



Rethinking the ethics of rare disease research

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ASTERIX Moral Framework

‘Ethical benchmarks for rare diseases research’

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- Empirical Ethics study
- Based on Emanuel et. al. What makes clinical research ethical?

The ASTERIX Moral Framework

1. Form collaborative partnerships
2. Enhance the social value of rare diseases research
3. Maintain similar standards for scientific validity
4. Promote rare diseases research
5. Recognize specific ethical aspects in the risk-benefit assessment
6. Ensure expertise on rare diseases research in the ethics review
7. Ensure voluntary informed consent and provide adequate information
8. Ensure respect for privacy

ASTERIX Moral Framework

- What is the task which an moral framework should do?
- The conditions under which “research in the field of orphan diseases can be considered ethically acceptable.”
 - What makes research ethical?
 - **(Could research that did not have this characteristic be ethical?)**

ASTERIX Moral Framework

An important distinction:

1. How should we govern or organise research in our society?
 - If it's badly organised, research will be difficult to carry out and won't be as good as it might otherwise be.
 - But this is not about the research itself – it is about the institutional structures surrounding research
2. What research is ethically acceptable?
 - **What is an acceptable offer?**
 - Consent (How are participants enrolled?)

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ASTERIX Moral Framework

How should we govern or organise research in our society?

- **Form collaborative partnerships**
 - An important practical consideration – can't do the research otherwise
- **Promote rare diseases research**
 - Research priority setting – very important ethical issue but not
- **Ensure expertise on rare diseases research in the ethics review**
 - About research governance

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ASTERIX Moral Framework

- **Enhance the social value of rare diseases research**
 - Establishment of registries and international databases of patients and research interventions – organisation and governance?

Or

- Social value as more overall benefit for society – impact, ensuring that we gain as much and the most useful knowledge from the research (looks like scientific validity and effectiveness)

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- Ensure voluntary informed consent and provide adequate information
 - This is clearly an ethical matter and should certainly be a condition of ethically acceptable research.
 - But, for the most part this is not too much of an issue here
 - One caveat is a point about coercion, small populations and patient groups – there is a danger that the pressures of being one of a small number can play an important role: “everyone must pull together”

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ASTERIX Moral Framework

- **Ensure respect for privacy**
 - This is also clearly an ethical matter and should certainly be a condition of ethically acceptable research.
 - It is an example where I suggest that the possibilities and so the ethical standards need to be adjusted
 - In a small population confidentiality is hard – we can pay attention to access to data, but in the context of detailed registries, the standards that we can maintain cannot be to the level of other kinds of conditions

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ASTERIX Moral Framework

- Maintain similar standards for scientific validity
- Recognize specific ethical aspects in the risk-benefit assessment
 - These are clearly an ethical matter and should be articulated clearly.
 - In my view the relationship between these two is THE key ethical issue in research on rare diseases
 - I'm not sure that we can capture this relationship by depicting the two as distinct – the trade-offs that we make in ethics are between these two

Participants and Future Patients

- In research ethics, the central tension is between:
 - **Risks and potential benefits to participants**
 - **Benefits to future patients**
- Some initial observations:
 - Distinction b/n risk/benefit ratio and 'absolute' risk
 - Uncertainty (and how to manage it) is key here:
exposure to risk vs. learning about risks and benefits
 - Benefits -> Scientific method, standards of evidence
 - The step from knowledge to benefit is vital

Participants and Future Patients

- Benefits to future patients (standards of scientific validity)
- **ASTERIX moral framework:**
 - A lower 'level of evidence' – no *a priori* reason
 - Appropriate endpoints – not just hard clinical
 - Novel designs - adaptive randomization - sequential designs – 'play the winner'
 - Conditions: (i) keep type 1 error, (ii) prospectively planned meta-analysis and (iii) reported methods

Participants and Future Patients

- Benefits to future patients (standards of scientific validity)
- **Hasford and Koch (2017):**
 - A lower 'level of evidence' is necessary
 - Surrogate endpoints can be used in rare situations
 - Could relax type 1 error rate – but problems getting better evidence after authorisation
 - No pilot studies – these don't end up being taken as pilot studies!

Participants and Future Patients

- Risks and potential benefits to participants
- **ASTERIX moral framework:**
 - Exposure to higher research risks
 - Something needs to go wrong in order to learn
 - Level of benefit during the trial and the use of placebo
 - This is a key tension: placebo is a good example
 - Post-trial access: difficult commercial and reimbursement consequences
 - Consent and a fair offer

Rarity and Ethics

- 'Being rare' is not a morally relevant property, certainly for the purposes of research or resource allocation
- The disadvantage arises not because the condition is rare
 - if the condition was rare but the treatment very inexpensive the issue would not arise
 - If the condition was rare but very mild the issue would not arise
- Instead, the disadvantage arises from a number of contingent consequences of rarity, each of which are morally relevant

Rarity and Ethics

- These consequences include:
 - Identification/diagnosis of the condition/history of our knowledge of the condition
 - Amount of research conducted
 - Quality of the evidence
 - Market interest
 - Cost of treatment
 - Severity of the condition
 - Uniqueness of the condition (alternative treatment vs. symptom management)

Rethinking Research Ethics

Complete Pathway Ethics

- Risks/benefits are always traded off against knowledge and scientific validity
- Both sides are moveable – ethics is not fixed! Ethics is about trade-offs
- The ethical decision is what constitutes a fair offer: a trade-off between participants now and patients later
- “Does the study yield useful information even if the experimental treatment is not successful?” (Hasford and Koch) – We cannot lose information, there is not enough!

Rethinking Research Ethics

Complete Pathway Ethics

- Ethics at the research end of the pathway must be informed by the funding/reimbursement end of the pathway
- We need to be clear about (and continue to be clear about) the trade-offs that are required at each point
 - All stakeholders, at each point
- The commercial model is what we have and should ethically acknowledged
 - It need not be uncritically accepted however