Submission of comments on ' Optimisation of Safety Data Collection E19' (EMA/…/…)

Comments from:

Name of organisation or individual
Arbeitskreis Medizinischer Ethik-Kommissionen in der Bundesrepublik Deutschland e.V. (Association of Medical Ethics Committees in Germany)

Please note that comments will be sent to the relevant **ICH EWG** for consideration in the context of Step 3 of the ICH process.

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)

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 appreciate that the ICH has initiated a public consultation on the draft ‚Optimisation of Safety Data Collection E19' . This offers the chance to contribute to the improvement of this document.

General Comments:

Given the mission statement of ICH:" ICH's mission is to achieve greater harmonisation worldwide to ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner." we miss such a statement in 1.1 Objective of the Guideline. The objectives...'..reducing the burden to study participants...' and ‚...facilitate global participation in clinical studies.', mentioned here do not cover the most important reasons for proactively collecting high quality safety data. These are: to provide the population with drugs, whose benefit/harm evaluation results in treatments that provide more chances for benefit compared to the risks of harm. Thus the frequently used term „sufficiently" needs definitely a definition.

Since 2002 Pharmacovigilance (PV or PhV), also known as **drug safety**, is understood as the pharmacological science relating to the *collection, detection, assessment, monitoring, **and prevention*** of adverse effects with pharmaceutical products.(WHO 2002).
This mission statement is endorsed by the so-called Pharmacovigilance Regulation and the Pharmacovigilance Directive: "Pharmacovigilance rules are necessary for the protection of public health in order **to prevent**, detect and assess adverse reactions to medicinal products placed on the Union market.."
As stated on the homepage of EMA: Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem.
Thus, there is universal agreement that the prevention of adverse events and adverse drug reactions is an absolutely essential part of using collected safety data of drug treatments.

Therefore it is necessary to devote considerably more substance in this document how this prevention can effectively be achieved. We think that at least 1000 exposed patients with comprehensive and complete safety data sets should be available. Thus the chance to monitor an SAE with an incidence of 3.3 o/oo at least once, is around 95%. Such a sample size may often be sufficient to allow for multivariate analyses of risk factors for the occurrence of ADRs. If not, only larger samples size can be considered as ‚sufficient'. Finally there are many neglected or vulnarable groups where typically only few or no safety data are available, e.g. senior multimorbid patients, pregnant women and women with child-bearing potential, minors, patients with rare diseases, etc. For these groups specified sample sizes for further analyses have to be defined, to allow for the analyses as mentioned before. In the case of rare diseases e.g. we cannot see that there ever will be sufficient safety data available to restrict safety data collection.

We cannot see a sound rationale for restricting the collection of safety data before marketing authorisation. Only during this premarketing phase controlled, typically randomised and often blinded trials with protocolls that specify in detail the collection of safety data (assuring equality of observation of all study participants) can provide the best available evidence re safety. It seems to us an absurd idea to limit during this phase the collection of high quality safety data of any kind. To do this will result contraintentionally not an an ‚Optimisation' but rather in the contrary. After marketing authorisation observational study designs dominate, often with no adequate control groups, often poor or incomplete data etc.. Thus their level of evidence is typically much lower compared to the premarketing studies.

The title of the Guideline starts with ‚optimisation' but the content focusses on restriction of collection of safety data only. It is hard to assume that a restriction results in optimisation. What is missing is in our opinion the responsibilty of NCAs, EMA, FDA and ICH to standardise and harmonize the collection of safety data per disease/indication in such a way that the safety profiles of the therapeutic alternatives can be compared in a valid manner.

The current ICH draft definitely does not represent the current state of the art, and thus needs in our opinion extensive modifications.

A last point to consider: The professional code of conduct for physicians in many countries request that physicians carefully record and report all suspected adverse drug reactions or even adverse events. Thus this current ICH proposal creates conflicts with the well accepted code of conduct for physicians.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes
34-39		Comment: What is the exact meaning of " …the safety profile of a drug is sufficiently characterized." ? It is well accepted that the safety profile a drug is (almost) never completely known. One of the more prominent and relevant experience in the recent past was the discovery, after more than 10 - 25 years of marketing, that most NSARs have the potential to severely impair the proper function of the heart and the cardiovascular system. Given that ICH E1 states: "Usually 300-600 patients should be adequate. " (for the assessment of safety), and the EU Member states got about 500 millions humans, we see very littly room to restrict the sound assessment of safety even further. Interestingly the objective of the guideline does not even mention the mission of EMA to try hard to provide the population with effective and safe medicinal products. Is there any reliable evidence that patients (study participants) consider the collection of safety data, e,g. by interviews etc as a burden ? Of course, we support any initiative that may facilitate global participation in clinical studies and the efficiency (how is efficiency measured?) of clinical studies as long as a satisfactory evaluation of the safety profile of a new drug is not hampered. See General Comments too. Proposed change (if any): Rewrite whole paragraph and define relevant terms, like efficiency, sufficiently characterised, etc. That
41-58		Comment: This whole paragraph sounds like being written by a sales representative of a pharmaceutical manufacturer. All our comments for line No. 34-39 apply here too. In addition the statement:" Throughout the course of medicinal product development and subsequently while the drug is marketed, sponsors collect extensive safety-related data, including all vital signs, laboratory data, and adverse events." is evidently wrong. There can be no doubt that e.g. all adverse events, that in health care occur are not collected. There are many examples: There are many drugs on the market often for dozens of years and there are still no reliable safety data re special groups of patients like pregnant women, senior multimorbid patients and minors just to mention a few.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Proposed change (if any): Completely rewrite of the paragraph.
59-70		Comment: Please specify what a '…late stage development' is vs. 'post-approval study' . Proposed change (if any):
77 113 115 134-137 160		Comment: There are many non-serious adverse events that may seriously impair the patients' quality of life and present a considerable distress and burden for the patient, e.g. hair loss, impaired vision, acnei-form visible (face) skin reactions, fatigue etc. In our opinion such patient-relevant AEs should generally be collected under all circumstances. It is of high importance to have sufficient numbers of affected patients with complete data to allow for the identification of risk factors for the occurrence of such ADRs. As for such analyses information on concomitant medications (which might interact with the study drugs) are essential, comedications have to be collected too. In addition, the CTR 536/2014 requires in many Articles (e.g. 28, 31, 32,33, 35) that trials have to be designed in such a way that distress and burdens have to be minimal and constantly monitored, e.. Art. 28 1.(e):" the clinical trial has been designed to involve as little pain, discomfort, fear and any other foreseeable risk as possible for the subject and both the risk threshold and the degree of distress are specifically defined in the protocol and constantly monitored." How can a sponsor or investigator comply with these requirements when not all AEs/ADRs get collected, recorded and analysed? Comment: "…has received marketing authorisation from a regulatory authority…" . Do you mean any regulatory authority in the world and irrespective of the date of authorisation? This would not be acceptable. Please clarify. Comment: "Availability of….." is much too vague, as there will be available most often some safety data. But most often they quality-wise too poor to allow for a sound benefit/harm assessment, in particular across the relevant therapeutic alternatives.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
160 onwards		What is meant by "….if sufficient safety data are available…"? See: General Comments. New indications may go along with new comorbidities, which may increase the risk for ADRs, well-knowns and unknowns ones. Please revise the remaining text in agreement with our comments made.

Please add more rows if needed.