



WMA Satellite Meeting during the 11th World Congress of Bioethics:  
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# Should the Declaration of Helsinki become more “risk-based”?

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## The case for “risk-adapted” research protections

Risk-adapted systems of research oversight 1) calibrate various safeguards and protections to the level of risk posed to participants (e.g., ethical review) and 2) set upper risk limits for certain types of research (e.g., pediatric research)

### Ethical case

- Balance between protecting study participants and promoting valuable research
- Focus oversight on risky research

### Regulatory case

- Efficiency in ensuring that ethical and regulatory requirements are met



## The risk-adapted Declaration of Helsinki (2008)

### Explicit risk-adapted elements

- Research with incompetent subjects that has no likelihood of benefit for them: only if minimal risk and minimal burden (§27)
- Medical research with medical care: only if no adverse health effect (§31)
- Placebo controls when a proven intervention exist: only if no risk of serious or irreversible harm (§32)

### Implicit risk-adapted elements

- Waiver of consent in research with identifiable human material or data when consent is impossible or impractical to obtain (§25)
- Emergency research without informed consent if the research cannot be delayed (§29)



## Problems of current research protections

### Overprotection in low-risk research

- Criticism from stakeholders
- Current framework developed in reaction to blatant abuse
- New research methods that generally pose low risks (e.g., genetic research, biobanking, health services research)

### Underprotection in high-risk research

- Cases of poor risk management (e.g., TeGenero dosing)
- No explicit upper risk limit in research with competent consenting participants



## Proposals for risk-adapted research oversight

### International

- OECD Global Science Forum (2011)
- European Commission (2011)
- European Medical Research Council / European Science Foundation (2009)
- Roadmap Initiative for Clinical Trials in Europe (2010)
- European Medicines Agency (2011)

### National

- U.S. Department of Health and Human Services / FDA (2011)
- U.K. National Research Ethics Service (2008/2010)
- U.K. Department of Health, Medical Research Council, Medicines and Healthcare Products Regulatory Agency (2011)



## Stratification of research risks

### 1) Risks of “non-beneficial” research interventions

- Minimal / greater than minimal risk (U.S. DHHS, U.K. NRES)

### 1) Risks of “beneficial” research interventions

- Marketed interventions used under licensed indication (ECRIN, OECD, U.K. DH / MRC / MHRA, EC)
- Marketed interventions used outside of licensed indication (ECRIN, OECD, U.K. DH / MRC / MHRA)
- Non-marketed interventions (ECRIN, OECD, U.K. DH / MRC / MHRA)

### 1) Mixed approach (EMRC / ESF)



## Risk-adapted safeguards and protections

### 1) Research ethics review

- Excused, exempt, expedited, full review (U.S. DHHS, U.K. NRES, ECRIN, OECD, EMRC / ESF)
- No continuing review, continuing review (U.S. DHHS)
- Informational risks excluded from review (U.S. DHHS)

### 2) Informed consent process

- “Light” patient information, regular information (ECRIN)

### 3) Safety monitoring & management

- Simplified safety reporting, periodic safety reporting (ECRIN, EC)
- Safety monitoring (ECRIN, OECD, EMRC / ESF, U.K. DH / MRC / MHRA)
- Insurance (ECRIN, OECD, EMRC / ESF, EC)



## Critical appraisal of current proposals

### Risk stratification

- A more nuanced risk stratification is needed, but the marketing status of study interventions is a poor indicator of risk

### Risk-adapted protections

- Research ethics review is widely calibrated to risk: sensible in terms of protecting participants' interests, but participants' rights also need to be protected (e.g., research involving deception)
- Safety monitoring & management are widely adapted to risk: sensible since the goal is to protect participants' interests
- Risk-adapted requirements for the informed consent process are not widely endorsed: appropriate since the relationship between risk and consent remains to be clarified





## Recommendations for revising the Declaration

- 1) Clarify the role of risk in research
  - 2) Streamline the use of risk (maintaining the minimal risk threshold)
  - 3) Accommodate risk-adapted ethical review
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- 1) Introduce risk-adapted safety monitoring & management



## 1) Clarifying the role of risk in research

- Revise §6 “(...) the well-being of the individual research subject must take precedence over all other interests” to emphasize that it is ethical to expose participants to some level of risk for the benefit of others
- ★ *Proposed wording §6 : “In medical research involving human subjects, the individual subjects should not be exposed to excessive risks for the sake of scientific progress or social welfare”*
- This revision also removes the inconsistency between §6 and §21 “Medical research (...) may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects”



## 2) Streamlining the use of risk

- Streamline the different uses of risk and replace with “minimal risk” defined as a low likelihood of harm or burden
- ✦ *Proposed wording: “A research interventions poses minimal risks if it is associated with a very low likelihood of serious physical, psychological or social harm (e.g., <math><0.1</math> per 100’000) and/or a low likelihood of significant harm (e.g., <math><10</math> per 100’000)”*
- Adapt the provisions on research without informed consent (§27) and add minimal risk requirements to the paragraphs on waivers of consent (§25) and emergency research (§29)
- Adapt the provision on placebo controls (§32): minimal risk in research without informed consent, no excessive risk with consent



### 3) Accommodating risk-adapted ethical review

- Revise §15 “The research protocol must be submitted for (...) approval to a research ethics committee before the study begins (...)” to allow for exceptions from ethical review and ethical review by less than a full committee in low-risk research
- ✦ *Proposed wording §15: “Review by less than a full research ethics committee may be appropriate in research involving no more than minimal risks.”*



## Accommodating risk-adapted ethical review ctd.

- Revise §15 “No change to the protocol may be made without (...) approval by the committee” to allow for exceptions from continuing review in minimal risk research
  - ✦ *Proposed wording §15: “Changes to the protocol should normally be approved by the committee, but exceptions may be appropriate in minimal risk research.”*
- Add factors unrelated to risk that should trigger regular ethical review
  - ✦ *Proposed wording §15: “Full ethical review is required in research that raises concerns other than risk (e.g., research involving deception, research with vulnerable populations).”*



## 4) Allowing risk-adapted safety management

- Revise §20 “Physicians may not participate in a research study (...) unless they are confident that the risks (...) can be satisfactorily managed” to encourage risk-adapted safety management
- ★ *Proposed wording §20: “Researchers should monitor and plan for addressing adverse events. Safety monitoring should be proportionate to the risks posed by a study.”*



## Objections and replies

### 1) Risk-adapted provisions weaken subject protections

No, they specify the combination of safeguards that is necessary for protecting participants at the given level of risk

### 2) Risk-adapted provisions weaken the Declaration

No, they strengthen the Declaration by better balancing research and protection and staying in sync with current practice and developments

### 3) Risk-adapted provisions require setting controversial risk thresholds

No, controversy will be limited by continuing to use the minimal risk threshold

### 4) Considerations of risk do not exhaust the ethics of research

Yes, this will become evident in other parts of the Declaration



**Thank you**

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