The Asterix benchmarks for ethically sound research in rare diseases

R van der Graaf1, KCB Roes1, S Dekker1, E Biesheuvel2, MC Jansen-van der Weide3, JJM van Delden1

Why ethical benchmarks for rare diseases?

People who are diagnosed with a rare disease often face high unmet medical needs since proven effective treatments are usually lacking. Although research in rare diseases is increasingly promoted, it remains complex since populations are typically small. These circumstances raise unique ethical challenges.

In the FP7 EU project Asterix ethical benchmarks were developed based on existing norms for human subjects research that were further specified. We used a mixed method approach, combining empirical methods and ethical analysis. We collected data from literature reviews, interviews with relevant stakeholders such as patient representatives, and focus groups with physicians, regulators, biostatisticians, and employees from pharmaceutical companies. We combined these data with existing ethical principles and ethical theories on utilitarianism and justice. The benchmarks resulted from this empirical-ethical process.

Benchmark 1. Collaborative partnership

From the design phase until the dissemination phase researchers, sponsors, third party payers and patient organizations should form collaborative partnerships. Part of the documentation provided to Research Ethics Committees should be a proof of involvement of patient organizations. Where possible, researchers should form networks of expertise.

Benchmark 2. Social value

The justification of rare diseases research lies in its potential to improve the health and well-being of those with high unmet medical needs. Moreover, research into rare diseases may yield insights in the causes of more common diseases.

At the same time, in order to ensure or enhance the social value of rare diseases research:
- **policymakers and national governments should centralize the creation and use of registries; and**
- **researchers should include patient preferred centered outcomes where appropriate.**

Benchmark 3. Scientific validity

As a general rule, scientific validity for rare diseases research should be similar to common diseases research. If the population size, sample sizes and disease course are substantially different from common diseases research, alternatives to customary standards of evidence (power, type 1 error) may be considered, provided that:
- **criteria are pre-specified and thus independent from the data resulting from the trial**
- **the type 1 error can be assessed (and is controlled)**

Benchmark 4. Favourable risk-benefit ratio

To justify imposing any research related risks on participants in health research, risks must be minimized and appropriately balanced in relation to the prospect of individual benefit and the social value of the research.

As regards individuals who are not capable of giving informed consent, such as children and adolescents, for research interventions or procedures that have no potential benefits for these groups, two additional conditions apply:
1. **the risks must be no more than minimal, and**
2. **they must be studied in individuals who can give informed consent first, when these interventions and procedures are targeted at conditions that affect persons who are not capable of giving informed consent as well as those as who are, unless the necessary data cannot be gathered without participation of persons who are not capable of giving informed consent.**

A research ethics committee may permit a minor increase above minimal risk for research with persons who cannot give informed consent, if:
1. **the social value of the studies with such research interventions and procedures is compelling, and**
2. **these studies cannot be conducted in individuals capable to give informed consent , and**
3. **patient organizations (if existent) support a higher exposure to research risks**

Benchmark 5. Post-trial access

Before initiating rare diseases research, sponsors, third-party payers, patient organizations and researchers should agree about the provision of the study medication post-trial. This agreement should be part of the study protocol. Before the trial starts patients should be informed about the outcome of this negotiation process. They should be informed whether:
- **compassionate use of a drug is feasible**
- **compassionate use may be discontinued before the drug is available through the local public health care system**
- **there is a risk that the compassionate use may be discontinued**
- **close relatives or others diagnosed with the same disease will be provided with compassionate use**

Benchmark 6. Informed consent

Researchers and research ethics committees should assess that patients have given individual voluntary informed consent. Patient organizations should be involved in the information process.

Benchmark 7. Respect for privacy

Although anonymization of data cannot be guaranteed in rare disease research, researchers should strive for the highest standards on the de-identification of patient data.

1. UMC Utrecht, Julius Center, Netherlands, 2. Danone, Utrecht, Netherlands, 3. Academic Medical Center, Pediatric clinical Research Office (PRO) | Woman-Child CenterAmsterdam, Netherlands
Correspondence: Dr. Rieke van der Graaf; r.vandergraaf@umcutrecht.nl