Gain of Function Research:
Ethical Analysis

Professor Michael J. Selgelid
Director, Centre for Human Bioethics & WHO Collaborating Centre for Bioethics
Monash University
Melbourne, Australia
michael.selgelid@monash.edu

GOF Research Ethics White Paper

I.   Review and summarize ethics literature on GOF research

II. Identify and analyze how ethical and decision-making frameworks may be relevant to (1) evaluation of risks and benefits of GOF research, (2) decision making about the conduct of GOF studies, and (3) the development of US policy regarding GOF research

III. Develop ethical and decision-making framework to be considered by NSABB when analyzing information provided by risk-benefit analysis, and when crafting its final recommendations

--especially focused on policy issues regarding funding and conduct of GOF research

Literature review

I. Literature explicitly concerned with ethics of GOFR
    - Terms in titles/abstracts/key words/ body of papers
    - Note that few papers with *explicit* ethics focus and/or authored by ethicists
    - Much of the GOF literature/debate, on the other hand, is implicitly about ethics (what should be done?)

II. Especially relevant literature on ethics of dual use research more generally (ferret studies, RBA, funding)

I. Literature on ethics and biosafety
    - Asilomar, RDNA, GMO's, etc

Common Themes:

- Shift in focus to include biosafety as well as biosecurity threats

  – Conditions under which work conducted

  – Includes concern about proliferation of studies (in less safe conditions)

  – Magnitude of risk

  – Measurable risk?

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Common Themes

- Calls for increased transparency and broader community engagement/consultation

  - Concern about leaving debate/decision making to scientists (with potential conflicts of interest) as opposed to those exposed to risks or most likely to benefit from the research

- Calls for objective/quantitative/transparent risk/benefit analysis

Common Themes

Regarding Risks

- Appeal to principle "do no harm"

- Concerns about some imposing risks on others (without consent of latter)

- Claim that risks must be minimized (in various ways)

- Debates about (calculating) magnitude of risks--and whether risks outweighed by benefits (proportionality)

- Debate about whether (same) benefits can be achieved with less risky research—i.e., is GOFR necessary (to answer scientific questions or reach PH goals)?

Common Themes

Regarding Benefits

- Debate over specific benefits of initial H5N1 ferret studies— e.g., regarding surveillance and development of vaccines.

- Debate regarding whether key public health questions were answered:

  - Translatability of ferret studies to humans. Concerns regarding epistasis.

  - Did policy/practice change in important ways?

- More general concerns about realizing benefits from GOFR or DURC (given dependency on background conditions)

Common Themes

Regarding benefits:

- Debate concerning "Epistemic Value"

    – Is GOFR only or ideal way to answer key questions and/or achieve relevant public health goals?
    – Or are there equally good/less risky ways achieve ends?
    – Acknowledgment that benefits from scientific advance are often long term and hard to predict/appreciate in advance—spin offs. Claim that such benefits nonetheless need to be factored into RBA.
    – Concerns about chilling of important research areas
    – Questions regarding the value of knowledge

Delineating Research of Concern

- GOFRC (like DURC)

- Being GOFRC (like DURC) does not necessarily mean research should not get done (as opposed to warranting scrutiny)

- GOF with non-PPPs can be concerning (e.g. increased toxin production)

- Some PPPs more dangerous than others. R/e biosafety, level of pathogen danger (rather than GOF per se) should be main concern? Is existing biosafety regime for existing PPPs inadequate? Want/need general framework for extraordinarily dangerous research rather than GOF per se?

Values at stake

- Public Health

    – Aggregate # lives saved/lost

    – Aggregate # DALYs averted or caused

- Aggregate well-being

- Distribution of lives saved/lost, DALYs, well-being

- Security

- Scientific advance (and good things thereby enabled)

- Academic freedom (but note difference between refraining from funding and other kinds of interference)

- Economic

- Flourishing of individual careers/labs

Values at stake

Hard questions:

- Causing harm versus preventing harm

- Risk/harm to identifiable versus statistical persons

- Current versus future generations

- Plural and conflicting values—issues of weighting

→ No fact of the matter r/e how values should be weighted? Risk/benefit analysis and policy should reflect values (and weightings) of the people?

→ Should focus on metrics such as lives saved/lost and/or DALYs averted (i.e., given especially high stakes, and to simplify)?

RBA

Important input to policy making, but there are limits:

- Complex
    - # of scenarios
    - # of factors

- Dependence on data/assumptions
    - Uncertainty
    - Unknown unknowns, unknowable unknowns

➢ Even w/best/perfect data RBA wouldn't necessarily indicate whether risks outweigh benefits. This depends upon:
    - How values (r/e different costs/benefits should be weighted)
    - Risk taking strategy

Decision Frameworks for Risk/Uncertainty

- Expected Value

    -requires prediction/estimates r/e possible outcomes, their probabilities, and extent of harm/benefit in each

    -risk neutral—but it is arguably apt to trade off expected value to protect against disaster

- Precautionary—"maximin"

    – costly, extreme

- Ambitious—"maximax"

➢ Each might be apt in certain circumstances. Rather than choosing between them, could hybrid/pluralistic account.

Decision Frameworks for Risk/Uncertainty

➢ There might be clear cases r/e what should be done.

➢ Doubtful that science/logic will provide exact equation/algorithm. Judgment may be required in hard cases.

➢ Much depends on weight/extent of risk aversion.

➢ No fact of matter what is right risk-taking strategy. Want/need decisions to reflect risk-taking strategies of those effected—hence need for community engagement/research.

Towards a Decision Framework for GOFRC Funding

- Necessity/importance of research
- Proportionality
- Minimization of risks
- Justice
  - Fair distribution of benefits and burdens of research
- Evidence based decision making (ethical mandated that relevant research—e.g., RBA and community outreach--gets done)
- Democratic/transparent
  - Decisions should reflect values and risk-taking strategies of those affected
- International outlook

- ➢ Necessary conditions versus scalar approach (dimensions on which can perform ethically better or worse)

Conditions

- Various ways to reduce/mitigate risks addressed in the literature.

- Note that decision not to fund does not imply that research should not get done. Such a decision (e.g., by NIH) may sometimes reflect judgment that should not get published.

- Are risks manageable?

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