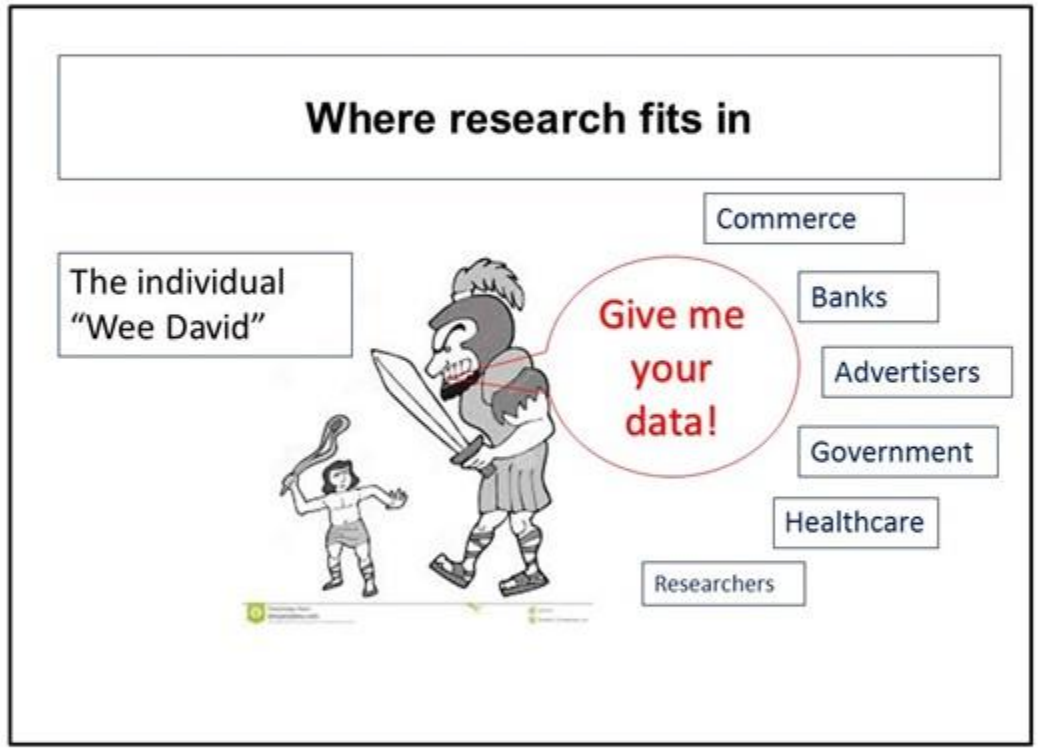
Hobson's choice

Given the nature of this work it's crucial there is a full explanation, so participants understand what they are agreeing to.

Personal data should be handled appropriately (confidentiality)

Access to personal data must be balanced against people's expectation of privacy.

Agreed "rules of engagement" are thus essential to maintain trust between all involved.



There should be fair reimbursement, payment for participation and recompense for injury.

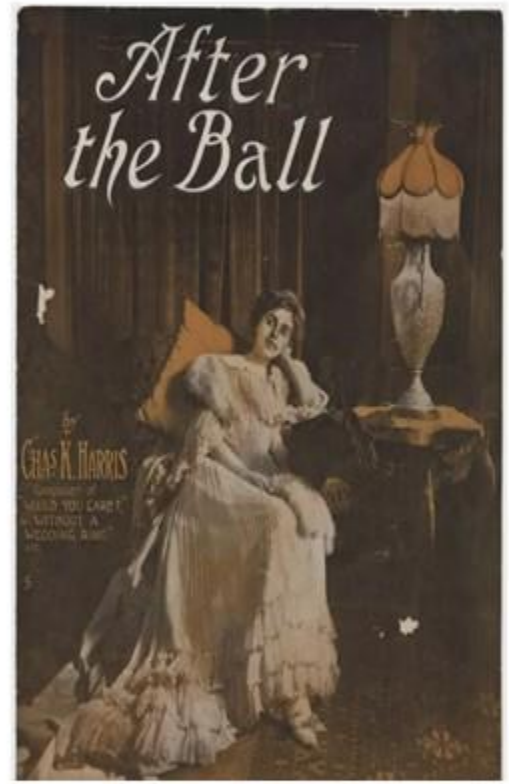
As a concept, payment is accepted but shouldn't represent undue influence.

Compensation arrangements must also be in place.

Fair payment?

Once the study is finished participants should receive appropriate care.

Eradication of the infection (if needed) is a crucial part of the study. As participants are healthy volunteers, no further treatment should therefore be needed although follow up to ensure there are no further problems should be considered.



The project should be registered and results placed in the public domain.

Results are valueless otherwise, research is of no benefit and hence likely unethical.

MUCK – no good unless it's spread

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Part 2

SARS COV-2 Human Infection Challenge Studies

https://jme.bmj.com/content/49/5/322

Principles

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1. There are legal, policy and professional requirements that research involving human volunteers undergoes independent review.
2. Research can’t proceed until a favourable opinion is received.
3. **When the UK government announced its support for these Studies, the UK Health Research Authority (HRA) convened a specialist ad hoc REC to undertake ethical review**.

Preparations

1. Staff within the HRA were recruited to support the committee.
2. [illegible]cular* UK RECs,
3. [illegible]

Those recognised to re[illegible]
Clinical Trials of Investi[illegible]
Medicinal Products (
Phase 1 studies in h[illegible]
volunteers, particularly t[illegible]
experience of vaccine

Opportunity to meet. The first provided background, the second to help the committee think through “Questions and Considerations that would arise (“How to think” not “What to think”).

Procedures

1. We met virtually (with its advantages and disadvantages).
2. **We followed existing HRA Standard Operating Procedures.**
3. Sub-committees reviewed correspondence and amendments.

Principles

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1. Review is not conducted in a vacuum – we had to use expertise of others.
2. Although much of the review was unstructured, we used the WHO criteria* as a foundation
3. We realised we needed to work with applicants (while avoiding collusion).

*https://www.who.int/ethics/publications/key-criteria-ethical-acceptability-of-covid-19-human-challenge/en/

WHO Ethical criteria

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1. Scientific justification
2. Assessment of risks and potential benefits
3. Consultation and engagement
4. Coordination
5. Site selection
6. Participant selection

Problems / “Tricky Issues”

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1. Reaching a common position
2. Considering alternative designs in review
3. Benefits, Harms and the balance between these
4. The place of “Rescue” medication
5. Selection – Risks to participants and the validity of results
6. Selection - Discrimination
7. Payment and compensation
8. Consent

If we did it again!

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1. Being prepared.
2. Developing clearer processes after the opinion.
3. Promoting speed.
4. Organising ongoing review – we must keep up to date and learning.

The UK ad-hoc specialist REC established to review SARS COV-2

Phew!
The end!

THANK YOU!

hughtdavies@gmail.com