ARBEITSKREIS MEDIZINISCHER ETHIK-KOMMISSIONEN

IN DER BUNDESREPUBLIK DEUTSCHLAND e. V.

- DER VORSTAND -

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Comments regarding the Consultation Document Good Clinical Practice for Advanced Therapy Medicinal Products

The Association of Medical Ethics Committees in Germany represents all Ethics Committees in Germany that are involved in the assessment of clinical trials with medicinal products and medical devices. We greatly appreciate that the European Commission has initiated a targeted stakeholder consultation on the draft Guidelines on Good Clinical Practice for Advanced Therapy Medicinal Products. This offers the chance to contribute to the further improvement of this important document.

<u>Line 95 ff, staggered approach</u>

In principle we agree with the text but one has to keep in mind that a staggered approach might result in a later availability of an authorized beneficial treatment for younger or very young patients. To address this topic, the expert group on clinical trials for the implementation of CTR 536/2014 gave a recommendation on “Ethical considerations for clinical trials on medicinal products conducted with minors” (18 Sep 2017; Paragraph 9.1) stating: "Based on the experience gathered in the last ten years, a ‘staggered’ medicine development approach, starting by the older and going sequentially to the younger age groups, may lead to delays in data availability, and result in prolonged off-label use in younger age groups (especially neonates) and difficulties in conducting any trial in these groups once the medicine is on the market."

In the past, the development of

- BiTEs and CAR-T-cells in children´s and adolescent´s acute lymphoblastic leukemia,
- Brentuximab Vedotin in childhood and adolescence Hodgkin’s disease, and

- Vemurafenib/Mek inhibitors in adolescent´s melanoma

was aggravated by hesitation to allow young individuals on trial. Cases of death during the waiting period, e.g. until the age cohort was allowed to fill by the bureaucratic procedure, are known. This should not be repeated in the ATMP area.
Children and adolescents should have identical chances as adults to enter trials with potentially curative or overall survival-prolonging ATMPs. From the experience with previous classes of drugs, particularly in oncology, no specific risks can be seen for young individuals on trial, with the exception of restrictions to enter trials.
Exceptions from this should, of course, be made, if there is any previous evidence that a specific ATMP or class of ATMP carries increased risk for children and adolescents.

Line 115 ff
Single blinded trials are performed comparatively rarely. In practice, it is difficult for the informed investigators (and ethically problematic too) to keep the treatment allocation secret, in particular during longer treatment periods. Thus, we recommend the use of blinded outcome assessments whenever possible in trials where blinding/masking of the treatments is not feasible.

Line 121 unreasonable risk
The term 'unreasonable risk' is much too vague, when invasive procedures are planned for in the placebo group. As the patients receiving placebo do not have any chance to benefit from the placebo treatment the acceptable disadvantages from participating in a research project has to be limited to minimal risk and minimal burden, in particular if minors are recruited. Our proposal is in agreement with articles 28 1. (d) and (e), and 32 1. (g) (ii), CTR 536/2014. Thus this sentence should be modified to "... control groups receiving placebo only should not be subjected to a procedure if it presents more than minimal risk and minimal burden."

Line 134 cohort size
Cohort size should depend on a statistical sample size estimation too, even if small sample sizes have to be accepted for orphan diseases. But not all ATMPs will be used in orphan diseases only. Sample size estimations are essential for safeguarding that the research questions can be answered reliably and for calculating for a sufficient number of study centers needed to successfully conduct the study.

Line 196
Instead of "This strategy may need…" better: "This strategy typically will go…."

Line 278
Instead of "…measures that should be followed…" better: "… measures that must be followed…"

Line 350 Informed Consent

The information provided to the research subject shall empower him/her (or the custodians) to make an informed decision, thus he/she needs information about the expected or expectable benefit (e.g. as assumed in the sample size estimation) too, not only about the risks.

Line 351

Instead of "…should receive adequate information.." better: ".. has to receive adequate information…"

Line 354

Instead of "…the subject should also be informed…" better: "..the subject has also to be informed…"

Line 358

Instead of "…precautionary measures should be clearly communicated.." better: "…precautionary measures have to be clearly communicated.."

Line 364 ff

We do not think that a non-interventional study (NIS) is the right instrument for long-term follow-up of patients treated within an ATMP study. NIS can, according to current legislation, performed with authorized medicinal products only. Clinical trials in this context will often be done with unauthorized ATMPs. Thus the term non-interventional study should not be used as a possible "nature of follow-up ... in the clinical trial protocol." In addition, with NIS there is typically no standardized diagnostic work up and monitoring during follow-up. Finally, Ethics Committees should be involved in the discussion with the sponsor and the NCA regarding the duration and tasks of follow-up too as it is one of the premier responsibilities of Ethics Committees to safeguard the well-being of the research subjects.

Line 378-383

There is an additional problem that should be addressed: Often there is just one or very few study centers offering the treatment with ATMPs. Thus patients may have to travel very long distances to receive the treatment. Once treated, these patients look for physicians nearby to their home for the follow-up exams. However, these (local) physicians may not be certified investigators in the regulatory sense and may not be part of the team of approved investigators. We recommend allowing for pragmatic solutions as long as no unique medical qualifications are needed for the follow-up exams.

Gräfelfing, 27.10.2018 Prof. Dr. med. Joerg Hasford, President