EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Overview of comments received on ICH guideline E19 on optimisation of safety data collection (EMA/CHMP/ICH/173706/2019)

Comments from:

Stakeholder no.	Name of organisation or individual
1	Souzi Makri - ENFA
2	Nicola Connor - International Primary Care Respiratory Group (IPCRG)
3	Sue Jordan – Professor at College of Human and Health Sciences - Swansea University
4	Prof.Dr.Joerg Hasford, Vorsitzender - Arbeitskreis Medizinischer Ethik-Kommissionen in der Bundesrepublik Deutschland e.V. (Association of Medical Ethics Committees in Germany)
5	Gilead Sciences International Limited
6	BIFAP (ENCePP Partner), Spanish Agency on Medicines and Medical Devices (AEMPS)
7	EUCROF (Clinical Trials Legislation Working Group [CTL] and Pharmacovigilance Working Group [PV])
8	EFPIA
9	German Pharmaceutical Industry Association (BPI)
10	Silke Kern, Freelance Project Manager/Consultant Clinical Research and Dr. Ingo Rath, CliPS – Clinical Project Services
11	Clinical Trials Facilitation and Coordination Group, CTFG
12	Wilhelmina E. Hoogendoorn, PhD; Mariana Almas, MSc; Jaclyn Bosco, PhD, MPH; Deborah Layton PhD - IQVIA
13	ACRO (Association of Clinical Research Organizations)
14	Allergan Limited
15	Priv. Doz. Dr.med. Ruth Fritsch-Stork, PhD Chair of the scientific board of BIOREG (Austrian registry for biologic therapies in inflammatory rheumatic diseases)

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Stakeholder no.	Name of organisation or individual
16	Natacha Bolanos - Lymphoma Coalition
17	European Association of Hospital Pharmacists (EAHP)
18	AESGP

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

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2	"It would be useful if there is a section or 1-2 lines saying that there is a need for education so that safety issues are captured at a clinician level, and also that there is a need to facilitate the process at least at the clinician level SO to make it easier to report (eg in Greece its complicated). "
4	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. 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

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	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.
5	It would also give assurance to Sponsor that such a threshold having been reached does not need repeated discussions when future studies are being implemented, and that the selected safety collection will be consistent with any post-marketing commitments. This may also allow prior post-marketing commitments to be redefined so time and resources are not wasted. In general the possibility to be more flexible regarding safety data collection is welcomed

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	Reducing the extent of safety data collection could substantially ease the burden for participating study sites (especially for post-marketing studies) , however the current interpretation of GVP module VI (section VI.C.1.2.1.1.) requires the collection of all adverse events (unless specific protocol–defined MedDRA term AEs are excluded from that requirement) for studies based on primary data collection. Clarification is sought how this draft guidance could impact GVP Module VI requirements. ICH should ensure that existing guidance such as GVP Module VI is updated to align with this ICH guidance. Other existing guidance should also be considered for alignment such as the FDA guidance on selective data collection in late phase trials.
6	We are very much concerned about this guideline. It is difficult to understand why is needed and, more importantly, may jeopardize the collection of safety data from studies. It is stated that its aim is to optimise the safety data collection in some late-stage preapproval or post-approval studies when the safety profile of the drug is sufficiently characterised. However, this is never the case before authorisation, and very seldom early after authorisation. Any limitation to the safety data to be gathered in clinical studies decided in advance and based on general principles such as those proposed in this guideline would preclude further characterization of new safety concerns arising post-marketing. Non serious events could be very relevant to patients; a general exception is not justified and would limit further characterisation of safety issues. Therefore, the "relaxing" philosophy throughout the guideline in relation to safety, is neither understood nor shared. The text mix up very different scenarios and situations, compromising its comprehension: eg. examples mix-up database studies with clinical trials needing a CRF, with studies for approved drugs and drugs under investigation. Each situation is completely different, and not a general guidance can be given for such a different scenarios and methodologies. It seems not very adequate to include non-interventional studies, since in most of the cases the reason for conducting them is safety, and data collection is determined by the study objectives. In fact, most of the guideline refers implicitly to clinical trials, but the scope of the guideline tries to cover all studies. The objective of this guideline is to "improve the efficiency of clinical studies while reducing the burden to study participants". By nature carrying out a non-interventional study does not entail any additional burden to study participants. This is obvious for non-interventional studies that use only secondary data collection. Non-interventional studies that use only secondary data collection are mostly represented by studies performed using databases of electronic medical and administrative records in local, regional or national healthcare systems. This type of data sources like BIFAP nowadays represents a relevant proportion of all post-authorisation studies. To apply the proposed guideline to this context will only generate confusion. Even for non-interventional studies with primary data collection procedures , if diagnostic or monitoring procedures in addition to

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	normal clinical practice are applied to study participants the clinical study will then be interventional (a clinical trial) and not a non-interventional study (according to Clinical trials Regulation EU No 536/2014). It is also inappropriate to establish in a guideline the type of data that may be appropriate, since this will depend of many factors, and differ from one study to another. In some instances, the text describes situations that are obvious and inherent to current procedures.
7	EUCROF welcomes the opportunity to provide comments on this new ICH E19 Guideline. The Guideline is important as selective safety data collection is seen frequently and a frequent subject of discussions between stakeholders during protocol development, whereas adequate regulatory background is missing. Therefore, this Guideline is closing a gap between available legislation and common practise. *Given the topic of this guideline, EUCROF involved two working groups: the Clinical Trial Legislation and, as it is a safety subject, the Pharmacovigilance Working Groups. We have, thus, included a reference to the WG which expressed the comment:* • *[CTL] for comments from the Clinical Trial Legislation Working Group* • *[PV] for comments from the Pharmacovigilance Working Group.* *All comments reflect a consolidated consensual feedback.* EUCROF would like to express the following general remarks: 1) *[CTL]* EUCROF suggests to introduce – if not definitions – at least clarifications around some terms that are frequently used in the Guideline. Examples are: Late stage pre-approval study Selective safety data collection Comprehensive safety data collection Full safety data collection (same as comprehensive?) Participation in a clinical study / study participants (investigator, patient, both?)

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	2) *[CTL]* Also, as the scope of the Guideline are clinical trials and non-interventional studies (NIS), the term "sponsor" - which is exclusively used - is not the right term when the study is a NIS. It would be welcome to have clarification on how the term "sponsor" is being used in the Guideline or use Sponsor/Marketing Authorisation Holder instead. 3) *[PV]* This guideline represents a definite evolution, it seems very focused on later stages of drug development interventional phase IIIb or IV clinical trials. The guideline might benefit from a larger consideration of the multiple objectives and related study designs of post authorisation observational non-interventional studies, not necessarily related to drug development, but to drugs marketed for a long time. 4) *[PV]* Clarifications about safety information to be collected during a direct contact with a patient within a non-interventional study would be valuable. 5) *[PV]* The guideline clearly focuses on safety data collection, but some connections with safety event reporting and submission concepts may help understanding for non-PV experts. 6) *[PV]* Re the organisation of the document: section 2.1 is very detailed and precise compared to section 2.2 and 2.3, which provide more general contextual considerations. It might be easier for the reader to start with general considerations (i.e. 2.2 and 2.3) to then move to more specific requirements (2.1).
8	**Preclinical Safety:** When considering the selective approach to safety data collection, there are minimal references to pre-clinical sources, including DMPK, PD, toxicology or reproductive toxicology data. Line 188 refers to '…a finding from a nonclinical study…' for example. It would be advantageous to have an expert in preclinical safety review this document, and add multiple references to important areas of preclinical safety testing. Notably it is proposed that in some instances to limiting or stopping collection of concomitant medication could be considered. If this is done, it would be logical to limit information collected based on evidence from DMPK studies. Thus, data collection would be evidence-based. **2 General principles** It is generally understood what kind of investigational drug is targeted based on Section 1 (objective, background, and scope of this guideline). With abstract expressions and no definitions, the criteria in Section 2 (General Principles) are ambiguous when applying

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	the guideline. At the stage of examining the pros and cons of utilizing selective safety data collection in a study, it is difficult to determine when to start the study on selective safety data collection. If more guidance is provided in Section 2 on criteria (i.e., minimum number of cases, minimum observation period), it would be relatively easier to judge when to utilize selective safety data collection for the study. It is suggested the term "clinical study" should be defined upfront in the beginning of the guideline to include "interventional and non-interventional studies, in the post-approval setting and, for specific cases, in the pre-approval setting". The term "clinical study" is frequently used in this draft guideline and it may be confusing if it is considered only applicable to the clinical study or can be applicable to all the interventional and non-interventional studies. Please consider to add that this guidance only covers data collected as primary source, i.e. data collected and analysed as secondary data use are not in scope. From a practical standpoint, it is not clear how some details (e.g. concomitant medications) will be collected for certain events. For example, adverse events (AEs) of special interest: does it mean that, if an AE of special interest occurs, the investigator retrospectively enquires about concomitant medications? Otherwise, concomitant medications would need to be collected in case an AE of special interest occurs. **2.1 Types of Data for Which Selective Safety Data Collection May be Appropriate** **Obligatory data collection:** Section 2.1 – Suggest changing the order of sections "2.1.1 Types of safety data where it may be appropriate to limit or stop collection" and "2.1.2 Types of safety data that should generally be collected in all circumstances". It is important that Sponsors/MAHs first understand and agree to the data that must be collected, and only thereafter, they may consider where data collection may be stopped. **2.1.2 Reference to the RMP and potential risks:** Specific references should be made to potential risks specified within the RMP or REMS. In this case, it would seem prudent to ensure that the collection of safety data that might contribute to the evaluation and assessment of such risks should normally be collected.

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	2.2 When may selective safety data collection be considered Please consider scenarios which should never be considered for selective safety data collection. For example: marketing authorization applications that will use phase II data, that are granted fast-track or other expedited review, that are for chronic use or for use in the very vulnerable like infants, old-old, critically ill Consider all selective safety information collection schemes should be approved by IRB (via protocol approval) and implementation stage-gates (for studies where some sites or some sub groups or a portion of patients will have full data and the rest selective data) should have DSMB approval for transition between full and selective collection, or monitoring that selective data collection is achieving the data goals and not creating risk to patients or study objectives. Please consider this to be stated in the guidance. At what point selective data collection should be considered, is there a threshold or amount of safety/patient exposure required? It is suggested to clearly explain the amount or range of data to be accepted as "sufficient safety data" to justify utilizing selective safety data collection. A clear example or description would be helpful. It would also be helpful to provide additional guidance when it is appropriate for a sponsor to approach the regulatory agency to consider selective data collection since industry and regulatory agencies may have different thresholds. It would be useful to indicate a statistical thumb rule for what size of a controlled clinical program would be enough to decide that non-serious AEs are likely reasonably well investigated i.e. when can we accept that very uncommon non-serious AEs may not have been detected but would not have any significant implication for the B/R of the product. Data-collection in long-term safety studies should be considered a special case, where long-latency outcomes, e.g. neurodevelopmental delay, abnormal growth patterns, occurrence of SSPE, etc. would require particular care and attention. Please consider to add examples of different study/trial types e.g. NIS, RWE, pragmatic trial and low interventional trial where reduced safety data collection are accepted based on due justification. **Safety biomarkers:** Exclusion from selective data collection, or enhanced data collection based on the presence of a specific biomarker, or biomarkers, should be considered. It is clear that where a specific biomarker is present (or absent) the safety profile of a medicinal product will change. Thus, there is an opportunity to specify that if a relevant biomarker is detected, then either additional testing may be required, or such testing may be rendered irrelevant.

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	Exclusions: Consideration should be given to exclude certain classes of products from this paper e.g. ATMP and gene therapies. At this early stage in the general development of such products, the collection of comprehensive safety data should be required in order to fully elucidate the safety profiles for these products. It would not be justified to reduce data collection where no long-term benefit-risk assessment has been determined. This argument might be extended to all new chemical entities, and biologicals or vaccines subject to a novel manufacturing process. Hence it should be carefully considered whether exemptions from data collection may be granted to products under additional monitoring. **Section 2.6 Early Consultation with regulatory Authorities** Approaching each individual regulatory agency prior to study initiation of a study with selective safety data collection appears impractical in case of a global study. It could be helpful to include in the Guidelines further examples of scenarios when a selective approach is acceptable. How likely is it that there will be a harmonised view? Is there a mechanism we can use and would we would want to use, to enable a trial to be conducted in member states that do not share the same view on selectivity? There is no mention of ethics committees in the guideline. Does there need to be? They may have a view on use of a selective approach. There is potential for misalignment between the regulatory agencies and the ethics committees. Per GVP VI, National legislation should be followed as applicable regarding the obligations towards local ethics committees. **Section 3 Method of implementation** It could be highlighted that leaving out collection of non-serious AEs and other safety data may be limiting to evaluate a significance of a safety finding, would it be identified at the advanced stage of a study with selective safety data collection or upon its completion, and such a risk should be carefully weighed by the sponsor designing a study. Consider adding an additional paragraph in Section 3, addressing methods to collect the safety data, to spell out both standard "CRF collection / AE questions", and alternative methods to collect safety information such as registries, direct from patient approaches such as wearables and apps etc. This would be in line with the Bullet 6 in Section 2.3 on PASSes etc. and would also

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	open up for this in outcome studies as per Bullet 7 in the same section. **3.2 Comprehensive Safety Data Collection for a Specific Subset(s) of the Population, with Selective Safety Data Collection for Other Patients** Suggest adding to the guidance how to address any bias when selective data collection occurs in a study where comprehensive safety data collection occurs for a specific subset of the population (i.e. paediatrics) or when some regulators/countries allow selective safety data collection. Conducting analysis of ADRs in these scenarios may lead to identification of false signals, therefore suggest adding this consideration in the guidance. **Section 4, Relationship with other guidelines/regulation**, it would be useful to examine the relationship with the requirements and methods in the GVP Module VI, specifically sections: VI.C.1.2.1. Non-interventional post-authorisation studies & VI.C.1.2.1.1. Non-interventional post-authorisation studies with a design based on primary data collection.
9	Since agreement with regulatory authorities on the possibility and scope of selective safety data collection needs to be achieved in advance, it would be appreciated if regulatory authorities could be a bit more precise defining the scientific prerequisites before collecting selective safety data. Are all indications concerned? How many patients should be treated before selective safety data collection can be considered? To which extent is consistency of safety data throughout previous studies required?
	This guideline is written based on the assumption that some types of safety data are no longer required if the safety profile of a medicinal product is well-understood and documented and a comprehensive collection of all safety data may provide only limited additional knowledge of clinical importance (Lines 50 to 52). It could be argued, though, that we should not regard any additional knowledge of clinical importance as dispensable, even if it is only limited. Not collecting the data that are available anyway as per standard of care (as in the example given in lines 179 to 185) deprives us of the possibility of learning more – even if only in limited amounts – about the safety profile of a medicinal product without any additional burden to the subject. Assuming that we already know enough about the safety of a medicinal product seems like a form of scientific hubris. One consideration behind this guideline is that burdensome methods of safety collection might serve as a disincentive to participation in clinical studies (lines 43 to 46). It should not be underestimated, though, that one important incentive for patients to participate in a clinical trial is that they will

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	typically have more frequent and more thorough medical checks than they would have in standard of care without having to pay for them. Reducing the extent of safety data collection in clinical trials could therefore easily fail to reduce that assumed disincentive.
11	**Comment:** We do not support the concept of any selective collection of safety data prior to the first marketing authorisation of a new medicinal product. Since the marketing authorisation procedure is intended to demonstrate a positive risk-benefit balance based on the data collected during the clinical development program, limiting the collection of safety data could distort this risk-benefit assessment or/and unnecessarily introduce additional uncertainties at a time when the safety data are not yet very comprehensive. As drug development programmes have become increasingly shortened over the past decade, not least to speed up patient access to newly developed medicines, an additional reduction in available safety data should not be supported from this point of view. Nevertheless, a complete collection of all safety data seems to be not necessary in all cases in **post-marketing clinical trials**. A selective data collection approach in post-marketing trials could be acceptable for adverse events referring to those adverse reactions that are well characterised by type, outcome, severity and frequency. This applies in particular to frequent adverse reactions (in the sense of the legal definition of frequent) and for which there is no longer any regulatory interest in the collection of more precise incidence data. On the other hand, the requirements for recording and reporting adverse reactions should always ensure that rare or previously unknown/unanticipated adverse drug reactions can be detected regardless of their severity. As this guideline addresses investigators which are usually physicians it should be made clear that this guideline only concerns the documentation in the study documents (case report forms). The obligation for the medical documentation must remain unaffected, since in most Member States professional obligations require physicians to document adverse reaction reports and other patient reports in case of medical events. It should also be noted that in many Member States doctors are obliged to report adverse drug reactions to certain institutions or authorities. These reporting obligations cannot simply be overridden by a guideline. For adverse events not reported to the sponsor, but which the investigator considers to be an adverse drug reaction, appropriate rules must be put in place to allow the investigator to fulfil his or her reporting obligations. Even if at first glance it appears to be a simplification for the investigator to no longer report all adverse events/reactions, the investigator must still document those events in the patient medical files (source documents) as a medical adverse event. The investigator has then to check for each adverse event whether it is to be reported on the case report form or whether it falls under the study-specific exemption, which needs no documentation in the case report form. This might lead to even more work for the

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	investigator than if this distinction does not have to be made for each adverse event. **Comment:** Throughout the document, it seems that wording "adverse events" is in some instances meant to refer to "adverse reactions", that is, only adverse events related to the investigational medicinal product. However, this is not defined and therefore there is some doubt over the meaning of some points. Proposed change: A more concise guideline would be preferred. **Comment:** The scope of this guideline should be better specified. Even if the scope seems to covers "clinical studies"; a reference to **non-interventional studies** is only made in sections 1.3 and 2.6 *".*" Non-interventional studies should be left outside of the scope of this guidance. The usual goal of such non-interventional study is often to collect a large amount of safety data to better characterise safety concerns not enough of fully explored/observed in pre-approval setting and which could arise from the use of the medicinal product in a post-marketing setting (not controlled, no population defined etc..). Moreover the inclusion of non–interventional studies in the scope of this guideline would be contradictory with the aim of this draft guideline the objective of this guidelines as described in section 1.1 is the *"Optimisation of safety data collection using a selective approach may improve the efficiency of clinical studies <u>while reducing the burden to study participants</u>"* .Neither the burden on participants nor encouraging research seem to actually apply to non-interventional studies. Further, the range of non-interventional studies is wide and as oversight by regulators is not present it is not deemed appropriate to be suggesting reduced safety data collection. This draft document makes several references to a burden on participants which seems to be one of the main justification of this work. However, the link between "safety reporting requirement" and an alleged burden on participants is unclear. The goal of clinical trial regulation is to foster innovation whilst ensuring the protection of the participants in clinical trials as well as the quality and integrity of the trial outcomes. It is acknowledged that marginally, doing so, can limit requirements for some

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	diagnostic or monitoring procedures which could eventually minimise the burden of participants. But it is very unlikely that the means to reduce the burden to study participants is to optimise safety data collection. The burden to patients is not seen as sufficient reason alone to allow reduced safety assessments or reporting. Whilst this would always be considered in a protocol, this should not be encouraged as a reason alone to alter safety recording and reporting requirements. **Comment:** From the EU perspective, there seems to be no added value of this document as risk proportionate approaches to safety reporting is already identified by article 41 of Regulation No 536/2014. Especially, this article states that 'The investigator shall record and document all adverse events, unless the protocol provides differently.' In addition, it also provides investigators with flexibility on the requirement to immediate reporting for certain serious adverse events. This approach is further detailed in the 2017 Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use on a Risk proportionate approaches in clinical trials. These recommendations provide a clear an unambiguous framework to when and how risk adaptations can be considered for adverse event recording and reporting. With respect to these recommendations, the proposed guideline brings no further improvement. Despite existing risk based approach, the document favours references to an unclear and undefined concept of 'optimisation'. At least the risk based approach including recommendation should be taken up in this document. **Comment:** On the other hand, the message provided through the current version of the draft guideline should be clarified and the construction of the document leads to inconsistent redundancy. Especially, the provided, non-comprehensive, non-explained subjective lists of examples or factors is not found helpful. While some examples can help, the examples given when selective safety data may or may not be considered are very non-specific and open to interpretation (abuse) from sponsors. These require significant additional detail and thought. Therefore, these examples should be provided with adequate details and context to explain why and how it could be implemented in a particular situation.
12	When referring to optimising safety data collection it may be important to also distinguish between adverse events that are considered related (adverse drug reactions) and those that are not considered related. Throughout the document no reference is made to this distinction. It makes sense to limit data collection to adverse events that are considered related (in post-approval studies). This is a restriction in safety data collection that can be expected to reduce burden with a low risk of missing important

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	information. Noting that it is not always possible to identify events that are considered related in post approval setting since assessment of causality may not always be indicated. As the focus of this guideline is on collection of safety data, it is recommended that, at a minimum, data collection should comply with what is expected to be submitted to regulators according to global, regional and local regulations. Elaborating on what that minimum expectation is, will aid in identifying where there is room for optimisation. In the context of Non-Interventional Studies in Europe, there are different safety data collection and reporting requirements for primary and secondary data collection studies. Would be good to explicitly mention this in the context of selective data collection. Next to distinguishing between what should be collected and what should be submitted to regulators, it may also be useful to relate to what should be reported in aggregate reports, such as DSUR, PSUR/PBRER and PADER. The document does not address the inherent differences between products. For example biologicals or gene therapies may have additional safety considerations than small molecules, which may impact the possibility to perform selective safety data collection without running the risk of missing important safety signals. It would be helpful to cite the Risk Management Plan as a guide for determining which selective approach should be collected in post-approval studies. The information presented in RMP could be referred to as a starting point for considering what relevant safety data to collect (gives information on the topics mentioned in section 2.2). For late stage pre-approval studies, the content of a development RMP may be relevant in this respect if a sponsor constructed such a document. Some suggestions: Consider reflecting on when a safety concern can be considered adequately characterised, for example, the following (from Risk Management Plan) is known: potential mechanism; evidence source(s) and strength of the evidence (i.e. the scientific basis for suspecting the association); characterisation of the risk: e.g. frequency, absolute risk, relative risk, severity, reversibility, long term outcomes, impact on quality of life; risk factors and risk groups (including patient factors, dose, at risk period, additive or synergistic factors); preventability (i.e. predictability of a risk; whether risk factors have been identified that can be minimised by routine or additional risk minimisation activities other than general awareness using the PI; possibility of detection at an early stage which could mitigate seriousness); impact on the risk-benefit balance of the product; public health impact (e.g. absolute risk in relation to the size of the target population and consequently actual number of individuals affected, or overall outcome at population level). Emphasise the need to ensure post-approval studies address the important uncertainties about the medicinal product's safety concerns (from the Risk Management Plan). Information pertaining to those elements (adverse events of special interest) should be

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	part of the selective safety data collection, preferably also if assessment of safety is not the major objective of the study. Information on risk factors for the safety concerns to be addressed in the study should be part of the data elements to be considered as they can modify the frequency or severity of those adverse events (as mentioned in section 2.1.3). The details of safety concerns reported in the RMP should also be taken into consideration for the definition of inclusion and exclusion criteria and critical data elements to collect and for the consideration of which subgroups/subsets of population (as mentioned in the guidance) should be subject to comprehensive data collection. The concept of listedness/expectedness (i.e. adverse reaction already listed in the CCSI or the SmPC) should also be taken into consideration when selecting which safety data to consider.
13	The Association of Clinical Research Organizations (ACRO) represents the world's leading clinical research and technology organizations. Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics and medical devices, from pre-clinical, proof of concept and first-in-human studies through post-approval and pharmacovigilance research. In 2018, ACRO member companies managed or otherwise supported a majority of all biopharmaceutical-sponsored clinical investigations worldwide. With more than 130,000 employees engaged in research activities in 114 countries, the member companies of ACRO advance clinical outsourcing to improve the quality, efficiency and safety of biomedical research. ACRO welcomes the draft ICH E19 guidance and fully supports the objective of optimising safety data collection using a selective approach to improve the efficiency of clinical trials while reducing the burden to trial participants. ACRO agrees that adoption of an internationally harmonised approach to selective safety data collection may facilitate global participation in clinical trials. ACRO welcomes, in particular, the inclusion of late-stage pre-approval clinical trials in this initiative, although we recommend that the guideline should provide further detail to help sponsors understand the extent of pre-existing safety data that is required (especially when these data are coming from ongoing rather than completed trials) in order to initiate an additional clinical trial with selective safety data collection in the pre-approval setting. ACRO is concerned, however, that the draft ICH E19 guideline uses the term “clinical study” rather than “clinical trial” throughout the document. The use of the term “clinical study” does not accurately reflect the purpose/focus of ICH E19 and will cause

Stakeholder number	General comment (if any)
	confusion, rather than clarity, when it comes to the applicability of this work product. From a regulatory perspective, this is important as clinical studies can be studies other than clinical trials, as is clear from the EU and USA definitions below: Non-Interventional Study: Means a clinical study other than a clinical trial (as per Article 2.2(4) of Regulation EU/536/2014). Observational Study: A non-interventional clinical study design that is not considered a clinical trial [As per Glossary of Framework for FDA's Real-World Evidence Program - Dec 2018] We note that section 1.12 of ICH E6(R2), indicates "The terms clinical trial and clinical study are synonymous" but, based on the legal definitions provided above, this is not the case. The use of the term "clinical trial" is in line with the 'purpose' of the ICH Efficacy guidelines as stated on the ICH work products webpage "Purpose of the ICH Efficacy Guidelines: The work carried out by ICH under the Efficacy heading is concerned with the design, conduct, safety and reporting of clinical trials. It also covers novel types of medicines derived from biotechnological processes and the use of pharmacogenetics/ pharmacogenomics techniques to produce better-targeted medicines." There are significant concerns about the inappropriate use of ICH guidelines in clinical studies to which they are not applicable (e.g., the recently announced Wellcome Trust initiative to develop new guidelines for clinical research) and, for this reason, we strongly recommend that the terms "trial" and "clinical trial" should be used throughout the ICH E19 guideline. ACRO thanks the Agency for the opportunity to provide comments on this ICH guideline E19 on optimisation of safety data collection Step 2b (EMA/CHMP/ICH/173706/2019). Please contact ACRO (knoonan@acrohealth.org) if we can provide additional details or answer any questions.
14	Regarding non-interventional studies - Some products that have been on the market for a considerable amount of time may be used for off-label use (various facial regions, dose, number of injections, etc). Off-label use tends to be captured as an AE, however, if there is a lot of off-label use, then this can be very time-consuming for site staff to capture all of this information. Is there a suggestion as to how this could be better handled?
15	Dear ENCePP, with great interest I read the draft on "Optimisation of Safety Data Collection", and consider it an important step towards ameliorating the problems of low patient inclusion safeguarding adequate safety of a study. I have two questions:

Stakeholder number	General comment (if any)
	- what is the approach concerning safety data collection that have arisen in postmarketing phases and thus have not been raised in the original approval procedure. - what is the approach concerning safety data collection in drugs that have not been investigated concerning their influence on fertility. Is there an automatic "rule" to include these items into the selective data set in general, unless they have been investigated in the meantime?
16	I wonder if this guideline applies in the context of gen and cell therapy, where some aspects could be slightly different, for instance long term follow up and collection of adverse effects for CAR-T therapy or any cell and gene therapy (EMA recommended 15 years follow up and asked registries to put a strategy on place. I would have expected PRO to be included more systematically. I´m well aware of the challenges because of the lack of harmonized/validated tools but regulator should be pushing for this to happen. Patient outcomes many times allow to identify other impairments in the physical and cognitive function, which may be directly linked with safety concerns. The data collection should be focused on demonstrating the superiority of new treatments. Non-inferiority is not enough, specially in the context of cancer and hematologic malignancies.
17	EAHP would like to underline the importance of collecting post marketing events to get accurate data. Improved adverse event reporting of even well know events is important, since incidents may be lower in the literature than in reality due to lack of reports.
18	The concept to collect limited safety data is understood and welcomed. However, it is not clear practically how some parameters (e.g. concomitant medications) will be collected for certain events (e.g. AEs of special interest) but not others. Does it mean that, if an AE of special interest occurs, the investigator retrospectively asks enquires about concomitant medications? Otherwise, concomitant medications would need to be collected in case an AE of special interest occurs. Please consider introducing some acknowledgement of the potential usefulness of -digital technology tools -Real World Evidence methodologies

Stakeholder number	General comment (if any)
	in achieving the aims of the guideline. Although the guideline is focused on safety data, some recommendation on the collection of ancillary non-safety data needed to evaluate safety, such as lot/batch numbers, would be welcomed. Rationale: The collection of this type of ancillary data post-marketing is notoriously difficult so specific mentioning in the guidance should help towards improving their collection.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes
Title	11	**Optimisation** is an unclear concept. Reference should be made instead to a **risk-proportionate** approach to safety data collection. **Proposed change: Risk-proportionate approach to safety data collection**
2.1.1 & 2.1.2	3	**Comments:** This appears contradictory and they should be allocated to a single category. In my view, vital signs should be collected under all circumstances (2.1.2).
2.1.2	3	**Comments:** Definitions are needed for several terms e.g. 'serious adverse events', 'overdose'. 'Vital signs' also need clarification: do these include oxygen saturation, respiratory rates, standing BP?
2.4	3	**Comments:** 'Standard of care' needs to be defined.
		Comments: To ensure patient safety and gauge the impact of a medicine on patients' wellbeing, checklists of all signs and symptoms lists in the SmPC should be completed regularly either by nurses or patients, with oversight from nurses. Large electronic healthcare databases hold information on drug utilisation, mortality, medical diagnoses and reasons for hospital admission, but less serious outcomes which are important to patients are not recorded anywhere (Jordan et al 2018), reducing the likelihood of identifying adverse effects. Examination of records of older adults in care homes indicated that there is no recording of ~50% of potential ADRs. Many of these could be and were addressed when monitored (aOR 3.34, 2.57-4.11) (Jordan et al 2015).
2	10	**Comments:** The title of this guideline is somewhat misleading as it implies that it refers to a much larger range of trials than it actually does.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		No guidance whatsoever is given for optimisation of safety data collection in trials where comprehensive safety data collection is required. The title should therefore reflect the fact that only the approach of a selective safety data collection is addressed in this guideline. **Proposed change:** Change title to "Selective Safety Data Collection" or "Optimisation of Safety Data Collection in selected late-stage pre-approval or post-approval studies"
34-36	7	"… late stage pre-approval or post-approval studies, when the safety profile of a drug is sufficiently characterized" **Comments:** *[CTL]* There might be confusion with the term "late phase study". The term "late phase" is often used to cover the timeframe starting with the Marketing Authorisation Application, however this is not necessarily the case for the "late stage pre-approval studies" addressed in this Guideline. Clarification on the term "late stage pre-approval study" would be welcome. **Proposed change:** "… **late stage pre-approval studies (usually phase III clinical trials irrespective of whether or not a Marketing Authorisation Application has already been submitted), or post-approval studies. The characteristic of the late stage studies addressed in this Guideline is the fact that the safety profile of the drug under investigation is sufficiently identified**"
34-39	4	**Comments:** 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

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		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:** Rewrite whole paragraph and define relevant terms, like efficiency, sufficiently characterised, etc.
35	8	**Comments:** "pre-approval setting" is better defined in section 1.3 (that is in specific cases). Recommendation to use the same wording as in section 1.3. **Proposed change:** safety data collection in some late-stage pre-approval for specific cases, or post-approval studies when the safety profile of a drug is sufficiently characterized.
35-39	8	**Comments:** Characterization and clear definition of "safety data" may be useful. Before being a "safety data" these data are "clinical data" collected in a context of a clinical program that can be analysed for safety purposes. Recommendation to mention in the section that is it safety **related** data. **Proposed change:** safety **related** data

Line no.	Stakeholder no.	Comment and rationale; proposed changes
36	8	**Comments:** Reference to 'drug' is too restrictive. This guideline should be applicable to pharmaceuticals, biological and vaccines (as per some examples in the document referring to vaccines), and not applicable to advanced therapies or gene therapies. See general comment above.
36-38	11	**Comments:** While it is easy to understand that the costs for sponsors and investigators are reduced by a selective collection of safety data, it is not comprehensible that the collection of safety data could be burdensome for the study participants and thus discourage them from participating in the study. **Proposed change:** Addition: This presentation appears to be a pseudo-argument and should be removed.
36-38	10	**Comments:** The burden of the study participant that could be reduced by selective safety data collection is rather low. More importantly the overall administrative burden for site personnel, sponsor and data collection is lowered. **Proposed change:** Change wording as follows: Optimisation of safety data collection using a selective approach may improve the efficiency of clinical studies while reducing in particular the administrative burden to site personnel and sponsor, and also to study participants.
36-39	7	"Optimisation of safety data collection, using a selective approach, may improve the efficiency of clinical studies, while reducing the burden to study participants. Adoption of an internationally harmonised approach to selective safety data collection may facilitate global participation in clinical studies."

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Comment 1: *[CTL]* "global participation in clinical studies". The participation in a clinical study is always "local", however the study may be a global study. In addition, it is not clear, who is meant with "participants" or "participation". Is it investigators or patients or both? **Proposed change:** Optimisation of safety data collection using a selective approach may facilitate the conduct of clinical studies, **by reducing the burden to study participants (investigators and patients). The implementation** of an internationally harmonised approach to selective safety data collection may **make the conduct of global clinical studies more feasible**. **Comment 2:** *[PV]* The use of the verb "may" in the assertion "may improve the efficiency…" could induce the perception of a lack of conviction of the impact. **Proposed change:** (in addition to the proposed change above) "…using, **as appropriate,** a selective approach **will** improve the efficiency …
36 and 198-203	8	**Comments:** It seems that there is no worldwide harmonization in the concept of "the safety profile of a drug is sufficiently characterised" which is important when considering the local implementation of this guideline. **Proposed Change:** We suggest additional clarification on the meaning of this sentence to ensure it is understood on a worldwide basis and confirm that one can use data from countries outside of the own jurisdiction (e.g. Japan or China or US or EU). Please clarify in the guideline which data are required in ICH countries to characterise the safety profile of a drug sufficiently.
37-39	6	**Comments:** In late-stage pre-approval phase, safety profile of a drug is never sufficiently characterised. The objective of the guideline apparently covers all types of clinical studies regardless of if its interventional or not or if it is performed only with secondary data

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		sources. This implies that the guideline would reach the scenario of studies performed with population-based electronic health records (EHR). This would only add confusion to current guides and legislation related to this type of studies
38	11	**Comments:** Could the term "late-stage" be more defined (as this is a FDA related guidance term not defined in the EU regulation)? Only phase III trials? Long-term trials? The only phase II pre-approval clinical trial for an orphan drug can't be considered as a "late-stage study"
38-39	8	**Comments:** Reduced data collection would also potentially support faster collation and computation of statistical tables, thereby enabling more rapid evaluation and assessment. This in turn supports earlier access to medicinal products.
38-39	10	**Comments:** The burden of the study participant that could be reduced by selective safety data collection is rather low. More importantly the overall administrative burden for site personnel, sponsor and data collection is lowered. **Proposed change:** Change wording as follows: Adoption of an internationally harmonised approach to selective safety data collection may facilitate global study conduct for sponsors and participation in clinical studies for study subjects.
39	11	Many post approval studies are set-up in order to better characterise some "potential risks" or "missing information" related to the use of the products. So the idiom "sufficiently characterised" seems inappropriately used in this context. In addition, this document should provide clear principles about what is a "sufficiently characterised" safety profile. **Proposed change:** *"This Guideline is intended to provide internationally harmonised guidance on ~~an optimised~~* ***a risk-proportionate approach*** *to safety data collection ~~in some late-stage pre-approval or post-approval studies~~ when the safety profile of a drug is sufficiently*

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		characterised."
39-41	11	**Comments:** This draft document makes several references to a burden on participants which seems to be one of the main justification of this work. However, the link between safety reporting requirement and an alleged burden on participants is unclear. The goal of the European clinical trial regulation is to foster innovation whilst ensuring the protection of the participants in clinical trials as well as the quality and integrity of the trial outcomes. It is acknowledged that marginally, doing so, can limit requirements for some diagnostic or monitoring procedures which could eventually minimise the burden of participants. But it is very unlikely that the means to reduce the burden to study participants is to optimise safety data collection. **Proposed change:** "*Optimisation of safety data collection using a selective approach may ~~improve the efficiency of~~* ***facilitate the conduct of*** *clinical trials ~~while reducing the burden to study participants. Adoption of an internationally harmonised approach 41 to selective safety data collection may facilitate global participation in clinical studies."~~*
40	13	**Comments:** Per comment in the "General comments" section, the use of the term 'clinical study" does not accurately reflect the purpose/ focus of ICH E19 and causes confusion, rather than clarity, when it comes to the applicability of this work product. **Proposed change:** Replace "clinical study" with "clinical trial."
40-58	7	**Comments:** *[PV]* The ICH E19 guideline looks almost identical in their objectives to the FDA's guideline on "Determining the extent of safety data collection needed in late-stage premarket and post-approval clinical investigations" issued in Feb-2016. Furthermore, the two guidelines are frequently using similar wording (e.g. for some titles). In the ICH E19 background (1.2) section, there is no reference to the FDA guidance and feedback from 3-year use of the FDA guidance on actual operationalisation and outcomes. This might lead future users of ICH E19 to potential questions on alignment of ICH E19 with the FDA guidance. Some wording about

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		the FDA guidance and FDA's experience with applying the guideline in practice might solidify this section.
41	8	**Proposed Change:** "**<u>Regulators, Sponsors and Investigators</u>** have a shared interest in reducing the burden to study participants while facilitating the conduct of studies that could yield important new medical knowledge and advance public health."
41-43	13	**Comments:** All stakeholders involved in a clinical trial (including investigators and the trial subjects themselves) "have a shared interest in reducing the burden to study participants". This is not limited to regulators and industry. Our introductory comment in the "General Comments" section concerning the inappropriateness of the term "studies" also applies here. **Proposed change:** Replace "Regulators and industry have a shared interest in reducing the burden to study participants while facilitating the conduct of studies…" with "All parties involved in clinical trials have a shared interest in reducing the burden to trial participants while facilitating the conduct of trials…."
41-46	8	**Comments:** The sentence starting with "Regulators and industry have a shared interest in reducing the burden to study participants…" may not be entirely truthful: the biggest advantage of the guideline's application will be for the organisers of studies in reducing administrative, database and reporting activities and to a lesser degree to regulators. The burden to participants will not change substantially, the examples ("Frequent and time consuming patients visits) exaggerate this aspect. **Proposed change**: "Regulators and industry have a shared interest in reducing the burden (of comprehensive data collection) while facilitating the conduct of studies that could yield…public health." "Although safety monitoring of patients during clinical studies remains critically important, unnecessary data collection may **also** serve as a disincentive to participation in clinical studies. ~~e.g., frequent and time-consuming patient visits; laboratory tests; and/or physical examinations.~~"

Line no.	Stakeholder no.	Comment and rationale; proposed changes
41-58	4	**Comments:** 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. **Proposed change:** Completely rewrite of the paragraph.
43-45	13	**Comments:** As this guideline is specific to safety data collection, this should be reflected in the text. **Proposed change:** Replace "unnecessary and burdensome data collection" with "unnecessary and burdensome safety data collection".
43-61	6	**Comments:** The principle behind the guideline is that the burden to study participants (monitoring and data collection) should be balanced to the knowledge (efficacy and safety of medicines) to be obtained from clinical studies. However, this is clearly not applicable to non-interventional studies where by nature there is not such burden to study participants (normal clinical practice, routine care) and is simply out of context with regard to studies with electronic health records (patients even don't know when their data are used to perform a study). **The use of electronic health records to perform research exemplifies the increasing relevance of secondary use of clinical data collected for other reasons to get new evidence on effectiveness and safety of drugs. This is also the case of clinical trial datasets. the knowledge that can be obtained from the study does not end with the analysis as planned in the protocol. Clinical trials datasets are often re-analysed and meta-analysed as a result of safety signals of events usually considered unrelated to the study drug at the time of data collection. These secondary uses of**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		clinical trial data would not be possible if a selective safety data collection is performed based on general criteria assessed at the time of study protocol drafting.
43-61	11	**Comments:** The basic objectives of the collection of safety data in clinical trials is not described sufficiently. These essentially consist of creating a sufficient safety data basis for the evaluation of drug-related risks as a fundamental element of benefit-risk assessment. Currently, clinical trials are still the qualitatively best way to collect reliable data on the incidence of adverse drug reactions in both serious and non-severe adverse events. **Proposed change:** Addition:
44-46	11	**Comments:** The interest of public health should prevail on the interest of regulators and industry. Reference to a share interest between the two is unnecessary and unclear. As mentioned above, it is very unlikely that the means to reduce the burden to study participants is to optimise safety data collection. **Proposed change:** *"~~Regulators and industry have a shared interest in reducing the burden to study participants 44 while~~* ***It is in the interest of public health to facilitate*** *the conduct of studies that could yield important new medical knowledge ~~and advance public health~~"*
45-46	7	"… to participation in clinical studies, e.g., frequent and time-consuming patient visits; laboratory tests; and/or physical examinations." **Comment 1:** *[CTL]* One main reason for selective safety data collection is the reduction of documentation burden for investigators. It seems that here "participation" is only used as "patient participation", however that is not sufficient.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Proposed change: "… to participation in clinical studies, e.g., frequent and time-consuming patient visits; laboratory tests; and/or physical examinations, **or labour-intensive documentation of all adverse events**." **Comment 2:** *[PV]* The examples provided mainly relate to interventional (or low interventional) clinical trials and could be enriched by other examples to cover other traditional time-consuming tasks for all stakeholders in observational non-interventional studies (typically for prospective cohort follow up studies based on iterative primary data collection) **Proposed change:** … e.g. frequent and time-consuming patient visits; laboratory test; physical examinations; and/or **labour-intensive screening, documentation and assessment of all adverse events from medical records, patient reported outcomes questionnaires, or patient interviews transcripts.**
46	1	**Comments:** Add phrase below **Proposed change:** and Psychological burden
46-49	11	**Comments:** As mentioned above, it is very unlikely that the means to reduce the burden to study participants is to optimise safety data collection. **Proposed change:** *"~~Although~~ Safety monitoring of patients during clinical trials ~~remains~~ **is** critically important, ~~unnecessary and burdensome data collection may serve as a disincentive to participation in clinical studies, e.g., frequent and time-consuming patient visits;~~*

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		~~*laboratory 48 tests; and/or physical examinations".*~~
47-49	6	**Comments:** Is this a real reason? Most of the patient visits, laboratory tests and/or physical examinations are critical for assessing efficacy and will not be prevented relaxing safety data gathering. Why to limit safety data gathering? There are many ways for collecting such information, and not necessarily based in laboratory tests and physical examinations.
49, 55, 110, 184, 194, 201, 236	7	"… sponsors …" **Comments:** *[CTL]* The term "sponsor" is defined for interventional clinical trials and should be supplemented by "Marketing Authorisation Holders (MAH)" as this Guideline also covers post-approval non-interventional studies. In this context, the term "sponsor" is not correct. **Proposed change:** "… sponsors **and Marketing Authorisation Holders (MAHs)**" Alternatively, explain at the outset of the Guideline that the term "sponsor" is being used throughout the document and might refer to a sponsor of a clinical trial or a MAH being the initiator of a non-interventional study.
50-51	8	**Comments:** "In the later stages of drug development, and if the safety profile is well-understood and documented…" seems to apply to both the pre- and post-approval stage; a distinction is only made in the next chapter (1.3). For the pre-approval stage this text, most of the time, appears to be in contradiction to the reason for post-approval pharmacovigilance e.g. as described in the Background in ICH-E2c:" When a new medicinal product is approved for marketing, demonstration of safety and efficacy are generally based on data from a limited number of patients, many studied under the controlled conditions of randomised trials. Often, higher risk subgroups and patients with concomitant illnesses that require use of other drugs are excluded from clinical trials, and long-term treatment data are limited."

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Proposed change: "In the later stages of drug development, and if the safety profile is well-understood and documented, **mostly years after the first approval,** comprehensive collection of all safety data may provide only limited additional knowledge of clinical importance."
51-53	11	**Comments:** It is unclear to what post-marketing extensive safety data collection refers the current document **Proposed change:** "*Throughout the ~~course of~~ **life cycle of a** medicinal product development and subsequently while the drug is marketed, sponsors collect ~~extensive~~ safety-related data, **which can include** ~~including~~ ~~all~~ vital signs, laboratory data, and adverse events."*
52-53	6	**Comments:** Vital signs and laboratory data are normally not collected while the drug is marketed
53	8	**Comments:** Use of the word "adequate" suggests "good enough" rather than aiming for the best approach. **Proposed Change:** "In such circumstances, a more selective approach to safety data collection may be **appropriate** and optimal, as long as the study objectives and the welfare of study participants are not comprised."
53-55	6	**Comments:** Again, to state that in the later stages of drug development safety profile may be well understood and documented is very risky. Unfortunately, this is never the case. Otherwise, pharmacovigilance will not exist.
54	12	**Comments:** The following text 'if the safety profile is well understood and documented' in the context of drug development, needs further

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		clarification. This appears to contradict the underlying principle of PV in that not all hazards associated with use of medicines are known prior to marketing. Would suggest change to 'if safety profile is sufficiently characterised' (as per line 133)
55-57	11	**Comments:** Reference to a risk-proportionate approach should be favored. **Proposed change:** "*In such circumstances, a* ***risk-proportionate approach, including selective safety data collection, can be adequate.*** ~~*more selective approach to safety data collection may be adequate and optimal, as long as the study objectives and the welfare of study participants are not compromised"*~~*.*
57	11	**Comments:** Are we talking about actually doing assessments such as vital signs, or AE recording and reporting or both? This needs to be made clear. **Proposed change:** Clarify
58-59	6	**Comments:** Patients involved in a clinical trial (except rare exceptions) are not following routine patient care, but care is defined by a protocol. If referring to observational studies, it is clear, by definition, that routine patient care cannot be compromised by participating in the study.
58-61	11	**Comments:** How can patient care as 'standard of care' not be compromised if the IMP under investigation is not authorized yet for the topic of investigation?
59-70	4	**Comments:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Please specify what a '…late stage development' is vs. 'post-approval study' .
60-61	8	**Comments:** Per Line 61, non-interventional studies are in scope however it is not clear how this would align with GVP Module VI Rev 2. We recommend greater clarity on how this new guidance specifically applies to non-interventional studies and specifically those based on primary data collection.
60-62	7	"This guidance is intended to apply to collection of safety data during the late-stage development of medicinal products in interventional and non-interventional studies, in the post-approval setting and, for specific cases, in the pre-approval setting." **Comment 1:** *[CTL]* The logic of the above sentence is not clear: "late stage development" is most likely to be understood as pre-approval as the drug is still an "under development", but then a non-interventional study is not possible. See also comment for lines 34-36, clarification on late stage pre-approval studies. **Proposed change:** "This guidance is intended to apply to collection of safety data during **post-approval interventional and non-interventional studies, and, for specific cases, during late stage clinical trials in the pre-approval setting.**" **Comment 2:** *[PV]* From experience, there are frequent confusions between collection, reporting and submission and respective related requirements and procedures. Considering this guideline could be used by study stakeholders who are non-expert in the field of PV, we would suggest reminding readers that "collection" of safety data is different from "reporting" of an AE to a pharmacovigilance structure in charge of the study or to competent authorities (e.g. sending of an AE report form, CIOMS/Medwatch/Yellow card/CDSCO forms) and the "submission" (per EU GVP recent terminology) of valid cases to regulatory authorities (e.g. ICH E2B to Eudravigilance database). **Proposed change:** adding a sentence after "…in the pre-approval setting". **It does not cover reporting and submission (as opposed to**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		collection) of individual safety reports to Sponsor/MAH's pharmacovigilance, competent authorities, regulators or other stakeholders. Alternative wording if examples are perceived as useful: **It does not cover reporting and submission (as opposed to collection) of individual safety reports to Sponsor/MAH's pharmacovigilance or competent authorities (e.g. sending of an AE report form, CIOMS/Medwatch/Yellow card/CDSCO forms), nor the submission of valid individual case safety reports to regulators (e.g. ICH E2B to Eudravigilance database)**.
60-62	8	**Comments:** As written, this seems to de-emphasize data collection considerations in the pre-approval setting. Considerations in this guidance are also very relevant for Phase 3 clinical trials, for example large outcome studies in Cardio-Vascular development. Therefore, we suggest to include post-approval and pre-approval setting. **Proposed Change:** "This guidance is intended to apply to the collection of safety data **for both interventional and non-interventional studies during the late stage development of medicinal products; both** in the post-approval setting and in specific cases can include the pre-approval setting."
60-62	8	**Comments:** The introductory text of 1.3 speaks of pre- and post-approval setting, however the text only addresses pre-approval issues. How should post-approval study safety data collection be limited, or not, as authority's approval is not always required?
60-62	8	**Comments:** The text states that the guidance is intended to apply to collection of safety data during the late-stage development of medicinal products, in the post-approval setting and, for specific cases, in the pre-approval setting. Isn't late-stage development pre-approval? Or is it intended to mean post-approval but in a late stage of development? Regardless, I think the text is not clear. **Proposed change**:

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		"This guidance is intended to apply to collection of safety data during late stage ~~**development**~~ **pre-approval and post approval clinical investigations** of medicinal products in interventional ~~**and non-interventional**~~ studies~~**, in the post-approval setting and, for specific cases, in the pre-approval setting**~~ **(e.g. phase 3 clinical trials, large outcomes studies, studies in new indications)**.
60-62	13	**Comments:** The draft text states that "This guidance is intended to apply to collection of safety data during the late-stage development of medicinal products in interventional and non-interventional studies, in the post-approval setting and, for specific cases, in the pre-approval setting". However, according to the ICH website, the work carried out by ICH under the Efficacy heading is concerned with the design, conduct, safety and reporting of clinical trials. This being the case, "non-interventional studies" should not be included in the scope of ICH E19 guideline. This will create confusion and unnecessary dilution of the robustness of the clinical trial-related information being presented. **Proposed change:** Remove the reference to "non-interventional studies"
61	11	**Comments:** Inclusion of non-interventional studies in this guideline is not supported. GVP module VI provides reporting requirements for non-interventional studies. GVP VI says the following (regarding non-interventional post-authorisation studies with a design based on primary data collection): "Information on all adverse events should be collected and recorded from healthcare professionals or consumers in the course of the study unless the protocol provides with a due justification for not collecting certain adverse events." "For adverse events specified in the study protocol which are not systematically collected, healthcare professionals and consumers should be informed in the protocol (or other study documents) of the possibility to report adverse reactions (for which they suspect a causal role of a medicine) to the marketing authorisation holder of the suspected medicinal product (studied or not) or

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		to the concerned competent authority via the national spontaneous reporting system” All adverse reactions from non-interventional post-authorisation studies are reported to EudraVigilance postmarketing module, in a timeframe that is the same as for spontaneous ADRs (15 serious; 90 non-serious) **Proposed change:** Change accordingly.
62	8	**Comments:** Recommendation to add a statement to make clearer that PSP and MR are not in scope. **Proposed change:** to add: PSP and MR programmes are not in scope of this guideline.
63-63	6	**Comments:** Normally, non-interventional studies are not performed in late-stage development of a medicinal product. One of the main problems of this guideline is to mix-up in the scope interventional and non-interventional studies. Furthermore, the scope does not fit with the objectives (pre-approval phase is within the objectives, whereas here, it is stated that only for specific cases this guideline will apply.
63-65	8	**Comments:** This guideline does not provide a clear definition of "post-approval setting". Regarding the "post-approval setting", it should be clarified whether or not it is applicable to the post-marketing surveillance in Japan. Specifically, it should clarify whether post-marketing surveillance (e.g., drug use-results surveys, database surveys, and drug use-results comparison surveys) are consistent with the concepts of ICH-E19. In addition, if the handling of safety data collection differs between "post-approval setting" and "pre-approval setting", each safety data collection should be explained in a separate section.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
63-65	11	**Comments:** A shorter scope would be clearer and should not include non-interventional studies (see general comments). The guideline should be for interventional studies only as there is no regulator oversight of non-interventional **Proposed change:** "*This guidance is intended to apply to collection of safety data during ~~the late-stage development of medicinal products in~~ interventional ~~and non-interventional~~ studies~~, in the post-approval setting and, for specific cases, in the pre-approval setting~~.*
66	8	**Comments:** "however,…" suggest a contradiction to the previous, however both parts of this paragraph describe the pre-approval stage.
66	11	**Comments:** The collection of data in the pre-approval setting differs from the post-approval with the character of "being controlled". This is important to introduce the notion of "control" which does not exist (or is somehow relative) in the real life data collection setting. **Proposal:** *"In the pre-approval setting, comprehensive **and closely controlled** safety data collection is expected .."*
66-67	8	"…even before approval of a new medicinal product, if there is agreement with regulatory authorities that sufficient safety data are available" **Comments:** It is not so much the agreement of authorities, but the evidence that sufficient safety data have been collected; if convincing, also authorities will agree. An example might clarify this, e.g. the collection of (non-serious) AEs like nausea and vomiting, that used to be common in all patients with many anti-cancer (cytostatic) drugs.
66-68	7	"However, even before approval of a new medicinal product, if there is agreement with regulatory authorities that sufficient safety data are available or are being collected in ongoing late-stage studies, selective safety data collection may be appropriate in

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		certain studies." **Comment 1:** *[CTL]* Here, late-stage studies address "pre-approval studies". Please see also comment line 34-36 **Comment 2:** *[PV]* It is not clear which "specific cases" and "certain studies" of pre-approval settings are referenced and would likely to get the agreement of regulatory authorities. Similar to the FDA guidance background section, one could provide examples of specific cases and studies, in order to improve understanding and help for discussions with authorities.
67	6	**Comments:** In pre-approval setting, only common adverse reactions are identified, due to the limited number of patients included. So, it cannot be stated that safety data collection will elucidate frequency, severity, seriousness and dose-response of adverse events in general, but for adverse events frequent enough to be detected according to the number of patients studied.
69	7	**Comments:** *[PV]* "does not alter local" sounds like an affirmation. If the purpose is to say "is not intended to alter", it might be preferable to use the modal verb "should" instead. If it is a legal requirement then the modal verb "shall" should be used. **Proposed change:** …**should** not alter… Alternative proposal (similarly to FDA guidance: …this Guideline **is not intended to…**
69-70	8	**Comments:** Is it necessary to report on only what is collected or even that what is not collected?
75-76	7	**Comments:** *[PV]* Per GVP Module VI for NIS based on primary data collection, the protocol should remind HCPs and consumers about the possibility of spontaneous reporting of suspected ADRs for AEs which are not systematically collected per protocol (i.e. solicited

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		collection). Therefore, it could be interesting to clarify in the title that we are talking about solicited AE collection only. **Proposed change:** …or Stop **Solicited** Collection
75-76	13	**Comments:** In order to avoid inappropriate use of the provisions of this guideline, we recommend starting this section with the following statement. **Proposed change:** Begin this section with the statement "Any limiting or stopping of safety data collection should be agreed with the local/regional regulatory authority."
75-76	14	**Comments:** What determines whether safety data collection is limited OR stopped? What defines 'limit'?
75-80	8	**Comments:** Collection could be limited with scientific rationale and justification but not stopped. Per GVP VI a summary of AE/AR must be provided in the CSR. The same applies to all ConMed and to PhysExam
75-81	8	**Comments:** Section 2.1.1 has a title then immediately lists a set of studies therefore to avoid possible confusion; we suggest adding an introductory sentence here. Please see below suggestion. **Proposed Change:** **Add an introductory statement such as:** The following provides a list of suggested areas where it may be appropriate to limit or stop collection of appropriately defined

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		safety data depending on the type of study, population and approval status.
75-81	14	**Comments:** Are these examples of types of data or a complete list?
77	4	**Comments:** 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.
77	7	"Non-serious adverse events" **Proposed Change:** *[PV]* Non-serious adverse events **(unless defined of special interest for the study)**
77	10	**Comments:** Types of Safety Data Where It May be Appropriate to Limit or Stop Collection are listed here. However, for No. 1 the severity of non-serious adverse events should be considered as well as the relationship with the investigational medicinal product(s) (IMP). Events that are moderate or even severe or are related with the IMP should still be collected also in late stage trials, in particular, because a higher sample size might lead to increased occurrence. **Proposed change:** Change wording as follows: 1. Non-serious adverse events of mild [to moderate] intensity and that are not related [or unlikely related] to the IMP

Line no.	Stakeholder no.	Comment and rationale; proposed changes
77	10	**Comments:** Types of Safety Data Where It May be Appropriate to Limit or Stop Collection are listed here. However, also serious not or unlikely related adverse events represent a high administrative burden to the study personnel and to data collection. **Proposed change:** Add "Serious adverse events that are not [or unlikely] related to the IMP" to the list and adjust numbering accordingly.
77	12	**Comments:** Part of the safety data mentioned here are tests and examinations that can be performed. Suggest distinguishing between doing or not doing tests and examinations as part of a study for the purpose of active safety monitoring and considering results of tests and examinations that are done routinely in relation to adverse event reporting.
77	14	**Comments:** Would this include for instance treatment used in cancer patients where the number of NSAE could be high?
77-81	8	**Proposed Change:** Including an Appendix to this document that provides examples of when to/when not to include the collection of safety data listed under sub-section 2.1.1 would be beneficial.
77-82	18	**Comments:** It was proposed **among types of safety data where it may be appropriate to limit or stop collection:** Non serious adverse events: what about **unexpected** non serious adverse **reactions**? ECG and Routine laboratory tests: this will depend on the product (e.g. cardiotoxic products or oncology products) for which these tests are part of clinical practices to ensure the safety of these drugs. In addition, the collection of these information will be useful in the assessment of causality in case of a SAE occurrence afterwards (for example grade 4 neutropenia or sepsis)

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Proposition to add to this list: -Details on corrective treatment for all kinds of adverse events (serious and non-serious) -Adverse events occurring between informed consent signature and initiation of study treatment -Any planned or programmed hospitalization (before study entry) -Any hospitalization for routine check-up or underlying medical condition that exists in the patient's medical history before study entry (**excluding any aggravation or deterioration to this condition**) -Details on death and disease progression if included in the primary study end points (OS or PFS) (**excluding deaths of unknown origin and those potentially related to the study treatment or procedure; these latter should be well documented**)
77-101	11	**Comments:** While the intention of providing general principles on the types of data for which selective safety data collection may be appropriate is endorsed, this section should provide principles and not examples. The provided examples are not comprehensive, subjective, and generally found unhelpful. Presume this is not an exhaustive list so this should be clearly stated. Especially, it is noted that breastfeeding and drug abuse were not considered. **Proposed change:** Proposal: Overall, proposal would be to delete line 77-101 and instead provide principles illustrated with one or two detailed and contextualized examples. E.g. (Source: Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use on a Risk proportionate approaches in clinical trials): Detailed collection and reporting of adverse events (serious and non-serious) is particularly important where data about the safety profile of an IMP from available pre-clinical and clinical trials is scarce. As the knowledge of a medicine and its use evolve and increasing amounts of data become available in order to determine the benefits and risks of an IMP, the extent (range of events)

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		and level of detail of recording and reporting adverse events may be adapted in the protocol, in line with the scope and type of the clinical trial and the level of knowledge on the safety profile of the IMP tested and the disease profile of the trial subjects. This means in practice that the protocol may select only certain (and not all) adverse events to be recorded in the CRF and reported to the sponsor. This applies in particular to marketed products with a known safety profile, which are tested within the framework of low-intervention clinical trials. In this regard, the following situations apply: ☐ IMPs are used according to the conditions of the marketing authorisation: In this case, a reduced or targeted safety data collection may be appropriate if supported by data from post-marketing use and if the number of subjects exposed during clinical development was sufficient to adequately characterize the medicinal product's safety profile (even in terms of rare adverse drug reactions), and if the occurrence of expected adverse drug reactions was similar across multiple trials in terms of seriousness and severity. ☐ IMPs are marketed, but used differently to the conditions of the marketing authorisation: In such cases, any adaptation to safety reporting should be based on a trial-specific risk assessment. The risk assessment should consider whether the clinical trial under evaluation includes a new population (e.g. in terms of age, gender or other patient characteristics, or using a new combination therapy or a different concomitant medication), a new indication, a different dose or dosage regime or a different route of administration, compared to the conditions of use in the SmPC that may lead to more severe or more frequent adverse drug reactions, new adverse drug reactions or new drug-drug interactions.
78	6	**Comments:** Not agreed. Among other reasons, experience in the evaluation of safety signals in pharmacovigilance has demonstrated that information on non-serious events is relevant to understand and gain knowledge on serious adverse reactions of the same nature.
78	8	**Comments:** Proposal to gather all investigations mentioned in 2 and 5 under one concept: "investigations (eg., routine laboratory tests, electrocardiograms, …) **Proposed change:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Line 78 and 81: regroup bullet 2 and 5 and outline: investigations (eg., routine laboratory tests, electrocardiograms, …)
78	11	Non serious adverse events collection can be relevant when the safety profile of a drug is insufficiently characterized and could have an impact on compliance of treatment for patients (i.e recurrent diarrhea) **Proposed change:** Modify, non serious adverse events if no impact e.g. on compliance
78	12	**Comments:** Assume non -serious implies events that do not fulfil criteria of 'Serious'. If so please confirm
79	8	**Comments:** Concomitant medications and drug interactions are always a gap in safety information and difficult to gather in postmarketing/spontaneous AE reporting. **Proposed change**: Never waive the requirement to capture concomitant medication. Remove it from all 'examples' in this document.
79	13	**Comments:** We recommend that the statement on when it may be appropriate not to collect information on concomitant medications is expanded to explain the specific circumstances where this may be possible. **Proposed change:** Replace "Information on concomitant medications" with "Information on concomitant medications not expected to modify the disease under investigation or the pharmacological properties of the investigational product."
79, 81, 82	6	**Comments:** It will depend on the drug and the study

Line no.	Stakeholder no.	Comment and rationale; proposed changes
80	6	**Comments:** Information on concomitant medication is normally very relevant for assess imputability of an adverse reaction to the drug under study. Not agreed.
80	7	"Physical examinations (including vital signs)" **Proposed Change:** *[PV]* Physical examinations including vital signs **(unless defined of special interest for the study)**
80	11	**Comments:** Omitting information about concomitant medications may lead to loss of important information. For example, if there is a critical number of adverse reactions spotted while IMP is taken concomitantly with the same medication, it might be due to interaction between those two medications. Often the most important safety information which remains unknown is what the safety profile will be in patients on multiple concomitant medications and in terms of drug-drug interactions etc. Would view concomitant medications extremely important both for assessment of possible signals (in terms of identifying potential confounders) and in terms of gleaming new information on previously unidentified interactions. Or in the contrast, it might be that adverse reaction is adverse reaction of concomitant medication, not of IMP (but it is not recognised by the investigator). **Proposed change:** while recording of concomitant administered medications should be kept in the patient files, CRF.
80-81	8	**Comments**: Clarify selective data collection in physical examinations or electrocardiograms for routine situations. **Proposed change**: See suggested wording:

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		4. Routine physical examinations (including vital signs) 5. Routine electrocardiograms
81	8	**Comments:** Should wearables (Apple Watches for example) also be excluded as a data source for AEs along with ECG's. Please add the concept of 'anticipated' adverse events to this list.
82	7	**Comments:** *[PV]* Similarly to line 76, it could be interesting to clarify in the title that it is about solicited collection in CRF. **Proposed change:** … under All Circumstance **(solicited)**
82 (section 2.1.2)	8	**Comments:** For **Serious adverse events –** consider pointing out that if there are endpoints (such as certain SAE's for cardiovascular trials), then requirements for reporting can be different and events should not be double reported, in order to avoid duplication. For **Adverse events of special interest** – A well-characterized, common AE of SI may not need to be collected in all patients (after collecting data in a first pre-defined amount of patients). Suggest to consider re-assessing certain AE's of SI during ongoing Phase 3 clinical trials.
82-101	8	**Comments:** Section 2.1.2 heading phrasing seems ambiguous/conflicting – it uses the words: "types of safety data that should generally be collected under all circumstances". However, lines 84 through 101 then define specific circumstances (events) where such types of data should (always) be collected. The word "generally" also implies a further level of optionality and is perhaps redundant ("should" already implies ought to do, i.e. recommendation vs. "must" – mandatory).

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Proposed change: Clarify whether this data must or ought to be collected if the specific events defined in lines 87 through 101 occur
83	6	**Comments:** To eliminate "generally"
83	11	**Comments:** Use of "generally" means that it doesn't always need to be collected and there is room to justify limiting or stopping collection of that data. We cannot see a situation where no deaths or SAEs are recorded during the trial. **Proposed change:** Delete 'general'
83-101	11	**Comments:** In our opinion, the limitation of the collection of safety data to serious and significant adverse reactions (among others) described in Section 2.1.2 of the Guideline does not take this requirement into account, in particular the individual effects of adverse reactions on the well-being and quality of life of patients. For example, alopecia (balding), skin reactions, visual impairment, tinnitus and many others non-serious adverse reactions in a clinical trial do not necessarily meet the assessment criteria set out in Section 2.1.2, although they may affect the quality of life of women and men to a relevant extent. Therefore, the selective approach to safety data collection must ensure that all adverse events that would normally be identified as adverse events/reactions in the SmPC are included in the CRF, regardless of their severity. This is not sufficiently ensured by the current guidance text.
84-86	7	"For the following types of events/data, comprehensive details should generally be provided to allow adequate assessment of the event/data, e.g., history; associated adverse events; relevant laboratory values; concomitant medications; vital signs; and/or follow-up outcome." **Comments:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		[CTL] EUCROF thinks that these lines would be better placed right under the heading **2.1 Types of Data for Which Selective Safety Data Collection May be Appropriate** With this, guidance on which events/data should be considered during the risk assessment is given first, followed by examples for limited or omitted collection of safety data (2.1.1) and examples of data that should generally be collected under all circumstances (2.1.2)
84-86	8	**Comments:** While in general for all events of deaths and other SAEs, comprehensive details surrounding the event are typically collected and included as part of the narrative. However, with a selective safety data collection details such as associated adverse events, relevant laboratory values, con meds etc may not be available eg for non serious AEs leading to IP withdrawal. As currently written, it implies that comprehensive data collection will still be required to provide the level of detail suggested in the paragraph. **Proposed change**: "For the following types of events/data, comprehensive details**, where available,** should generally be provided to allow adequate assessment of the event/data, e.g., history; associated adverse events; relevant laboratory values; concomitant medications; vital signs; and/or follow-up outcome."
85	12	**Comments:** Information on comorbidities may also be important given that an exacerbation of an existing condition can be considered an adverse reaction and it is also key information used when assessing causality of adverse drug reactions (in the context of pharmacovigilance reporting). In addition, any information regarding dechallenge or rechallenge (if available) is also of relevance to collect when possible.
85, 88	11	**Comments:** The vocabulary in clinical trials uses "related adverse events, ie adverse reactions" when referring to AEs related to the IMP. Therefore, wording "*associated* adverse events" is slightly confusing. Also see general comment.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Proposed change: line 85: delete "associated" [or change "associated adverse events" to "related serious adverse events, ie serious adverse reactions" (see General comment)]
86	6	**Comments:** If concomitant medication, laboratory parameters, vital signs etc are under the types of safety data where it may be appropriate to limit or stop collection, such data will not be registered when deaths, serious adverse events, significant adverse events etc appear (especially if the patient die).
87	10	**Comments:** Among the Types of Safety Data That Should Generally be Collected under All Circumstances also adverse events with a relationship to the IMP that are moderate or severe in their intensity should be added in line with the previous comment. This should not add much more burden to the study participant. **Proposed change:** Add "Non-serious adverse events of [moderate to] severe intensity that are related to the IMP" to the list and adjust numbering accordingly.
87-88	7	**Comments:** *[PV]* "Death" is by default part of "Serious Adverse Events". However, if we consider selective collection of SAEs (see comment below) this should be kept in addition to SAEs as clearly expressing the need to collect all deaths whatever the relatedness with a study drug.
87-88	8	**Comments:** The introduction of this chapter 2.1.2 ("For the following types of events/data,…") may support the misconception that death is an (adverse) event, while it is actually an outcome.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Proposed change: Merge nrs. 1 and 2: 1 Serious adverse events, especially those with a fatal outcome.
87-101	7	**Comment 1:** *[PV]* As this section is listing AEs almost "mandatory" to collect under all circumstances, i.e. including in NIS, it would be interesting to focus on suspected Adverse Reactions and not Adverse Events (which are more clinical trial oriented). **Proposed change:** line 88: Serious adverse **reactions (even if just suspected)** 89: ~~Significant~~ adverse **reactions (other than those meeting definition of serious)** that led to an intervention, **especially** withdrawal or dose reduction of medicinal product or addition of concomitant therapy **to treat the reaction**… **Comment 2:** *[PV]* We would suggest to add to the list other safety data where it may be appropriate to limit or stop solicited collection especially for NIS on mature medicinal products **Proposed change:** **6. SAEs for which relatedness with study drug or study procedures is clearly excluded by investigator or as defined in study protocol** **7. Lack of therapeutic efficacy with no harm to patient** **8. Detailed Patient history** **9. Off-label use of the study drug which does not result in patient's harm (especially for studies aiming to assess compliance to guidelines and potential off-label use)** **10. Safety reports from patients or relatives during a direct contact (remotely or face to face) performed by a non-**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		health care professional and for other purposes than patient care or safety monitoring. Typically, non-solicited but "stimulated" safety reports arising during an interview to assess a PRO questionnaire; to get qualitative information on general burden of disease/treatment; or during a simple reminder for a study visit). The patient may be prompted to report any suspected adverse reactions directly to the concerned investigator or through the national reporting system (in post-marketing non-interventional studies) **Comment 3:** *[PV]* Item 7 "if defined" contradicts with the title "under all circumstances" Item 8: Laboratory data, vital signs, ECG can be regrouped into item 7 examples **Proposed changes:** Adverse events of special interest (**as defined in the protocol**). These adverse events may warrant collection of additional information across the entire study population to better characterise these events (e.g., particular laboratory parameters; vital signs; risk factors; **electrocardiograms**; concomitant therapies; and/or concomitant illnesses). For example, if gastrointestinal haemorrhage was an adverse event of special interest, one might want to proactively collect concomitant antithrombotic therapy across the entire study population.
87-101	13	**Comments:** The term "intervention" is used in line 89 but is not accompanied by any definition of what would be considered as an intervention. Additionally, there are further special situations (as listed below) in which we recommend that data should generally be collected in all circumstances. **Proposed change:** Define the term "intervention". Add abuse, misuse, medication error, occupational exposure, and medicinal products used in critical conditions or for the treatment of life- threatening diseases to the list.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
87-101	18	**Comments:** Clarification on the need to collect "medication errors" and how simplification could be applied to its collection would be welcomed.
88	10	**Comments:** According to this guideline serious adverse events should be collected under all circumstances; this actually represents a big burden in large late stage trials, in particular with longer duration. The data collection should be restricted to related serious adverse events, i.e. serious adverse reactions only. **Proposed change:** Change wording as follows: 2. Serious adverse events that are related to the IMP
89	7	"Significant adverse events" **Comment 1:** *[CTL]* These are usually called "Important Medical Events (IME)" (for example in EU Detailed Guidance CT-3, but also in MedDRA). Why not use this term here as well? **Comment 2:** *[PV]* There is a concern with term "significant adverse event" that could be a tricky word and could be understood as medically significant/important medical event these criteria being by definition serious. One may want to remove the term "significant" while keeping the examples given and, similarly to item 4, adding at the end of the item 3: "(other than those meeting the definition of serious)".
89	8	**Comments**: Words like 'significant' are subject to interpretations, creates problems for audits, consistency, etc. **Proposed change:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Simply state "Aes that require intervention."
89	8	**Comments:** It would be helpful to clarify the concepts of "significant adverse events" and/or "marked laboratory abnormalities (other than those meeting the definition of serious)", as these seem potentially subjective (e.g., caveat that this is subject to appropriate medical/scientific judgment).
89	12	**Comments:** Isn't point 3 a subset of point 2? Also what defines 'significant'? - would suggest 'medically' or clinically important.
89-90	8	**Comments:** This category is contradictive as "…dose reduction of investigational medicinal product or addition of concomitant therapy" are generally not captured in a study in which non-serious AE collection is not included. Questionable if this information adds value unless the AE qualifies for being a serious event or AEOSI - note that the current text indicates "Significant adverse events…"
89-90	11	**Comments:** Suggest that "significant adverse events" meet the definition of seriousness under ICH E2A (which outlines the basis for medically significant/IME reactions) "*important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious".* **Proposed change:** Change accordingly.
91	5	**Comments:** Marked laboratory abnormalities (other than those meeting the definition of serious). **Proposed change:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Proposal to change to Grade 3 or 4 laboratory abnormalities
91	7	„Marked laboratory abnormalities" **Comment 1:** *[PV]* It is not clear what could be an example of "marked laboratory abnormalities (other than those meeting definition of serious)" **Comment 2:** *[CTL]* align terminology with ICH E6: **Proposed change:** **"Laboratory abnormalities identified in the protocol as critical"**
91	8	**Comments:** 'marked' is a very non-specific term and open to interpretation **Proposed change**: We suggest alternate wording of 'abnormalities outside protocol pre-specified ranges'
91	8	**Comments:** Suggest not to include 'Marked laboratory abnormalities. Either such data will be part of Bullet 8 'Laboratory data, vital signs, electrocardiograms of special interest' or it will just be to randomly collected and not of real value unless accompanied by an SAE. These arbitrary findings will also difficult to collect if laboratory collection is not included in the protocol
91	8	**Comments:** 'Marked laboratory abnormalities' – would these be collected if reported? Otherwise need to collect all lab abnormalities to decide which are 'marked'?

Line no.	Stakeholder no.	Comment and rationale; proposed changes
91	11	**Comments:** Wording "marked laboratory abnormalities" is rather vague and needs to be clearly defined with reference to lab abnormalities as this is too subjective when used without further context bullets 7 and 8?. Information on laboratory abnormalities should be kept in the patient files . **Proposed change:** Change "marked laboratory abnormalities" to "high clinically significant abnormalities in laboratory results"
91	13	**Comments:** There is no formal definition of "Marked laboratory abnormalities (other than those meeting the definition of serious)". **Proposed change:** As the definition may be dependent upon the patient (sub)population and treatment, ACRO recommends that the final guideline should state that the clinical trial protocol should define the changes that will be considered marked laboratory abnormalities within the context of the specific trial.
91	18	**Comments:** 'Marked laboratory abnormalities' – would these be collected if reported? Otherwise need to collect all lab abnormalities to decide which are 'marked'?
91-94-101	8	**Comments:** With regard to the brackets: (eg, particular lab. Parameters, …), there is an unclarity between the safety data to be collected, and the degree of documentation of these AESIs, … **Proposed change:** Line 91-94-101: remove mention laboratory data in bullet 7 and remove from bullet 8.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
92-93	8	**Comments:** Abuse, misuse and lactation should be added in the types of data that should generally be collected under all circumstances. **Proposed change**: Overdose / **abuse/ misuse** Pregnancies **/ Lactation**
93	6	**Comments:** What about outcome of pregnancies?
93	8	**Comment/Proposed change:** We suggest including 'breastfeeding' as a type of safety data that should be generally collected under all circumstances, ideally with collection of breastmilk whilst on medication for holding in a biobank.
93	14	**Comments:** point 6 - Please specify whether this pertains to study participants only or also to their 'pregnant' partners.
94	12	**Comments:** As mentioned in "general comments" section, RMP safety concerns addressed in post-approval studies could be considered as adverse events of special interest to ensure they are subject to comprehensive data collection.
101	6	**Comments:** What is electrocardiograms of special interest?
101	8	**Comments:** This could provide confusion with line 78

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Proposed change: to avoid confusion we suggest addition of 'with the exception of routine laboratory data' or say 'protocol specified additional laboratory data'
101	8	**Comments:** Consider clarifying in line 101 that laboratory data, vital signs, and ECGs of special interest should be collected if monitoring or further characterization of these aspects is required. Once the effects of a therapy on laboratory parameters, vital signs, and ECGs are well-characterized, it should not be necessary to continue to collect these data or laboratory abnormalities in every study. **Proposed change**: Item number 8 could either be deleted from the list of items that would generally be collected under all circumstances or the text could be modified to clarify the situations in which these items should generally be collected.
103-105	7	**Comments:** *[PV]* Our understanding of the first sentence of this section is the need to collect full baseline data without possibility of selective approach as appropriate and according to study objectives and methods. For some pharmaco-epidemiologic studies with very limited inclusion/exclusion criteria and open approach for inclusion (e.g. studies assessing patterns of use of a marketed drug, off label use monitoring, compliance to new critical pathways, etc.), a selective approach for baseline data collection would make sense as well. For example, a too extensive data collection requirement may alert the site and generate a selection bias (e.g., site will not include patients for which they discovered their prescription was indeed off-label). **Proposed changes:** Would it be possible to nuance a little this section by a wording considering this concern?
108	8	**Comments:** Suggestion to clarify that the Benefit/ Risk of the drug is to be considered for the specific population of interest.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Proposed change: "… can be important in considering the benefit-risk of the drug **in the population of interest.**
109	8	**Comments:** The question mark "?" at the end of title should not be necessary. This paragraph does not answer the question when to consider selective data collection. It rather explains what should be considered if selective data collection is considered. **Proposed change**: Remove question mark: "2.2 When May Selective Safety Data Collection Be Considered~~?~~"
109-130	8	**Comments:** As off line 109, there are a number of criteria for when selective safety data collection may be considered. It would be good to clarify further in the introductory text that this list of items are not criteria that need to be met in order to consider selective safety data collection. It should be reinforced that these are simply considerations for making a decision on selective safety data collection. **Proposed change**: The purpose of the list of items from line 113 to 130 should be clarified. Some of these items are written as if they are criteria that need to be met for selective safety data collection, rather than items that should be considered in making that determination.
109-137	7	**Comments:** *[PV]* The factors listed in section 2.2 make sense for peri-approval studies but do not seem to consider the post-authorisation setting sufficiently where study objectives, design and feasibility are important factors to consider as well. For example, a study investigating the long-term incidence of a specific AE of special interest; studies based on survey design; researches focusing on cognitive assessment or patient interviews. It would be beneficial to consider the full range of studies with primary data collection, including those with no solicited safety data collection.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
110	12	Focus here is on the importance of a scientific justification for selective safety data collection. Suggest including a discussion about what role the (development) risk management plan can play in standardisation and documentation of the reasoning behind the choice to do selective safety data collection. Also the factors listed here are indicated as factors to consider, but maybe these could also be translated into requirements that need to be met in relation to these factors. (See also under General comments).
110-111	13	**Comments:** We recommend the following change to the text in order to make clear that hypothetical justifications for reducing the collection of safety data should be avoided. We also recommend that the final guideline should state explicitly that the justification should be included in the clinical trial protocol. **Proposed change:** Replace "a scientific justification" with "an evidence-based scientific justification" and state explicitly that the justification should be included in the clinical trial protocol.
110-131	6	**Comments:** Most of this implicitly refers to clinical trials. Post-authorisation safety studies will have a specific objective of identification, characterization or quantification of specific safety issues, and therefore, all these items will not apply.
110-138	11	**Comments:** 1-While the intention of providing general principles on when Selective Safety Data Collection may be considered is endorsed, this section should provide principles and limit examples to one or two detailed and contextualized examples. The provided list of factors is not comprehensive, subjective, and generally found unhelpful. It seems also redundant and inconsistent with previous sections. Especially, lines 114 and 115 *"The medicinal product has received marketing authorisation from a regulatory 114 authority for the indication under investigation"*, the proposed criteria seem too large and do not appear sufficient to consider selective safety data collection. In general, the standards of Marketing Authorisation grating may largely vary form a country to another. This should be used with caution and it should be specified that this requirement "must" be completed by the other listed. Also the degree of

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		knowledge may differ (e.g. fast track approvel) and certain post approval studies might be necessary. Risk based approach should apply. **Proposal:** deletion and merger in one part on the general principles on selective safety data collection, including what and when. At least further explanation, limits and risk based approach.. 2/The section line 135 to 138: *"In the pre-approval setting, selective safety data collection may be justifiable if sufficient safety data are available from completed studies. Moreover, when sufficient safety data will be forthcoming from one or more ongoing late-stage study(ies), selective safety data collection may be appropriate for a concurrently conducted study-initiated pre-approval"* **Comments:** This proposal has its limitations, as the sponsor conducting the new study could not have access to such information considering it can be confidential at the time the sponsor decides to undertake the study. A precision such as "when available" should be introduced. **Proposal:** delete
111	8	**Comments:** Change of word should to must may ensure more widespread consistency. **Proposed change:** *When sponsors choose to implement selective safety data collection for a clinical study, a scientific justification* ***~~should~~ must*** *be provided.*
111-112	8	**Comments:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Consider including that implementation of selective safety data as dependent on one or more of the factors listed. **Proposed Change**: "Factors that contribute to a determination that selective safety data collection would be appropriate to include **one or more of the following:"**
113-114	7	"1. The medicinal product has received marketing authorisation from a regulatory authority for the indication under investigation" **Comments:** *[CTL]* This point is not in line with what is said in line 161 "1. New indications of approved drugs" and might add confusion. **Proposed change:** "1. The medicinal product has received marketing authorisation from a regulatory authority **and is used either according to the marketing authorisation or in new indications with comparable patient populations** (see also point 4)"
113-114	8	**Comments:** The fact that (any) one authority has authorised a drug does not necessarily mean that sufficient safety data have been collected so far, if only because Authorities' standards are different and many authorities approve a medicinal product with the assumption that additional safety data will be collected (also if not specifically required in a post-approval commitment) **Proposed change**: "…has received marketing authorisation from at least two major regulatory authorities like e.g. FDA and EU, without extensive post-approval commitments regarding safety data.
113-115	4	**Comments:** 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

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		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?
113-130	8	**Comments:** Items 1 to 9: some state specific criteria that need to be fulfilled (e.g. bullets 1, 3,4, 6), whilst the other bullets state a factor to be taken into consideration without providing any specific criteria. **Proposed change**: It would be helpful to provide some criteria for items 2, 5, 7, 8 and 9. E.g. minimum acceptable patient exposure (item # 5).
114-115	11	**Comments:** For example IMP has a MA in adults and will be administered in children, but no MA in children. Likely that no studies performed in this population before (as refered to in line 120-123). Therefore, selective safety data collection should not be considered in different population as marketing authorisation, e.g. children. Examples may be of help. **Proposed change:** The medical product has received meeting authorisation from a regulatory authority for the indication ***and population*** under investigation.
115	8	**Comments:** What does 'availability' mean? Is it a certain amount of data (numbers of AE reports)? Is it accessible to the sponsor of the specific study seeking selective safety data collection (i.e., public data like WHO/FDA AERs versus private/MAH Safety Database data)? **Proposed change**: Re-write to explicitly state what is meant by 'availability'
115	8	**Proposed change:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Suggest adding at the end of the current sentence. '…or a closely related indication where the safety profile can be expected to be similar.'
116	7	"3. The dose, dosing regimen, dosage form, route of administration …" **Comments:** *[CTL]* Pharmaceutical form would be more precise than "dosage form" **Proposed change:** "3. The dose, dosing regimen, **pharmaceutical form**, route of administration …"
116-118	8	**Comments:** What is meant by 'comparable'? Does it mean that most of these variables are the same but some may not be (e.g., frequency and duration are the same but route of administration is not). Or does it mean each of these factors is similar (and what is considered similar in terms of route of administration? Frequency? Is BID similar to QD or TID?). **Proposed change**: Be explicit about what must be the same or how to assess that each parameter is 'comparable'.
120	1	**Comments:** To add **Proposed change:** Phenotype
123-124	8	**Comments:** It is not clear what is the "number exposure to drug" means, and what would be the threshold to determine when exposure is

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		enough to consider qualifying for selected safety data collection. **Proposed change:** Provide guidance if there is a specific threshold where exposure is enough to support selective safety data collection. Additionally see proposed language for clarification: "Exposure in previously conducted (or ongoing, if applicable) studies that contribute to the overall safety database, i.e., number **of patients exposed** to drug, treatment duration"
123-124	8	**Comments:** Factor #5 is an incomplete sentence, which could cause confusion. **Proposed Change:** "Exposure in previously conducted (or ongoing, if applicable) studies that contribute to the overall safety database, i.e., **number of patients exposed to drug**, treatment duration"
123-130	8	**Comments:** Lines 113-122 are worded in a comparative way. For consistency, consider phrasing lines 123-130 in a similar way. **Proposed change**: "5. Sufficient representative ~~E~~exposure in previously conducted (or ongoing, if applicable) studies that contribute to the overall safety database, i.e., number of patients exposed to drug, treatment duration 6. Consistency of the safety profile across previous studies 7. Sufficient similar ~~C~~characteristics of previous studies, e.g., study design; study conduct; adequacy of safety monitoring/safety data collection; availability of protocols; statistical analysis plan; and/or access to data 8. Sufficient ~~K~~knowledge of the mechanism of action of the medicinal product under study

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		9. Sufficient ~~K~~knowledge of the safety profile of approved drugs in the same pharmacologic class"
123-130	8	**Comments:** Compared to the Bullets 1-4 and 8, Bullets 5-7 and 9 just state 'categories' to be considered and not the "Factors that contribute to a determination that selective safety data collection would be appropriate…" that is indicated in line 111-112. **Proposed change:** More appropriate wordings could be: Bullet 5: **Sufficient** exposure in previously conducted (or ongoing, if applicable) studies… (See also General Comment) Bullet 6: **High** consistency of the safety profile across previous studies… Bullet 7: **High consistency in the** characteristics of previous studies, e.g., study design; study conduct; Bullet 9: Knowledge of the **consistency of** safety profile **compared to** approved drugs in the same pharmacologic class
124	1	**Comments:** add **Proposed change:** comorbidities
124	8	**Comments:** The term "database" in unclear. We recommend clarifying per the below. **Proposed change**: "the overall safety ~~**database**~~ **profile**"
124	7	"number exposure to drug"

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		Comments: *[CTL]* Something missing?
124-125	6	**Comments:** Difficult to understand. What is "number exposure to drug"?
125	8	**Comments:** Please clarify if the previous studies are for the same or different indications **Proposed change**: Clarify and be explicit if the previous studies are for the same or different indications
125	8	**Comments:** Selective safety data collection may be considered if there is data showing that in previous studies the safety profile was consistent, while previous studies would not have used the selective safety collection approach. We have proposed some clarifying wording on this aspect. **Proposed change:** *Consistency of the safety profile across previous studies* ***where comprehensive safety data collection was used.***
126	6	**Comments:** Consistency of the safety profile across previous studies is not a guarantee for a selective data collection. It will depend on the design of previous studies and design of the future study
126	1	**Comments:** add in brackets after study design

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		Proposed change: inclusive of patient perspective
126-128	8	**Comments:** What about the characteristics (specifically study design, study conduct and statistical analysis plan) of previous studies would lend to limited safety data collection? There is no guidance here. And what does 'study conduct' mean anyway? **Proposed change**: Re-write to clarify (for example: is it meant to say this selected data collection studies should have similar characteristics of previous studies, e.g., similar study design, similar study conduct, similar statistical analysis plans)?
126-128	8	**Comments:** We feel point #7 does not add value. **Proposed change**: We recommend removing this point.
127	7	"Availability of protocols" **Comments:** *[CTL]* Protocol information and study result information must be available **Proposed change:** "Availability of protocol and study result information"
129	10	**Comments:** It is not clear how the knowledge of the mechanism of action could be a factor in favour of a reduced safety data collection. Typically, the mechanism of action of a medicinal product is known from preclinical trials. Consequently, this factor would apply to

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		almost all clinical trials. **Proposed change:** Delete the whole line and adjust numbering of the listed factors.
129	13	**Comments:** The overall pharmacological properties of the product under study contribute to the determination as to whether selective safety data collection is appropriate. Therefore, the factors that contribute to a determination of selective safety data collection should include specifically the pharmacokinetic and pharmacodynamic properties of the product. Additionally, the draft text refers to "the medicinal product under study." However, while section 1.33 of the ICH E6(R2) guideline defines the term "investigational product" there is no ICH definition of "medicinal product". Consequently, we recommend the term "investigational product" is used. **Proposed change:** Replace "8. Knowledge of the mechanism of action of the medicinal product under study" with "8. Knowledge of the pharmacokinetic and pharmacodynamic properties of the investigational product."
130	6	**Comments:** Knowledge of the mechanism of action of the medicinal product under study is not a reason. Normally, this is known for all drugs, but besides this, not all adverse reactions are derived from the mechanism of action of the product.
130	11	**Comments:** If two medicinal products belong to the same pharmacologic class it doesn't mean that they will have the same safety profile. For example some receptor inhibitors are more selective for some receptor subfamily within the same family of enzymes/receptors, and this can lead to different adverse reactions. It usually happens that the first investigated inhibitor in pharmacologic class is less selective for receptors in one family, and later investigated IMPs specifically targets one subfamily of receptors, and this leads to adverse reactions in lesser extent. In addition the compound's own (chemical structure) safety profile will always be in addition

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		to class effects. In postmarketing, while assessing PSURs, it is not enough that some ADR is expected in that class, it has to be observed with particular medicinal product. Consequently, to include ADR in section 4.8 of the SmPC of product X, there have to be well documented cases of ADRs with product X (and not other products in the same class). And in most cases, ADRs reported in postmarketing are difficult to assess because they don't have as much information as clinical trials cases. So cases from clinical trials are more preferred. Therefore class effects are a hint but no justification for not recording and reporting adverse events. **Proposal:** delete this bullet point.
131	6	**Comments:** Knowledge of the safety profile of approved drugs in the same pharmacologic class is not a guarantee. Not all adverse reactions are class effects.
131-133	8	**Comments:** Where is this assessment and outcome documented? In the protocol? Should the documentation show assessment of each listed criteria? **Proposed change**: State that this assessment and outcome is captured in the protocol (although captured in Section 3, clarification would be helpful here), in the safety section where it will be reviewed (and therefore approved) by IRBs/ECs.
131-133	8	**Comments:** It is recommended to mention in the 1st paragraph rather than at the end of the section that the factors listed should be considered in determining whether the safety of the medicinal product has been sufficiently characterised to provide justification

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		for selective safety data collection in the proposed study. **Proposed change:** move paragraph from line 131 to 133 to line 111 after sentence ending '…should be provided.'
132	8	**Comments:** When describing the factors to prove justification for selective safety data collection, further explanation of what is meant when a factor has been *sufficiently* characterised. What are we using to measure 'sufficient'?
132	11	**Proposed change:** 'the above factors ~~should be considered~~ **are examples** in determining whether…."
132-133	13	**Comments:** As above, the term "medicinal product" is used again without definition. **Proposed change:** Replace "…whether the safety of the medicinal product has been sufficiently characterised…" with "…whether the safety of the investigational product has been sufficiently characterised…"
134-135	8	**Proposed change:** In the pre-approval setting, selective safety data collection may be justifiable if sufficient safety data are available from completed studies **with regards to same treatment, indication and patient characteristics**
134-137	4	**Comments:** "…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.
135-137	13	**Comments:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
and 231-239		Line 136 refers to "late stage study(ies)"; within the biopharmaceutical industry, this term can be used to refer to Phase III clinical trials or to any clinical studies or trials conducted post-approval. The context in which the term is used here is not clear. ACRO welcomes and supports the concept that selective safety data collection may be justified in a pre-approval setting; however, we recommend the following addition in order to provide greater clarity on the situations in which this may be acceptable. **Proposed change:** Explain what is meant by late stage study(ies) in this context, and provide more text to describe the safety data that should be available from ongoing clinical trials before an additional clinical trial using selective safety data collection can be initiated. For instance, we assume (given the relative absence of pre-existing safety data) that it would not be possible to initiate three Phase III trials, two with full safety data collection and one with selective data collection, at the same time. Further guidance to help sponsors understand where the balance should lie in initiating a clinical trial with selective safety data collection in the pre-approval setting would be most welcome.
136-138	6	**Comments:** One cannot take such decision based on data gathering from on-going studies. Not all studies are completed, or have sufficient sample to identified not so common adverse reactions.
137-138	11	**Comments:** The meaning of wording "study-initiated pre-approval" is unclear. Does the sentence mean "…selective safety data collection may be appropriate for a new study."? If studies are ongoing where regular safety data collection is done, the outcome is open and knowledge of safety profile is still not sufficient. Therefor start new study/ies with reduced safety data collection prior outcome of ongoing studies safety collection can't be sufficient justified and is not warranted. **Proposed change:** Delete, or modify while add 'while start of studies only when sufficient safety information is available (not ongoing)'.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
138-146	7	**Comments:** *[PV]* The considerations developed in this section 2.2.1 sound fairly easy to implement for interventional trials where populations exposed to studied drug(s) and subsequent safety data collection requirements can be clearly defined/imposed in protocol. However, in post-authorisation observational, non-interventional setting, it is challenging to anticipate and control the Real-World condition of use of drug(s) and exposed populations, which are under prescribers' control and may evolve over time. It could thus be challenging to operationalise different safety data collection strategies for some of these studies. There is a concern of potential strict and conservative application of this section 2.2.1 by regulatory authorities and ECs leading to non-applicability of selective safety data collection in many post authorisation non-interventional studies.
139-140	12	**Comments:** Here it is recognized that the contribution of non-serious adverse events (adverse drug reactions??) to the benefit-risk profile of a drug may differ depending on the indication of use and patient characteristics. Suggest to also address here that (patterns of) non-serious adverse reactions may also provide information on possible more serious adverse reactions that may be anticipated. Further, among all types of "Safety Data Where It May be Appropriate to Limit or Stop Collection" (also considered in section 2.1.1) why are only non-serious adverse events listed? Expected adverse reactions, or unrelated adverse events, etc. could also be mentioned.
139-142	8	"It should be recognized … of patient populations and the applicability of selective safety data collection." **Comments:** It is important to capture development/lifecycle stage of the product as a factor as well.
139-147	6	**Comments:** This section is difficult to be understood. Does this mean that only reactions that compromise the benefit-risk should be collected? This approach is not shared, since a number of non-serious reactions could be severe, impair the quality of life of the patient and, therefore, relevant to be identified and quantified (although will not affect the benefit-risk). Studies provide meaningful information on adverse reactions that healthcare professionals and patients should know, even if they are not key to the benefit-

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		risk.
140	8	**Comments:** Characteristics of the IMP (eg., dose, dosing regimen, …) are not mentioned as a contributing factor in the occurrence of NSAE. **Proposed change**: …patient characteristics (e.g., age and/or cardiovascular risk factors) **and, characteristic of the drug (dosage, regimen,…)**
147-155	7	**Comments:** *[PV]* There are other impacting factors than extent of exposure. This section could have been named "**Impacting factors**" and been extended to include requirements based on: product-specific, population-specific, clinical outcome-related (large / limited)
148-156	11	**Comments:** While the intention of providing general principles on considering exposure for selective safety reporting is supported, this section is unclear, redundant, and generally found unhelpful. **Proposal:** deletion and merger in one part on the general principles on selective safety data collection, including what and when.
149-151	8	**Comments:** We believe that the following sentence could be confusing given that in the next section outcome studies which are often of very long duration are cited as a study type to exempt. **Proposed change:** Conversely, selective safety data collection would generally not be acceptable if higher doses ~~and/or longer treatment durations~~ than previously studied are planned.
152-156	6	**Comments:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Not supported.
157	6	**Comments:** This heading of section 2.3, and the heading of section 2.2 are in fact referring to the same issue. In 2.2, reference is made to factors, and in 2.3, reference is made to examples, but to disentangle both is difficult, because some factors can be considered as examples and viceversa.
157-172	11	**Comments:** While the intention of providing general principles on Selective Safety Data Collection is endorsed, the provided list of examples is not comprehensive, subjective, redundant, and generally found unhelpful. Although not an exhaustive list, is too vague to be of use. The examples could apply to almost any trial and need to be much more clearly defined. Especially, 161: A new indication is not a criteria to consider selective safety data collection since a new indication of an approved drug can concern a different population (pediatric patient for example, or rheumatoid arthritis and oncology) 165: 3rd bullet point: This type of studies should be detailed. Indeed, they could be common and numerous in the pre-approval development 168: only because of use of registry doesn't implies that selective safety data collection is given and accepted **Proposal:** deletion and merger in one part on the general principles on selective safety data collection, including what and when.
158	8	**Comments:** when reading section 2.3 and especially the point 1 it seems that the circumstances where we can use these selective data are somewhere contradictory because something is missing. Actually, it is the combination of several situations. This should be more

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		emphasized. **Proposed change**: reword sentence "These **examples can be selected individually or in combination and** are not the only circumstances…"
160	1	**Comments:** add **Proposed change:** extrapolation
160	4	**Comments:** "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.
160	7	"New indications of approved drugs" **Comments:** *[CTL]* This is not in line with line no 113, where it says: "The medicinal product has received marketing authorisation from a regulatory authority <u>for the indication under investigation"</u>
160	8	**Comments:** Clarify the scenario of new indications of approved drugs only apply in the situation where the subjects were represented in previously conducted studies. Although this is captured in Section 2.2, clarification would be helpful here. **Proposed change**:

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		"1. New indications of approved drugs in patient populations where subjects were represented in previously conducted studies"
160	8	**Comments:** 1. "New indications of approved drugs" will most likely require new (parts of) populations to be exposed; populations that have not been investigated previously. **Proposed change**: Remove this
160	13	**Comments:** Selective safety data collection may not be appropriate for all new indications of approved drugs. Therefore, we recommend that the current statement is qualified as follows. **Proposed change:** Replace "1. New indications of approved drugs" with "1. New indications of approved drugs with comparable exposure."
160 onwards	4	**Comments:** 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.
160-169	18	**Comments:** Post-Authorisation Safety (PAS) studies with the sole aim of evaluating the effectiveness of additional risk minimisation measures, such as educational materials, Patient Alert Card, etc, are good candidates for optimisation of safety data collection. We propose to specifically mention these types of studies in the list of examples where selective data collection may be considered. **Proposed change:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Post-Authorisation Safety (PAS) studies with the sole aim of evaluating the effectiveness of additional risk minimisation measures (e.g. educational materials, Patient Alert Card, etc.)
161	6	**Comments:** **Not agreed. A new indication could lead to a different safety profile if populations are different**
161	11	**Comments:** New indications are not agreed as a good example as this is often a new indication with a potential new safety profile, or a new population such as elderly or children. Completion of trials for MAA can still be in a relatively small number of patients and allowing a blanket proposal that MA is a reason to consider reduced safety oversight is a dangerous precedent. **Proposed change (suggest this point is removed):** New indications of approved drugs *unless the safety data accumulated in the licensed indication are not applicable to the trial population or the safety database to date remains small.*
161-162	8	**Comments:** Although quality of life (QoL) and health-related quality of life (HRQoL) are used interchangeably in the literature, each has its own meaning. QoL is a broader concept which covers all aspects of life. HRQoL has a focus on the effects of illness and specifically on the impact treatment may have on QoL **Proposed change**: Change "quality of life" to "health-related quality of life"
161-163	12	**Comments:** It may be useful to relate the examples provided here to the factors listed in section 2.2. For example in case the focus is on studying a new indication of an approved drug, the patient population from previously conducted studies may very well be different.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
161-163	16	Original text: To study additional endpoints, e.g., patient-reported outcome for symptomatic improvement; quality of life; and/or outcome studies (e.g., mortality; morbidity; and/or specific safety issues) **Proposed change:** patient-reported outcome should be listed, rather than included as an example
162	12	**Comments:** Consideration should be given to definition of broader endpoints where it may not be possible using RWD to fulfil all criteria as may be used in clinical trials. A footnote to understand current regulator opinion in this regard is suggested.
164-165	8	**Comments:** Leaving out the collection of specific safety data from comparative efficacy or superiority studies may appear to reduce the burden on the development program, however, it should be noted that this separation of efficacy/effectiveness and safety may require specific safety studies later on, e.g. if efficacy was found to be comparable or no superiority was found. **Proposed change**: Add a note to this list stating e.g. for point 3 and 4 please note that comprehensive safety data collection may provide differences with comparators, even if the study objective (better efficacy/superiority) was not attained.
165	6	**Comments:** Comparative effectiveness research is the direct comparison of existing health care interventions to determine which work best for which patients and which pose the greatest benefits and harms. Then, a key element of comparative effectiveness is safety. Any selective data collection will limit the validity of the study.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
166	6	**Comments:** Demonstration of superiority when non-inferiority has been demonstrated: the study aimed at demonstrating superiority will obviously have to include a larger sample size that the study that demonstrated non-inferiority. Therefore, selective data collection does not seem a good idea, since such study could identify less common adverse reactions.
167	6	**Comments:** This is obvious. In a study aimed at characterisation of adverse events of special interest, the protocol will define the events that will be collected. The other suspected adverse reactions will be reported as regulated.
168-169	6	**Comments:** Studies using secondary data collection such as registries and electronic health records will obviously gather the data as per protocol.
169	8	**Comments:** Limiting the collection of safety data in large population pre-approval studies will put an extra burden on any post-approval activities/studies to collect these data **Proposed change**: include a modifier when this may be correct
172	13	**Comments:** This section heading refers to studies. Per comment in the "General comments" section, the use of the term 'clinical study" does not accurately reflect the purpose/ focus of ICH E19 and causes confusion, rather than clarity, when it comes to the applicability of this work product. **Proposed change:** Replace "studies" with "clinical trials."

Line no.	Stakeholder no.	Comment and rationale; proposed changes
173	11	**Comments:** Section 2.4 does not differentiate between recording and reporting of events. Recording events in a CRF or trial document is different to requirements for reporting (usually serious) events to the regulator or from the investigator to the sponsor. This difference needs to be discussed and made clear as we may allow reduced reporting but expect the same recording, so a safety profile is fully documented by the sponsor but the regulator does not need to always be informed. It is also suggested to move the section ***"2.4 Ensuring Patient Safety within Studies"*** before 2.1, 2.2 and 2.3 in order to pass the message that that is a "prerequisite" for the conduction of any study **Proposed change:** 1. Differentiate between recoding and reporting. Change accordingly, that recording is not matter of selective data collection, while reporting is. 2. Move the section ***"2.4 Ensuring Patient Safety within Studies"*** before 2.1.
174	12	**Comments:** The safety monitoring section is focused around tests. It may also be useful to specifically distinguish between collection of data focussed on (spontaneous) symptom reporting (safety surveillance) and collection of data for which tests and examinations are actively performed (monitoring based on examinations).
174-176	6	**Comments:** In our view, patient safety monitoring serves more purposes than the two stated. Not only serves to protect participants and to accumulate safety information for the assessment of the benefit-risk for the proposed indication, but to gather further knowledge about the risks of a drug in order to inform adequately healthcare professionals and patients and to put in place mechanisms to minimise such risks. The view given is very much focused in clinical trials pre-authorisation. In fact, the full paragraph, as most of the guideline, makes reference to clinical trials.
176-179	8	**Comments:**

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		Edit proposed to reduce the likelihood of any ambiguity as to what has to be reported under all circumstances and what might fall under selective safety data collection. **Proposed change**: Although certain safety data, e.g., non-serious adverse events, **except for those listed under section 2.1.2,** would not need to be recorded in the case report form (CRF) when selective safety data collection is determined to be appropriate, the protocol should stipulate that patients are monitored per standard of care.
178	12	**Comments:** Suggest modifying the statement that "non-serious adverse events" do not need to be recorded. In some cases it may be relevant to collect also those for example if the focus is on characterising the frequency of a certain safety concern we would need to collect all occurrences of that safety concern (whether they are considered serious or non-serious). See also comment for line 139/140.
179	8	**Comments:** It is recommended that to remind that data collection is still investigator responsibility. **Proposed change:** Line 179- Proposed addition to the sentence:… **and remains the responsibility of the study investigator.**
179	8	**Proposed change**: Suggest to add .. are monitored per standard of care by spontaneous reporting.
180	11	**Comments:** There is a difference between recording events in the CRF and monitoring per standard of care, they are independent of each other. Allowing reduced recording of events is one aspect. Reducing monitoring to that of SOC is another. Monitoring as per SOC

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		will still often need to be defined and justified. It is often seen in extension parts of a protocol, but if the safety profile is still not fully elucidated then reduced monitoring to SOC may not be appropriate. It should also be clear what recording *is* expected – not recording non-serious could be agreed, but serious events should always be recorded. **Proposed change:** Change accordingly.
180-181	8	**Comments:** In the example of hyperglycemia, this guideline considers the sufficiency of the safety profile on an event basis, whereas other sections (e.g. 3 "METHODS OF IMPLEMENTATION") considers it on a product basis. **Proposed change**: This guideline should clarify whether the adequacy of the safety profile is based on the event or the product. Based on this, the description of the guideline should be unified or supplemented.
180-186	11	**Comments:** Will severity of non-serious adverse drug event/reactions be considered. It is not clear if non-serious adverse event is considered related and therefore non-serious ADR should this be recorded or not? As of the example given –hyperglycaemia, it will be reported to the sponsor if associated with serious adverse reaction or if AR is reported at a higher than known severity grade. For example if AR was mild or moderate previously, but now was reported as severe and therefore should be recorded and reported. Furthermore even if the safety profile is known, and the recording may be waived, adequate risk mitigation measures for already known safety profile should always be present in the protocol. **Proposed change:** It is proposed to consider severity as well as seriousness compared to known safety profile. Serious should always be recorded, increase in known severity should also be recorded, especially for some laboratory values. Please, clarify if non-serious ADR (if assessed to be related to the IMP) should be recorded or can this be also exempt.

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		It is proposed to underline that even if the safety profile is known, adequate risk mitigation measures for already known safety profile should be present in the protocol.
181-185	8	**Comments:** These 2 sentences seem to contradict each other. Recommend amending the second sentence by adding a "however", to show the contrast between the 2 sentences. **Proposed change:** "If hyperglycaemia is well-characterised with this medicinal product, the glucose data do not need to be recorded in the CRF or reported to the sponsor in studies using selective safety data collection. However, ~~G~~glucose levels would be recorded in the CRF and reported to the sponsor if stipulated in the protocol, e.g., as an adverse event of special interest, associated with a serious adverse event."
184-185	14	**Comments:** More exact wording would be beneficial **Proposed change:** would say "as clinically relevant, based on protocol definition and only if assessed as serious adverse event".
185	7	…, "associated with a serious adverse event." **Comments:** *[CTL]* not really clear **Proposed change:** "…, **to be processed in the same way as a serious adverse event"**
186	12	**Comments:**

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		It is not clear from this sentence if adverse events of special interest should be considered serious adverse events.
187-188	14	**Comments:** additional clarity needed regarding what would be an unexpected safety issue **Proposed change:** "confirmed new signal or new important identified risk" suggested to be used instead of just signal
187-188	14	**Comments:** finding from a non-clinical study is considered a too vague example. Would a publication on a case represent a finding from non clinical study? **Proposed change:** Suggest to just focus on new confirmed signal, new important identified risk, higher withdrawals.....
187-191	8	**Comments:** Clarify who would make the decision to change the selective safety data collection approach. Additionally, the use of "warranted" is not clear. **Proposed change**: When an unexpected safety issue arises during the course of a study, e.g., a postmarketing safety signal; a finding from a nonclinical study higher than expected withdrawals; and/or concern from a data monitoring committee; the sponsor should consider if a change in the selective safety data collection approach is necessary ~~may be warranted~~, e.g. denoting a new adverse event of special interest; and/or reverting to comprehensive safety data collection.
187-191	8	**Comments:** "reverting to comprehensive safety data collection when an unexpected safety issue arises during the course of study"

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		does not seem to be a practical solution in the middle of a trial. It will not allow for retrospective collection of data on events classified as an unexpected safety issue and at the time of analysis and reporting the dataset is incomplete and the dataset may not contain enough data to make a statistical statement. The protocol and clinical database would require an amendment which takes time. Would the trial be put on hold until the amendment is in place and approved? Please clarify how this situation is handled.
187-192	11	***2.5 Changes in Approach to Safety Data Collection*** The possibility to revert to comprehensive safety data collection, must be detailed in the study protocol and a "detailed" plan on how this can be "promptly" performed during the course of the study must be detailed and anticipated (i.e: preparation and distribution of complete CRFs including non-serious AE collection) **Proposal:** add accordingly
187-192	12	**Comments:** The paragraph is not easy to read. Suggest to add the examples into brackets: "e.g., a post-marketing safety signal; a finding from a nonclinical study; higher than expected withdrawals; and/or 189 concern from a data monitoring committee" so that is clear then what is the consequence: change in the selective safety data collection approach may be warranted. Also suggest rephrase 'unexpected safety issue' to unexpected safety signal'
188-191	5	**Comments:** The guideline states that 'when a safety issue arises, e.g., a post-marketing safety signal; … a change in the selective safety data collection approach may be warranted, e.g. … reverting to comprehensive safety data collection.' Such an *ad hoc* change to the system and procedures of safety data collection might endanger the compliant conduct of the study and validity of the results. It should be clearly stated in the guideline, that such a change is only performed, for example, in the case of an emerging safety issue, a safety issue with potential major impact on the risk-benefit balance of the medicinal product

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		and/or on patients' or public health and not for any new (even important) safety signal.
188-192	5	**Comments:** Clarification is sought from the ICH that any changes in the safety collection should be considered substantial amendments requiring respective approvals prior to implementation.
189	12	Suggest to rephrase "a finding from a nonclinical study" to "a significant finding from nonclinical or clinical study".
190-191	8	**Comments:** It is recommended to clarify the term "reverting" : whether it is referring to proactive and/or also retroactive documentation of cases. Please make clear that in case of SAE, FU information can contain a request to data which was initially considered as not needed to be collected. **Proposed change:** and/or reverting **(e.g. proactive and/ or retroactive documentation of cases depending the situation)** to comprehensive safety data collection
191	8	**Comments:** when a change in the selective safety data collection approach occurred in the middle of study conducting, the impact on the safety analyses needs to be carefully evaluated and described in the protocol and data analysis plan amendment. **Proposed change:** add a sentence line 191: It is recognised that such situation would have an impact on study management (e.g protocol amendment..)
191	14	**Comments:** The safety analysis will need to be updated to reflect this.

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192-203	7	**Comments:** *[PV]* As currently worded, the early consultation with Regulatory Authorities can be understood as a **systematic** procedure to be performed ahead of protocol development for **all** interventional trials and imposed/required non-interventional studies. If so, this systematic consultation requirement sounds very constraining in daily practice, especially for some studies that qualify as (low) interventional due to follow up procedures imposed by protocol while being observational by scientific study design and/or not having safety objectives. It is also unclear how this consultation should be managed and testified. Would it be possible to clarify and nuance this requirement? Could we consider that this consultation is recommended, but not mandatory for studies (interventional and non-interventional) that are not imposed as an obligation by regulatory authorities to investigate a safety concern, while requiring that scientific rationale for selective safety data collection and planned methods should be detailed in the protocol submitted to Ethics Committees?
194	13	**Comments:** The text uses the term "interventional studies". In the absence of an agreed (by ICH partners and stakeholders) definition, we recommend that this term is avoided. **Proposed change:** Replace "interventional studies" with "clinical trials."
194-196	8	**Comments:** This statement implies a regulatory agency discussion prior to submitting the clinical trial application. Given this potential interpretation, inclusion of this recommendation could cause delays in initiating studies that have selective safety data collection. In addition, regulatory agencies approve trials through the clinical trial application process, so there is already a mechanism in place to engage regulatory agencies and present a justification. We recommend removing this statement. **Proposed change**: This statement in line 194 should be deleted or modified to state that a justification for selective safety data collection should be provided in the protocol.

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194-196	10	**Comments:** According to this guideline sponsors should discuss their scientific rationale and planned methods for selective safety reporting with regulatory authorities prior to initiating the study(ies). If there is no other rationale for sponsors to ask for scientific advice for their trial, it is an additional burden to sponsors to prepare such scientific rationale and planned methods for selective safety reporting only. It could be seen as a disadvantage and time loss, i.e. as an extra burden to sponsors, so that they would prefer to rather collect any safety data that could be received. In this respect it should be clarified that this "discussion" is a) not a "must do" and b) does not mean to go through the timely long lasting standard scientific advice process but should be handled in a less burdensome way. **Proposed change:** Change wording as follows: When sponsors are considering selective safety data collection in interventional studies, it is advisable that they ~~should~~discuss their scientific rationale and planned methods with regulatory authorities prior to initiating the study(ies) without going through the standard scientific advice process.
195-197	11	**Comments:** A scientific advice may be recommended, also a sufficient justification during the authorisation assessment of a clinical trial may be sufficient, depending on the degree of selective recording/reporting.
196	13	**Comments:** The text refers to non-interventional studies. As noted earlier, according to the ICH website, the work carried out by ICH under the Efficacy heading is concerned with the design, conduct, safety and reporting of clinical trials. This being the case, "non-interventional studies" should not be included in the scope of ICH E19 paper. This will create confusion and unnecessary dilution of the robustness of the clinical trial-related information being presented. **Proposed change:** Delete the last sentence of the paragraph.

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196-197	8	**Comments:** The comment on non-interventional studies is not clear. Selective safety data collection would not be applicable?
198	13	**Comments:** The text uses the term "clinical study". Per comment in the "General comments" section, the use of the term 'clinical study" does not accurately reflect the purpose/ focus of ICH E19 and causes confusion, rather than clarity, when it comes to the applicability of this work product. **Proposed change:** Replace "clinical study" with "clinical trial."
198-200	8	**Comments:** As it could create challenges expecting all regulatory authorities to agree in a multi-country setting, we suggest the following deletion of text. **Proposed Change:** "It is possible to conduct a multi-regional clinical study using a single protocol with selective safety data collection if the safety profile of the product is considered to be sufficiently characterised." ~~and all regulatory authorities agree with the proposed approach."~~
201	13	**Comments:** The text uses the term "clinical study". Per comment in the "General comments" section, the use of the term 'clinical study" does not accurately reflect the purpose/ focus of ICH E19 and causes confusion, rather than clarity, when it comes to the applicability of this work product. **Proposed change:** Replace "clinical study" with "clinical trial."

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204-209	5	**Comments:** We welcome the guidance as it relates to a single protocol across multiple regions, but in practice we feel this may be more difficult to achieve. Would the ICH consider strengthening the language around this or providing guidance to help Sponsors negotiate or discuss with regulators when there may be disagreement between regulators?
209-210	11	The sponsor should be reminded that the 'safety and statistical analysis plans" must carefully consider both situations and appropriately discuss the results from the study in which selective safety data approach was not allowed. **Proposal to introduce a word:** *" Use of selective safety data collection can introduce important complexities in study conduct,* ***set-up*** *and safety analysis".*
209-211	7	"The specific approaches should be carefully planned and clearly delineated within the relevant study documents, e.g., protocol; monitoring plan; and/or statistical analysis plan, with a reference to this Guideline." **Comments:** *[CTL]* In line with ICH E6 and the requirement for a risk-based approach to quality management, a risk management plan or 1. version of the Periodic Benefit-Risk Evaluation Report (PBRER) should be listed here as well. Proposed change: "The specific approaches should be carefully planned and clearly delineated within the relevant study documents, e.g., protocol; monitoring plan; **risk management plan/first Periodic Benefit-Risk Evaluation Report (PBRER)** and/or statistical analysis plan, with a reference to this Guideline."
210	1	**Comments:** add **Proposed change:** After the word protocol , with the involvement of the patient perspective

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210-211	18	**Comments:** Suggest to add "Safety Monitoring Plan" or equivalent to the list of study documents where the selective safety data collection should be mentioned.
212-217	8	**Comments:** Reference should be made to the RMP, particularly in respect of medically important identified risks, and monitoring of potential risks.
213-217	8	"When the selective safety data collection approach is used for a clinical study, … and/or Common Technical Document (CTD)." **Comments:** Consider that the approach should be described in the CSR only, as selective collection would be applied to a given study.
213-217	18	**Comments:** Given the guidance recommendation to clearly identify those studies using selective safety data collection, please consider the use of some sort of generic study type identifier/code in their name, code or title such as SSDC (for selective safety data collection) or other.
216-217	8	**Comments:** PBRER is the formal ICH naming. The PSUR designation (for the same document) is only used in the EU legislation – redundant?
221-222	6	**Comments:** Under methods of implementation, it is stated that the data supporting these approaches are more likely to be available in the post-approval setting than in the pre-approval setting. This should be reflected in the general objectives of the guideline.
226	8	**Comments:** See line 79: Concomitant medications and drug interactions are always a gap in safety information and difficult to gather in

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		postmarketing/spontaneous AE reporting. **Proposed change**: Never waive the requirement to capture concomitant medication. Remove it from all 'examples' in this document.
226-228	11	We should specify here that some or all of parameters can be not collected. **Proposal:** *"Conversely, **some or all** the parameters listed in Section 2.1.1, General Principles, can be are not collected, e.g., non-serious adverse events; routine laboratory values; concomitant 227 medications; physical examination data; vital signs; and/or electrocardiograms."*
231-239	8	**Comments:** The example might not be the best one. What if in such a trial the LDL-cholesterol lowering effect is as expected, however, the number of cardiovascular events/deaths is unchanged (compared to non-treatment)? Then safety data, that were considered less relevant (and were not collected), may just give a clue to this outcome by comparing the details of both study populations. I suggest that (directly) related efficacy and safety outcomes (LDL lowering (not?) leading to less cardiovascular events), should not be investigated separately, esp. not in trials with less safety data collection. **Proposed change**: Provide an alternative example
235-240	6	**Comments:** The example is not shared. Obviously, the study with a hard endpoint, as major cardiovascular events, will need to recruit a much larger sample than the studies already completed with LDL cholesterol as the primary endpoint. Therefore, the power to detect infrequent adverse reactions will be larger. Why to select the adverse events that will be registered? This study will be the best opportunity to identify, characterise and quantify adverse reactions, serious and non serious, that spontaneous reporting or other

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		smaller studies cannot do.
241-248	8	**Comments:** A study design with different data collection requirements for subsets of patient population would be challenging for investigator sites to implement. Using the example in the document – comprehensive data collection for those over 65 and selective data collection for those under 65 – we believe that this type of trial design would be challenging for sites to implement correctly. We have a recent example trial for which we asked sites to not complete the AE eCRF for protocol specified endpoints which was quite challenging and not implemented correctly by many sites. We believe that the requirements described in section 3.4 (lines 258- 273) are more easy to implement and a good starting point.
244 -245	14	**Comments:** suggest clarifying that the subset of population with insufficient data should be determined based on the target population for each product
249-273	8	**Comments:** These approaches (e.g., comprehensive collection from only some study sites or for the first certain # of patients enrolled) must ensure diversity in that cohort such that full safety data is available on all necessary sub-populations. **Proposed change**: add language to require that any implementation plan ensure diversity in patient population for which full safety data collection occurs reflects diversity of entire study population (especially targeted diversity, not just actual diversity which may fall short of study-diversity goal).
250-257	6	**Comments:** The argument is not shared. It will depend on the frequency of the adverse reaction. As stated somewhere above, non-serious adverse reactions can be very relevant for the patient.

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250-257	12	**Comments:** If the main study endpoints are related to safety (for e.g. a Post Authorisation Safety Study assessing characterising the incidence rate, estimate the rate ratio or rate difference in comparison to a non-exposed population), considerations with statistical power still need to be taken into consideration. Suggest modifying as the current wording suggests that those considerations are not important.
252	12	**Comments:** It is not just efficacy studies that must enrol thousands of patients to achieve adequate statistical power. Suggest including some additional language such that line 252 reads… "In some cases, efficacy or safety studies must enrol…….'
254-256	10	**Comments:** It is understood that in large trials the collection of some safety data like for non-serious adverse events should be restricted. However, undertaking full data collection at randomly selected sites would give more administrative burden to sponsors, as study documentation like CRF completion manual, AE handling manual, site initiation visit presentation/training material would have to include specific handling and documentation guidelines only for those selected sites. This might lead to misunderstandings later on by site personnel, in particular for those sites without the need of that data collection. Another, less burdensome way should be considered. **Proposed change:** No specific text proposed. Depends solution to be found.
254-256	13	**Comments:** ACRO recommends the following addition to the text. **Proposed change:** We recommend that the guideline should state that the means of determining which patients will be subject to selective safety data collection is described in the clinical trial protocol. For instance, in the example given in the draft guideline, the method to be

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		used for randomly selecting sites should be described in the protocol.
258-274	6	**Comments:** Same arguments as above. Studies with longer follow-up will allow the detection of reactions appearing after long exposures. Spontaneous reporting is not a good tool for identifying reactions after long-term exposures, since suspecting association is less intuitive. Less frequent study visit intervals will not preclude the collection of adverse reactions, since other strategies can be applied.
269-271	8	**Comments:** Safety data collection could be limited with scientific rationale and justification but not stopped. Per GVP VI a summary of AE/AR must be provided in the CSR. Does the selective approach allow to discontinue collection of AEs, vital signs, lab tests, etc. Is this in line with other regulations? Would this be equivalent to "limitisation" because it would not be allowed from start of a study.
271-273	8	**Comments:** Consider adding to the guideline that the data monitoring committee may also need to re-assess continuously, if any unexpected safety issue arises, that may warrant change of the protocol to back to comprehensive safety data collection. **Proposed change**: "The protocol should include a prospective plan for concurrence of a data monitoring committee prior to the change to selective safety data collection. Similarly, the data monitoring committee should regularly assess the safety data collected and in case of an unexpected safety issue, revert the study back to comprehensive safety data collection."
271-273	8	**Comments:** Safety Data collection must be described in the protocol, change to selective upon DMC decision needs protocol amendment (substantial change)

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271-273	14	**Comments:** This is a good suggestion. However, please consider that there could be an interactive time effect (so for e.g. increasing age of patient plus treatment for condition may result in emergence of new non-serious adverse events toward later stages of study in these patients).
274-284	7	**Comments:** *[PV]* All listed guidelines are ICH guidelines. The title may then be "Relationship with other **ICH** guidelines/regulations. We understand that ICH guidelines traditionally do not refer to other non-ICH guidelines. However, given the needs for scientific justification of selective safety data collection, pre-existing guidelines on the same topic and different regulatory requirements for PV collection based on study qualification (interventional vs NIS) and design (primary data collection vs secondary use of data), there might be a benefit to reference further scientific Guidance documents in addition to ICH guidelines. To avoid confusion and ease updates, they could be clearly separated from ICH references, e.g. listed in appendix (or in a dedicated section or sub-section of section 4 titled "other non-ICH scientific guidelines of interest") and stipulated as just a non-exhaustive cross reference list that can support this selective data collection approach. Guidelines of interest, among others and for example, could include: GVP Modules VI and VIII, ISPE guidelines for Good Pharmacoepidemiology Practices, ENCePP Checklist for Study Protocols complemented by the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, FDA guidance for Industry on "Determining the extent of safety data collection needed in late-stage premarket and post-approval clinical investigations" and further relevant guidelines from the various ICH contributor countries. Similarly to the check list ENCePP developed for Post Authorisation studies, it would be interesting to develop a check-list to assist future users in the appropriate choice and argumentation of a selective safety data collection approach ((http://www.encepp.eu/standards_and_guidances/documents/ENCePPChecklistforStudyProtocolsRevision4_000.doc
276	13	**Comments:** The text uses the term "clinical studies". Per comment in the "General comments" section, the use of the term 'clinical study"

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		does not accurately reflect the purpose/ focus of ICH E19 and causes confusion, rather than clarity, when it comes to the applicability of this work product. **Proposed change:** Replace "clinical studies" with "clinical trials."