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Institute for Quality and Efficiency in Health Care

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TSC 01/2018 on GCP for ATMPs

Dear Sir or Madam,

IQWiG appreciates the opportunity to comment on the Consultation Document on Good Clinical Practice (GCP) for Advanced Therapy Medicinal Products (ATMPs). IQWiG proposes to specify three issues on clinical trial design.

First, mentioning self-controlled research designs is certainly helpful in the field of ATMPs. It also is true that such designs eliminate inter-subject variation, which helps “to generate reliable and robust data” as specified in Art. 3 of Regulation (EU) No 536/2014 on clinical trials. This overarching aim of clinical research can nevertheless only be reached if self-controlled studies use randomization. We recommend adding this important issue in the text. Furthermore, it also should be emphasized that statistical testing in self-controlled designs should be done by using appropriate tests that consider the paired nature of the data (e.g. paired rather than unpaired t-test).

Current version of text (line 111 to 114)	Suggested text
For some ATMPs an intra-subject control might be appropriate. For example, the investigational product could be injected into one eye and the untreated eye is used as a control. Comparison of local effects can be facilitated in this way by eliminating inter-subject variation.	For some ATMPs an intra-subject control might be appropriate. For example, the investigational product could be injected into one eye and the untreated eye is used as a control. Especially when combined with randomization, self-controlled designs can generate reliable and robust results. Comparison of local effects can be facilitated in this way by eliminating inter-subject variation.

	Statistical testing should be performed by using tests that are appropriate for paired data.

We secondly propose to add a general comment to highlight the importance of randomized controlled trials (RCTs).

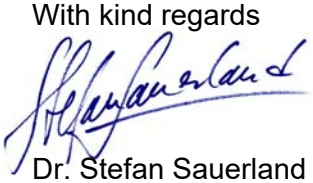
Current version of text	Suggested text (insert after line 110)
-	Once an ATMP shows the potential for improving health, it is essential to compare it with the current standard of care. Measures to minimize bias, including randomization and blinding, should be preferred in order to generate reliable and robust data on effects.

Thirdly, the text on blinding is misleading, as it suggests that blinding of research participants is easier than it is for investigators. Moreover, the term “double blinding” should be avoided, as there are three – rather than just two – parties in a clinical trial, who can be blinded with regard to treatment assignments: study participants, health care providers, and data collectors (see: Devereaux et al., JAMA 2001; 285: 2000-3). In clinical research on ATMPs, the easiest option usually is that at least data collection (i.e. outcome assessment) is performed blindly. In this regard, ATMP research is similar to surgical research where about half of a studies were able to employ blinding (see: Speich, Ann Surg 2017; 266: 21-22).

Current version of text (line 115 to 117)	Suggested text
While comparison to standard of care or no treatment sometimes makes double-blinding not feasible for investigators/for the surgical investigator team, blinding for subjects should take place where feasible.	Blinding of study participants, health care providers, and outcome assessors should generally be performed where feasible. If the nature of an ATMP prevents blinding of health care providers and study participants, at least the assessment of key outcomes should be performed in a blinded fashion.

As an additional remark we may mention that the word “subject” (which is defined in Directive 2001/20/EC) should be replaced by “research participant” in all EU regulatory documents. Manufacturers and researchers should appreciate the patients’ willingness to take part in clinical research, as well-founded ethical principles protect patients from being "subjected" to experiments (see: Bromley et al., Am J Public Health 2015; 105: 900-8).

With kind regards



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