6 November 2015
EMA/739149/2015
Compliance and Inspection

Overview of comments on EMA/641479/2014 Draft proposal for an addendum, on transparency, to the "Functional specifications for the EU portal and EU database to be audited - EMA/42176/2014"

Comments received from public consultation (January – February 2015)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
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2	Charlotte Calov, Head of the GCP Unit, The GCP Unit at Odense University Hospital, JB Winsloews Vej 19, 2. floor, 5000 Odense C, Denmark
3	Kerstin Forsberg
4	European Organisation for Rare Diseases (EURORDIS), François Houÿez
5	Finnish Medicines Agency (Fimea)
6	Land Schleswig-Holstein, Germany
7	Standing Committee of European Doctors (CPME)
8	Region Sjælland, PFI Produktion
9	AllTrials Campaign
10	Medical Products Agency, Sweden
11	ACRO (Association of Clinical Research Organizations)
12	EUFEMED – European Federation for Exploratory Medicines Development
13	Hammersmith Medicines Research (early phase contract research organisation) &

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Stakeholder no.	Name of organisation or individual
	Trio Medicines (pharmaceutical company registered as an SME)
14	PECME. Programa de Estudios de Medicamentos y Productos Sanitarios en la Comunitat Valenciana (España)
15	The Medical Sciences Committee of Science Europe
16	ANDALUSIAN INITIATIVE FOR ADVANCED THERAPIES
17	Niedersachsen, Germany Ministerium für Soziales, Gesundheit und Gleichstellung, Abteilung 4, Gesundheit und Prävention, Referat 402
18	Freie und Hansestadt Hamburg, Germany, Ministry of Health and Consumer, Protection, Pharmaceutical Inspectorate
19	NISCHR Academic Health Science Collaboration, UK
20	Arbeitskreis Medizinischer Ethik-Kommissionen in der Bundesrepublik Deutschland e.V.
21	GKV-Spitzenverband, Reinhardtstr. 28, 10117 Berlin, Deutschland / Germany
22	Budapest Working Group (BWG; joint initiative of the European Medical Writers Association [EMWA] and the American Medical Writers Association [AMWA])
23	Professor Francesco Muntoni, FRCPCH, FMedSci Head of the Developmental Neuroscience Programme, Institute of Child Health Head of the Dubowitz Neuromuscular Centre UCL Institute of Child Health and Great Ormond Street Hospital for Children (GOSH), 30 Guilford Street, London WC1N 1EH, UK
24	European Hematology Association (EHA)
25	Initiative "Forschung und Therapie für SMA" im Förderverein für die Deutsche Gesellschaft für Muskelkranke e. V.
26	Multi-Regional Clinical Trials (MRCT) Center at Harvard University
27	L. Molteni & C. (Italy)
28	DARQA Association The Netherlands
29	Network of Coordinating Centres for Clinical Trials, Germany (KKS-Netzwerk)
30	ECRIN (European Clinical Research Infrastructure Network, www.ecrin.org)
31	Institute for Quality and Efficiency in Health Care (IQWiG), Im Mediapark 8, 50670 Cologne, Germany
32	Pharmaceutical Group of the European Union (PGEU)

Stakeholder no.	Name of organisation or individual
33	Apceth GmbH & CoKG, Max-Lebsche-Platz 30, 81377 Munich, Germany Dr. Volker Scherhammer, Head of Clinical Development
34	Federal Authority of Hessia, Germany, Regierungspräsidium Darmstadt, Luisenplatz 2, 64283 Darmstadt, Pharmaceutical Inspectorate II.23.1
35	European Confederation of Pharmaceutical Entrepreneurs – EUCOPE AISBL, Rue d'Arlon 50, 1000 Brussels, Belgium
36	Faculty of Pharmaceutical Medicine of the Royal Colleges of Physicians of the UK
37	Danish Health and Medicines Authority
38	Guild of Healthcare Pharmacists
39	Association Internationale de la Mutualité (AIM) Health Action International (HAI) Europe International Society of Drug Bulletins (ISDB) Medicines in Europe Forum (MiEF)
40	Cancer Research UK British Heart Foundation
41	Quotient Clinical Ltd
42	Spanish Sarcoma Research Group GEIS
43	Spanish Association of Pharmacists in Industry (AEFI)
44	EGAN The Patients Network for Medical Research and Health
45	Martin Robinson, IAOCR
46	The Clinical Contract Research Association (CCRA)
47	European Organisation for Research and Treatment of Cancer
48	International Plasma Fractionation Association (IPFA)
49	The Christie NHS Foundation Trust, Manchester, England, M20 4BX
50	Dr Tom Jefferson Cochrane ARI Group
51	German Pharmaceutical Industry Association (BPI); Friedrichstraße 148, Germany D – 10117 Berlin
52	Dr. Giovanni Ghibaudo Dr. Viviana Mascilongo
53	European Society for Paediatric Oncology – SIOPE
54	The UK Government

Stakeholder no.	Name of organisation or individual
55	Reckitt Benckiser Healthcare, Dansom Lane, Hull, HU8 7DS, United Kingdom
56	Eucomed
57	EuropaBio
58	Biotechnology Industry Organization, 1201 Maryland Avenue S.W., Suite 900, Washington, D.C. 20024, United States of America
59	Niche Science and Technology Ltd
60	Regeneron Pharmaceuticals Inc./Regeneron Ireland
61	LEO Pharma A/S
62	Mundipharma Research Limited, Cambridge Science Park, Milton Road, Cambridge, CB4 0AB
63	Germany: Federal Ministry of Health, Federal Institute for Drugs and Medical Devices, Paul-Ehrlich-Institute (BMG, BfArM, PEI)
64	European Brain Council
65	EFPIA - European Federation of Pharmaceutical Industries and Associations EBE – European Biopharmaceutical Enterprises VE – Vaccines Europe
66	REC of Saint John of God University Hospital of Barcelona (Spain) Dr. Pablo Ferrer Salvans – Technical secretary of REC.
67	European Forum for Primary Care
68	Teva pharmaceuticals Ltd
69	BEUC – The European Consumer Organization
70	EUCROF, European CRO Federation
71	European Generic medicines Association (EGA)
Comments received after deadline	
72	Amelia Cline, Peregrine Pharmaceuticals, Inc.
73	The European Association of Hospital Pharmacists
74	Mika Scheinin, MD, PhD Professor of Pharmacology, University of Turku, Finland; Marjut Salokannel, LL.D., Docent, Adjunct Professor, University of Helsinki, Finland

Stakeholder no.	Name of organisation or individual
75	Leeds Institute of Clinical Trials Research, University of Leeds
76	UKCRC Registered Clinical Trials Unit Network, United Kingdom
77	CCMO, The Netherlands
78	Agencia Española de Medicamentos y Productos Sanitarios
79	Bayerisches Staatsministerium für Gesundheit und Pflege, Haidenauplatz 1, 81667 München
80	European Society for Medical Oncology (ESMO)
81	AESGP
82	Ministry of Health and Social Affairs,

1. General comments – overview

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2	Section 4.4 It is unclear to us, who will decide exceptions from publication The procedure should avoid misuse and exception should be reviewed and approved by the authorities, and not rely solemnly on sponsors decision. It is recommended that the reason for (the granted) exceptions are made public and searchable in the database to reveal any systematic attempts to deviate from publication
3	Make use of modern data standards and access methods to make the clinical trial database developer-friendly, the data machine-processable and the studies and their components linkable. Leverage initiatives and use principles such as CDISC Standards in RDF http://www.cdisc.org/standards/dataexchange, that uses modern data standards from W3C stack of semantic web standards, openFDA https://open.fda.gov/api/reference/, that uses developer-friendly REST APIs providing JSON, and the linked data principles http://5stardata.info/.
5	As the transparency rules will be quite complicated, we fully support that they should operate in an automatic way and be based on data fields and metadata. In the decision of publication, the need for human intervention should only be an exception. It is unclear from this document that which rules for publication of information should be used when a marketing authorization is granted for a medicinal product (with the same substance, indication and form combination) during the life cycle of the clinical trial. Transparency rules described in this document set requirements to existing (or non-existing) European level marketing authorisation database. Capabilities to fulfil these requirements should be verified.
7	CPME welcomes the European Medicines Agency (EMA) public consultation on the Draft proposal for an addendum, on transparency, to the "Functional specifications for the EU portal and EU database to be audited – EMA/42176/2014". Transparency of clinical trial data and results is essential to the good conduct of medical research, to the development of new medicines and medical treatments, to expand scientific knowledge on those medicines and treatments and for patient safety. CPME has a longstanding policy on medical research and repeatedly advocates for the need to ensure full transparency of clinical research (CPME 2012/132; CPME

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	2013/019; CPME 2013/088). Ensuring transparency is a matter of drug efficacy and safety, whereby information on clinical trials is publicly disclosed and hence made available to patients, prescribers and researchers. The broad access to data is crucial to develop innovation and stimulate further research. Transparency is also a matter of public trust and confidence in the European research community and the EU regulatory system for a safe evaluation and supervision of drugs in Europe.
8	*Translated from Danish:* "To the European Medicines Agency (EMA) Region Zealand considers it to be positive that EU takes an initiative to establish a gateway/portal for trials on medicines in EU. We are happy to participate in the work to come up with a solution which ensures that Denmark can be part of the work to approve clinical studies within the framework set out for the processes and approvals."
9	All clinical trials should be registered and all results reported. Some pharmaceutical companies, such as GSK, do not distinguish between their clinical trials and have committed to registering and reporting all trials they sponsor. This is the standard that can be achieved. We still haven't heard of any examples of information from registration or summary results that should be commercially confidential. Any deferrals to making information public must be justified and those justifications should be independently audited and policed. The phases of trials must be clearly defined and a differentiation made between trials in healthy volunteers and trials in patients. There must be prompt and public reporting of any serious adverse events seen in trials. If a trial is stopped because of safety concerns, information about that trial should be made public immediately.
10	Repeated comments The Medical Products Agency (MPA Sweden) sent comments on the document before the meeting at the 13th of January. Many other MS had similar comments. For the sake of clarity, we repeat our comments that concern sections of the document which have not yet been changed. Legitimate economic interest of the sponsor Where the 'legitimate economic interest of the sponsor' is explained (mainly lines 67-71 and 457-479) it should also cover aspects addressing investments in research, where e.g. premature publication of trial data could affect stock markets and valuation of both

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	companies investing in research and those involved in the development of new pharmaceutical products Recommendation on templates for submitting information In some cases, presentation of information in documents that are sent to the portal, or errors in MS' or sponsors' redaction in such documents, might lead to subsequent involuntary publication of either protected personal data or commercially confidential information. One example is clinical trial result summaries (section 4.3.1, lines 379-381), that might include information that indirectly can be associated with individuals, even if the information about adverse reactions is structured according to Annex IV and V. Another example is notice and summary of a serious breach (section 4.6.3, lines 827-841), that might include similar personal data. Being the data controller of the database, EMA bears the legal responsibility to make sure no such information is made public. The MPA Sweden realises that it is not possible for EMA to manually check submitted documents before they are made public, to make sure they don't contain confidential information and protected personal data. However, we recommend that EMA design templates och guidelines for filling them in for the different situations where there otherwise might be a risk that data/information is made public when it should not be. Such a guideline is already mentioned in section 4.8.2. We recommend that the Agency's legal responsibilities as data controller regarding the content of the database should be further clarified. Annual Safety Reports It is not clear where the repository for ASRs will be located and how it will be linked to the portal/database. It is stated in Article 40 that Annual Safety Reports (Art 43) will be part of the Eudravigilance system. However, such a repository does not exist today and it is not defined how transparency regarding this repository will be handled.
11	The Association of Clinical Research Organizations (ACRO) represents the world's leading, global clinical research organizations (CROs). Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics and medical devices, from discovery, pre-clinical, proof of concept and first-in-man studies through post-approval and pharmacovigilance research. Each year, ACRO member companies conduct more than 11,000 clinical trials involving nearly two million research participants in 115 countries. ACRO advances clinical outsourcing to improve the quality, efficiency and safety of biomedical research. Representing global CROs with more than 100,000 employees engaged in research activities around the world (including 30,000 employees in Europe), the competitiveness of the European Union as a location for clinical research is a key priority for ACRO. ACRO is pleased to provide comment on the EMA's Draft proposal for an addendum, on transparency, to the "Functional specifications for the EU portal and EU database to be audited (EMA/42176/2014).

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	Because ACRO member companies collect and process clinical trial data on behalf of sponsors, ACRO believes that sponsors and their associations (EFPIA and EuropaBio) have a principal interest in issues of clinical trial data transparency and publication. On Questions 6 – 11 (which address data publication and CCI), ACRO supports the positions of our customers and their associations. ACRO is pleased to offer comment on other key issues discussed in this draft proposal – such as inspection reports, serious breaches, and unexpected events.
12	**Overview General Comments Section** Support of EMA draft proposal in relation to Phase 1 clinical trials: • Commercial sensitivity • Application of status of marketing authorisation – *Our choice of proposal* • Publication of Phase 1 clinical trials' registration information • Publication of study and product specific documents: – Our choice of proposal Remaining issues and proposals: • Definition of "Phase 1" • Publication of (lay) summary reports **Support of EMA draft proposal in relation to Phase 1 clinical trials: Commercial sensitivity** • 80: "Phase 1 trials are commercially particularly sensitive […]" • 345: "In the case of Phase I clinical trials in healthy volunteers there is particular sensitivity about the commercial confidentiality of information on the trial. • 617: "Thus, the extent of information made public could progressively increase during the development period to the marketing authorisation of a medicine from first in human Phase I trials to post-authorisation Phase IV and low-intervention trials."

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	Support of EMA draft proposal in relation to Application of status of marketing authorisation We support Proposal 1.3: Commercially confidential information should be considered taking into account, in particular, the status of the marketing authorisation using the following concept: • "Once a marketing authorisation has been issued, by at least one Member State, for a medicinal product using that active substance and for the indication and formulation/route of administration under study." Justification: • A significant number of clinical trials conducted by EU Clinical Pharmacology Units investigate new indications, formulations and/or route of administrations. These studies are considered Phase 1 (non-therapeutic) clinical trials. • Sponsors do not wish to disclose information on new indications and/or formulations early, as this may affect patent protection. • If a marketing authorisation has been issued, by at least one Member State for the active substance contained in that product, a wealth of information is available to the public for the active substance concerned. • For non-therapeutic trials it would be difficult to justify an overriding public interest requiring publication of study specific and product specific documents prior to marketing authorisation for the studied indication, formulation and/or route of administration. • If early disclosure would be required in the EU, it is likely that these trials would be conducted outside the EU. **Support of EMA draft proposal in relation to Phase 1 clinical trials: Clinical trials' registration information** We support that the sponsor will have the possibility "to opt to have only very minimal public information at the time of decision on the trial" and for the "remainder to be made public at the point when the summary of trial results is published". Justification: • Commercially confidential information is protected • The proposed minimal information to be published is not commercially sensitive

Stakeholder no.	General comment (if any)
	• The registration of all trials will assure the public that trials are bona-fide and authorised and that further information will be made available **Support of EMA draft proposal in relation to Study and product specific documents** We support Proposal 4: • the distinction between non-therapeutic/therapeutic trials • and the staging of publication accordingly Justification: • The public will be able to access relevant information for all types of trials via the summary reports at predetermined time points • Protocols in particular contain information (as outlined in the draft proposal's section 4.4.1.2), that is likely to be considered commercially confidential beyond the time of summary report publication • For non-therapeutic trials it would be difficult to justify an overriding public interest requiring publication of study specific documents at the time of the summary report being posted • For therapeutic trials on the other hand there may be conceivable benefits of public access to the specified study specific documents at the time of the first summary report being posted (e.g. development of best methods and trial designs) **Remaining issues and proposals: Definition of "Phase 1"** The draft proposal appears to limit the definition of "Phase 1" to trials in healthy volunteers. Our proposed definition of "Phase 1" for the purpose of applying transparency rules: Phase 1 trials are clinical trials • using IMP, device & IMP/device combinations • performed in healthy volunteers and/or patients without therapeutic (or prophylactic) intent.

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	Justification: • An increasing number of innovative, non-therapeutic/prophylactic early phase (including First Time in Human) studies are conducted in patients with the target disease and/or a combination of healthy volunteers and patients • Our definition of "Phase 1" is in line with current relevant legislation in the UK and Belgium. It would be very disappointing and against the objectives of the EU CTR, if its implementation would use a definition of "Phase 1" which is very out-dated and which would hinder research and innovation in the EU. • During this phase of drug development there is particular sensitivity about the commercial confidentiality of information on the trial • In the draft proposal, the definition of "Phase 1" impacts on the whether or not sponsors will have the possibility to opt to have only very minimal public information at the time of decision on the trial • Most potential benefits of public access to information at the time of decision on a trial are not applicable to non-therapeutic trials, whether in adult healthy volunteers or patients • Publication of details of trials in patients without therapeutic intent may even be misleading as the potential indications mentioned in the protocol may raise unrealistic hope especially in end-stage diseases • The limitation to healthy volunteers will lead to a decrease in innovative non-therapeutic trial designs being conducted in the EU **Remaining issues and proposals: Publication of (lay) summary reports** The issue: • The draft proposal does not allow for a distinction between development stages of the product (phases of clinical research, therapeutic/non-therapeutic trials) or marketing authorisation status where the publication of summary reports is concerned • It is inconsistent with the spirit of the document and the CTR's definition of Commercially Confidential Information that summary reports should be published in all cases within 12 months after the end of a trial • It is unclear why the draft proposal does not acknowledge that summary reports can "contain extensive detail of a commercially confidential nature" whilst it does acknowledge this e.g. for the subject information sheet and protocol

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	Our proposal: • The same application of commercial confidentiality should apply throughout • If it is decided that the publication of summary reports should be at a fixed point following the end of a trial we propose to set this at a later time when the published information has ceased to be commercially confidential
14	EMA criteria to exclude dossier information must be stated and published previously to implementation of the database. The use of concepts phase I, II, III and IV implies a subjective interpretation and are not supported by EMA guidelines (ICH Topic E8, Note for guidance on general considerations for clinical trials, CPMP/ICH/291/95, March 1998). In the text of this proposal is not clear whether "the investigator" is the principal investigator or any investigator (including coordinator investigator, sub-investigator) or all investigators.
15	1. We support the general approach of this document that attaches overriding importance to public availability of the EU database. 2. We also support the general notion that there may be circumstances under which public availability of data may not outweigh an important commercial , personal or public concerns. 3. However we are concerned that in the current document predetermined arrangements are published, which in our opinion do not sufficiently take into account that the decision to not make data public are a balance of interests that have to be determined on a case by case basis 4. We therefore find the current document deficient in several aspects which we will outline below.
16	In general terms we think that this draft meets what is registered in European Clinical Trial Regulation Nº 536/2014 and its objectives
19	The increased transparency rules of the new regulation are welcomed and this will improve information to the public and to patients about clinical trials they might want to participate in (or indeed those they have already participated in). Greater transparency with lay summaries accessible through the portal will greatly enhance the ability of researchers to give feedback to participants on the results of trials. There should be monitoring of the number and nature of withheld documents should be reviewed on an ongoing basis to ensure the aim of greater transparency has been achieved. A published summary of which documents are withheld and the reasons why they have been

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	withheld identified during the monitoring would also be welcomed.
20	We appreciate to have the opportunity to comment on the "*Draft proposal for an addendum, on transparency, to the "Functional specifications for the EU portal and EU database to be audited - EMA/42176/2014*". The Arbeitskreis Medizinischer Ethik-Kommissionen in Germany fully supports the intent of the regulation 536/2014 to increase the transparency concerning clinical trials, in particular of the design and the results. We understand too that there is transparency needed about the sponsor, and all those who have a major and/or decisive influence on the design, the conduct, the statistical analysis, the interpretation and the publication of a clinical trial, i.e. e.g., the coordinating investigator(s), the responsible statistican, all authors, and the members of steering and data monitoring committees. We are concerned however, that the elucidations under "4.3.2 Clinical trial investigators and their staff" (line 382-408) do not comply with the principle of proportionality and may violate the rights to personal data privacy when it includes all individual investigators of all trial sites. The text asks that all investigators should be made public by name, institutional affiliation, CV and all potentially relevant economic interests. The currently most often used financial disclosure/conflict of interest forms ask for the economic interests of spouses and of underage children, too. Thus even the privacy of people who are in no way involved in a clinical trial is at risk. Today most trials of phase II, III, and IV are multicentre trials. Thus there are many study centres and many (principal) investigators. Given the ex- and intensive quality control of clinical trials by, inter alia, monitoring, audits, and inspections, there is little risk only that an individual physician by having an economic interest (e.g. shares of the sponsor) can influence the results of a trial. The work contracts of most hospital doctors (at least in Germany) cover the cooperation in clinical trials as an official duty without extra pay. Therefore, if the current wording of the Draft Proposal is kept, an investigator, even if he/she has no own choice about his/her trial participation as an investigator, will be published with full personal details (including his/her spouse and underage children) on EMA's webpage. We think that Article 81 (4) a), specifying that personal data should be protected, pertains to (principal) investigators of individual trial sites , in particular to their spouses and underage children, too. The qualification and the economic and other potential conflicts of interests of each investigator have to be disclosed in part II of the clinical trial application. The competent Ethics Committee will evaluate these disclosures whether they might interfere with the proper conduct of the clinical trial and decide accordingly, e.g. by granting or refusing approval of the physician as investigator. In our opinion there is no legitimate public interest which overrides the local investigators' rights for privacy. These sensitive personal data should not be made publicly available. In addition to these concerns about violating personal data privacy, we are anxious that the transparency as suggested by the Draft

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	Proposal may reduce the willingness of investigators to engage themselves in clinical trials. Considering "4.6.1. Inspection reports" (lines 788- 794) one has to keep in mind that the rights for data privacy have to be protected as well. Do inspectors' findings of minor or moderate importance really justify publishing the investigator's and the trial's centre name? This sounds like the reintroduction of a medieval pillory. Here we ask to consider a more harm-proportionate approach. A possible solution which combines the requirement of transparency and the entitlement for data privacy of the individual investigators is to provide aggregated or anonymized data for each trial only, i.e. data without personal references. In addition, we recommend to arange for a limitation time.
22	*General comment from the EMWA-AMWA Budapest Working Group* CSRs need to comply with the principles of responsible clinical trial data sharing because of the forthcoming disclosure requirements. This inevitably brings risks. There are calls for the principles of responsible clinical trial data sharing to be applied in our industry - through the EFPIA/PhRMA joint statement, and most recently, the lengthy IoM report published in the last week of January 2015. The EMWA-AMWA Budapest Working Group (BWG) is actually applying these principles and providing a resource for writing CSRs that helps practical application of responsible clinical trial data sharing. The resource is called the **C**larity and **O**penness in **R**eporting:**E**3-based (CORE) Reference. CORE Reference, developed by the BWG, will be contributed to by Stakeholders including representatives from the Drug Information Association [DIA] Medical Writing Community, Clinical Data Interchange Standards Consortium [CDISC]), patient advocacy and medical establishment representatives as well as regulators (from EMA, FDA and HealthCanada). CORE Reference will be available unrestricted and open access by mid 2016. Not all Sponsors understand how to safeguard patient anonymity in their CSRs. Inadvertent disclosure of patient information that could lead to individuals being identified must be addressed. The practical way to avoid this is through use of the CORE Reference, which complies with ICH E3 & the 2012 Q&A update, and all other existing and relevant guidelines. CORE Reference is not intended to replace any such guidelines, but rather serve as a User Manual to support CSR authors comply with existing ICH guidances, whilst safeguarding patient anonymity.
24	The European Hematology Association (EHA) welcomes the opportunity to comment on the draft proposal for the addendum to the "functional specifications for the EU portal and EU database to be audited" on the issue of transparency. In general, EHA supports the drive towards greater transparency of clinical trial results. EHA believes that the proposed addendum should

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	allow for enhanced insight into the studies that serve to increase the knowledge base of biomedical research and, for the Agency and Member States, serve to base decisions for marketing authorization on. Moreover, transparency of clinical trial results should allow for better verification of (long-term) outcomes, additional analyses, and avoidance of duplicate research. In addition, and rightfully so, the proposal stipulates the importance of transparency of clinical trial results and information to uphold public trust in biomedical research and to facilitate access to trial information and thus advance access to IMPs for patients. EHA acknowledges that exceptions to (immediate) disclosure apply. However, where transparency is the norm, exceptions necessitate satisfactory justification. Preferably, these justifications should involve the tremendous importance of the advancement of science, both in terms of its contribution to the attractiveness of Europe as a knowledge economy and of its implications to public health and quality of life of patients. In general, this appears to be understood by the Agency. On a more mundane note, EHA appreciates if the Agency allows for a longer consultation period (12 weeks, not 4, seems to be the standard with Commission consultations) in future consultations. We would understand that circumstances do not permit longer consultation periods, but we would in such cases like to be informed what these circumstances are.
25	We do not have comments, everything is very well planned. Only one question: Will all studies being announced on the EMA website and the clinicaltrials.gov site?
26	The draft appendices 1-7 to the draft proposal are clearly laid out in color-coded blocks with respect to the data fields required and the timing of submission in relation to market approval. However, the guidance does not specify the required format of the data to be uploaded into the database and, importantly, whether EMA intends to harmonize these requirements with NIH's structured tabular data entry system (currently found on ClinicalTrials.gov). The data entry system of ClinicalTrials.gov provides maximum flexibility for results submission, permits effective searching, and facilitates cross-trial comparisons. However, the ClinicalTrials.gov data entry process places significant burden upon responsible parties and sponsors by requiring the manual placement of individual results data points into the website or XML file. This burden is further compounded when the responsible party must comply with a separate data format when submitting to the Food and Drug Administration. For this and other reasons, the MRCT Center at Harvard urges that the EMA amend its proposed rule by adopting a standard data format consistent with CDISC SDTM and ADAM Data Submission Standards, to which the Food and Drug Administration has already made a commitment, and to which the MRCT Center at Harvard has urged that the NIH and ClinicalTrials.gov also commit. This would allow sponsors to create one clinical trial results file that is in compliance with both EMA and FDA standards. This approach would allow interoperability of the data, minimize data mapping requirements, and permit maximal utilization of the data for science and the public good. Further, this requirement may encourage academic investigators and other sponsors that do not

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	submit to the FDA to adopt the CDISC Data Submission Standards, thereby facilitate the merging of datasets for analyses.
26	We applaud the inclusion of the requirement for a layperson summary, proposed in Annex 6 of the draft proposal EMA/42176/2014, which is consistent with Regulation (EU) 536/2014 Annex V. We have drafted a guidance document – the *MRCT Center at Harvard Return of Results Guidance Document* and the *MRCT Center at Harvard Return of Results Toolkit* which were developed by a multi-stakeholder workgroup comprised of more than 50 members from industry, academia, patient advocacy groups and non-profit centers, coordinated by the MRCT Center at Harvard. Our detailed guidance document is fully consistent with the layperson summary proposed in the Regulation. In addition, the *MRCT Center at Harvard Return of Results Toolkit* includes templates and sample summaries for returning results to study participants, a table with common clinical trial endpoints in simple language, guidance on neutral language, a sample notification to third party form, and checklists for Research Result Summaries Reviewers and Ethic Committees. These resources provide user-friendly tools for implementing the guidance and for reporting in lay language and are publicly available. Furthermore, the *MRCT Center at Harvard Return of Results Guidance Document* recommends compliance with health literacy and numeracy standards and use of non-promotional language. These are critically important considerations, and we suggest the EMA adopt language supporting this approach in its current communication. Lay summaries will have maximum impact if they are written in compliance with health literacy and health numeracy principles. Health literacy principles include the use of short active-voice sentences, familiar vocabulary, descriptive headings and subheadings, and bullet points. Health numeracy principles include the proper use of graphs and tables, use of numerical examples, and the inclusion of absolute risk as context for relative risk. In order to facilitate the use of health literacy and numeracy principles, the MRCT Center at Harvard recommends further that the EMA release guidance on how to format and write lay summaries that are easy for the general public to understand. The MRCT Center at Harvard strongly believes that non-technical lay summaries can be written using neutral language that is not promotional. To facilitate the use of neutral language, we recommend that the EMA release guidance on how to write summaries that are non-promotional. We recommend that the EMA provide resources including user-friendly tools and templates to facilitate the implementation of and compliance with the final Regulation.
28	Reviewing the document we conclude that transparency is a prerequisite for good quality clinical research with medicinal products. However, the mere amount of details is overwhelming and will definitely work not only for lay persons but also for experts blur the message

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	and will diminish transparency. We recommend prioritizing the information given in the public sector. Reading this document we are not convinced that the implications for Intellectual Property are covered for both investigators and sponsors? This will definitely lead to the reaction that many sponsors will be reluctant to start a clinical study with their medicinal product in the EU. When details on a clinical study will be published (e.g. all long term safety data from a Phase III confirmatory study), then the competitor can adjust his strategy easily. How long will a registration file be protected once the licence has been granted? Although the communication on serious breaches and unexpected events is of vital importance to learn how to prevent such situations in the future, there is great danger that privacy issues concerning the involved parties will appear. The communication on these events should be conducted carefully (compared to the FDA approach on serious breaches, warning letters) in order to prevent incorrect media attention. There is a risk that this transparency approach will be contra productive. Transparency can evoke privacy problems when names of principal investigators, and other involved parties like contract research organisations are published during the conduct of a clinical study. It will become transparent for which company this CRO conducts which trials. The Clinical Trial Regulation and related documents should comply with the General Data Protection Regulation that will become law in 2016. The EU Portal and database is a detailed database with information related to clinical research sponsored by the pharmaceutical industry. This industry will train, instruct and qualify personnel to learn how to cope with the new EU portal and database. For investigator-initiated studies where the principal investigator acts as the sponsor of the study with the obligation to request for a EudraCT number and fill out the EU portal, the pharmaceutical nomenclature is a challenge. The extent of the EU portal and database will lead to many errors in the database when there is no proper validation (check with the source in the clinic) of the information. We have our doubts because the system is too complex; our experience (more than 38 years) in clinical research taught us that you should keep administrative matters as simple as possible; plain common sense should prevail.
29	Two key objectives of the Regulation (see 4.4 of the consultation document) are to provide extensive public information on clinical trials and to promote the EU as a location for clinical research. We agree that a good balance needs to be achieved with regards to the aim to make as much information available to the public as soon as possible and the exceptions foreseen in the Regulation in article 81 (4). Unfortunately, we do not find that the current proposal is meeting the requirements of Regulation 536/2014. The objective of the Regulation, to increase transparency has fallen victim to the intention to

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	protect commercially confident information. The proposal is in a lot of its parts focussed on recital 68 of the regulation, negating more or less recital 67. It was an important objective of the Regulation that more information should be published in the database than the information already available in clinical trial registries and that in general all information send with the application all information which is part of the application dossier) should be made available as early as at the time of the decision on the clinical trial. In several proposals of the consultation paper the time point for publication of relevant data/documents such as protocol, patient information sheet, IB, IMPD is suggested to be postponed to more than 10 years after this decision. I our view this cannot be regarded as a reasonable approach and is not substantiated by declaring that this information would be commercially confidential. To achieve the aim to foster progress in clinical research for the benefit of patients it is important that the information is published at a time where this is still relevant for the scientific community for scientific purposes. The information is needed as early as possible in order to enhance the further development of existing medicines and evidence-based improvement of treatments (see line 112 of the consultation document) and protecting public health and fostering the innovation capacity of Europe (see line 121/122 of the consultation document). In the consultation paper it is stated that public access is provided amongst others to “Acting as a knowledge management resource to foster innovation and stimulate and accelerate further research by building on accumulated knowledge and technical ability. This aims to avoid unnecessary duplication of clinical trials, and repetition of trials that have been terminated due to major safety or efficacy failures, or have demonstrated such failures even is the trial was completed. (line151 – 155) We do not see how this would work with proposals that postpone information on the clinical trials to more than 10 years after the decision on the clinical trial. We therefore propose to only make a distinction between non-therapeutic and therapeutic trials and would allow for non-therapeutic trials to publish the full information at the time the summary of the results is posted in the database. For all other trials (therapeutic and prophylactic trials) the information should in general be made public at the time of the decision on the clinical trial. Exemptions from this rule for therapeutic and prophylactic trials would be subject to a deferral that would have to be substantiated by the sponsor and be assessed by the Member States during the initial assessment of part I of the clinical trial. In our view with a deferral it should only be possible to postpone the time point to no later than the time the summary of results is posted in the database.

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	Furthermore, in our view it is also especially and equally important that all the information regarding clinical trials carried out with non-authorised medicines, in the early phases of development prior to marketing authorisation, which are never later used in a marketing authorisation as the development is discontinued, is published. For the scientific community it is important to know that ideas / hypothesis which have been followed have not worked out (either for the product, the indication ...) so that a duplication of efforts in the wrong direction can be avoided. It should be avoided that for the sake of an easy and automated handling of the database key objectives of the Regulation are disregarded. In case of major disagreements with regard to whether the objectives of the Regulation have been met, these should be resolved by the Member States and the European Commission and maybe the Parliament. In general the consultation paper would have gained from more clarity and less redundancies.
30	The proposal is clearly an attempt to balance “patients’ and doctors’ needs, the publics’ entitlement to extensive and timely information about clinical trials and developers’ and researchers’ need to protect their investments.” Unfortunately, this balance does not seem to be sufficiently achieved as too often the practical application of the transparency requirements is opaque and restrictive. The exceptions and the possibility to postpone the data publication increase along the document. Some of the solutions proposed are too complicated and, as they should be implemented automatically, the impression is that non-disclosure will be the rule, not just the exception. According to the Regulation 536/2014, the proposal states that when an "overriding public interest" exists "the general public interest in having information made publicly available may outweigh considerations that the same information should remain confidential". The public interest in having information made publicly available should be the rule and not applied to few critical situations. The implementation of more fair guidelines for transparency would lead to a more balanced approach toward patients and doctors needs to access the information they strongly contribute to generate. **What can be considered commercially confidential?** Our major concern is related to the definition of commercially confidential information. "Any information contained in the data or documents submitted to the database that is not in the public domain or publicly available and where disclosure may undermine the legitimate economic interest of the sponsor" is too vague and too open to misinterpretations. For instance, safety alerts in clinical trials may be

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	considered as data that may undermine the company interests and thus be withheld. While this may be correct from the company perspective, the interests of patients and the public must prevail. If not, a proper ethical balance cannot be achieved. Study documents and product documents cannot be considered as having the same level of commercially confidential information. It is widely accepted that clinical data cannot be considered commercially confidential. The European Ombudsman recently confirmed this view. If it is true that "complex documents included in the database" contain confidential and non-confidential parts, it must be the responsibility of the sponsor to redact out any commercially sensitive data pertaining to the trial so that such data can be hidden from the public. Such commercially sensitive data should not lead to hiding the whole document, which is necessary to understand fully the benefits and the harms of the intervention(s) in question. The sponsor should give a detailed account of any request for exceptions needed to protect commercial interests, which should exclusively focus on the medical product and not on clinical trial data. **Access to individual patient data** A second concerns is related to the access to individual patient data. The statement that "the database will not contain any individual patient listing from clinical trials" to avoid the disclosure of personal data seems a simple defensive way of argumentation. Data should be submitted to the regulatory authority in non-identifiable form, and de-personalized data should be preferred over anonymous data. The small risk of re-identification, which may exist in some limited situations (e.g., very rare diseases), and the procedures to mitigate it should be discussed more thoroughly and deeply and the EMA functional specifications modified, accordingly. The EMA Policy 70 on access and publication of clinical data, which partially overlaps with the content of the present proposal, was also very restrictive on the access to individual patient data. We encourage the EMA to align both policies towards the highest transparency standards possible.
31	IQWiG would like to summarise its main comments as follows: • New models of dissemination of clinical trial information are currently being discussed. The EU database (and other databases providing comprehensive study information) will have a major role in this new model of medical knowledge generation and transfer. Therefore, the specifications of the database need to meet the requirements of future knowledge generation. This increase in transparency is required for a better contribution of clinical trials and their results to the protection of public health as well as to innovation as laid down in the objectives of the EU Clinical Trial Regulation. • The suggested definition of commercially confidential information does not consider the general ethical requirements for research in

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	humans and the requirements laid down in the EU Clinical Trial Regulation. To meet the basic ethical requirements of research in humans and to allow for clinical trials to improve patient care (which is an overriding public interest) the methods and results of a clinical trial generally cannot be considered commercially confidential.
35	**Introduction** EUCOPE welcomes the opportunity of being involved in the process of determining how the transparency rules set out by Regulation No 536/2014 will be applied in the new clinical trial database. EUCOPE supports EMA's aim to balance the right of patients and the public to access timely information on clinical trials, and the developers' and researchers' need to benefit from investments (cf. page 2 EMA/35075/2015). EUCOPE further supports EMA's commitment to enhance "the EU as a destination for innovative, cutting edge research and development of novel products and research into new and better use of existing products" (EMA/641479/2014 lines 51 - 53) in connection with the aim "to ensure that such investment is attracted to the EU and is sustained investors and researchers have to be able to benefit from their engagement…" (EMA/641479/2014, line 159-162). EUCOPE considers the (technical) conception of the new portal and the new database to be of key importance with regard to the practical application of transparency rules. EMA will be the "data controller" as defined in Article 2d of Regulation 45/2001. Thus, EMA's responsibility for the development and maintenance of the portal and the database is as important as the security of the data. This is particularly important in light of EMA's obligations under the WTO Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) including Article 39(3) which requires that WTO Members protect pharmaceutical test data against both unfair commercial use AND disclosure. The EMA has to respect these (and other) WTO obligations. While the EMA has taken steps to prevent the "unfair commercial use" of an originator's data by a competitor to seek marketing authorisation in the EMA, the EMA cannot, as a factual matter, protect against such use in markets outside the EU. Similarly, the "unfair commercial use" of such data disclosed by the EMA is in no way limited to situations in which the released data is used to seek marketing authorisation; such released data could be used in ways that are not immediately apparent to the EMA or the originator of such data, such as when a competitor uses the released data to anticipate a new medical use, or as a means to secure an unfair advantage in locating their

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	own clinical trial sites. Therefore, while EUCOPE appreciates EMA's invitation to contribute comments we consider it vital that compliance with the EU's international obligations is observed. Further, given the rather short consultation period in relation to the proposal's complexity, EUCOPE would like to underline the importance of a continuous stakeholder involvement also after the consultation has been closed. **General Comments** **Safeguarding public health, innovation and market exclusivity rules** The new Clinical Trial Regulation aims, *inter alia*, to increase transparency and availability of information on clinical trials and their results. The aim of increasing transparency needs to be carefully balanced with confidentiality. In this respect, it is important that international law and international standards are observed to avoid negative consequences to public health and infringement of the fundamental rights of the sponsors according to Article 7 and Article 17(2) of the Charter of Fundamental Rights (see Comments to Questions 5 and 6). Safeguarding public health, stimulating research, boosting valuable innovation and supporting the competitiveness of the industry form the core objectives of the law and policy of the EU with regard to the pharmaceutical sector. In particular, innovation by the pharmaceutical industry contributes continuously to the improvement of public health. Thus, the new rules shall in particular not have any impact on the data and market exclusivity rules as provided for in Directive 2001/83. According to Article 10(1) of Directive 2001/83/EC applications for authorisations of generic medicinal products are only accepted in cases where the reference medicinal product has been authorised for not less than eight years and generic medicinal products shall not be placed on the market until ten years have elapsed from the initial authorisation of the reference product ("8+2 rule"). The Draft Proposal implies that clinical study reports including their appendices shall be generally made public once the marketing authorisation has been granted. According to the definition in Article 2(35) of Regulation 536/2014 the clinical study report shall be prepared in accordance with Annex I, Part I, Module 5 of Directive 2001/83/EC. According to Annex I Part I, Module 5.2 c) and e) a complete set of the trial documentation (e.g. the case report forms) only needs to be made available if requested by competent authorities. As the practical experiences made so far show the submission of the study report (including its appendices) is sufficient in marketing authorisation procedures. If these study reports including their appendices became publically available immediately after the authorisation has been granted, competitors could easily download originators' reports and use them immediately for applications of marketing authorisations for generics

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	undermining the 8+2 rule. This would be possible, because for applications for marketing authorisation pursuant to Article 8 of Directive 2001/83/EC (as further outlined in Annex 1 to this Directive), solely the clinical trial results as such are required (Article 8(i) of Directive 2001/83/EC) but no additional statement to the effect that the trial sponsor (if different from the applicant) agrees to the use of the trial in the application. As a result, the 8+2 rule for generic applications under Article 10(1) of Directive 2001/83/EC could be easily circumvented. Instead of awaiting the 8 year period for generic applications, applicants could simply download from the EU database and use the clinical study reports of "foreign" sponsors for their own applications. According to current legislation the competent authorities have to accept those applications. Many investments of originators into clinical trials for marketing authorisations would, then, from an economic perspective not make sense any more. This would be contrary to the EC political intention to foster innovation in the EU. Therefore, EUCOPE proposes, in order to exclude such foreseeable practices with high political impact on the EU market, that at least the appendices of the clinical study reports should generally not be made public as long as Directive 2001/83/EC or its Annex 1 is not amended in a way to exclude such practices. This is also crucial in relation to achieve alignment with EMA Policy 0070 on publication of clinical data for medicinal products for human use. In the "Terms of Use" for users which have registered with the EMA website to receive access to the Clinical Reports, the user may not use the Clinical Reports to support an application to obtain a marketing authorisation and any extensions or variations thereof for a product anywhere in the world (pages 11 and 14 of the Policy). In addition, the transparency rules in relation to the EU portal and database must not interfere with the market exclusivity granted to authorised orphan medicinal products pursuant to Regulation 141/2000. Providing access to detailed clinical information undermines the balance struck by the EU legislation to stimulate the necessary development of products for unmet medical needs. Data for orphan medicines is particular difficult to obtain and there is less of it given smaller population pools and limited understanding of rare diseases. Releasing this information would cause disproportionate harm to companies seeking to develop orphan medicines by unfairly providing competitors with this valuable data. Creating such disincentives for research and development in therapies for rare diseases would be contrary to the intent of Regulation 141/2000 and would not serve the best interests of patients with unmet medical needs. EUCOPE therefore recommends that data related to orphan-designated medicines be exempted entirely from release under the EMA regime. EUCOPE highlights the following specific examples where data related to orphan-designated medicines most acutely warrants exemption:

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	1) Information on Product Development and Planning Orphan medicines are governed by Regulation 141/2000. The regime includes two special characteristics that provide for a unique competitive element: (i) The product first obtains an orphan designation, typically in the early phase of the development (based on the "orphan indication"). The ultimate approved therapeutic indication (part of the marketing authorisation) routinely falls within the orphan indication but is much more precise and narrow. The wording of the approved therapeutic indication - possibly further extended after variation procedures - defines (within the limits of the orphan indication) the scope of the market exclusivity. (ii) The market exclusivity blocks any approval of a second product with the same or similar active ingredient and for the same therapeutic indication for ten years. There is thus a need to obtain the first approval for a specific indication in a manner that is unique to orphan medicines. Based on these characteristics, the development programs of orphan medicine companies are inherently confidential and information on product development and planning should never be disclosed (except when the company disclosed them voluntarily). **2) Pharmacokinetic and pharmacodynamic details** Pharmacokinetic and pharmacodynamic details (including steriochemistry issues) can be of significant importance for ensuring optimal suitability of the orphan medicines for the specific target patient population, which is often defined in detail in the therapeutic indication. Such details can also be specifically relevant for demonstrating significant benefit over existing therapies (to obtain and maintain orphan designation) and for demonstrating clinical superiority (to break the orphan exclusivity of another product). Regarding clinical superiority, the Commission guideline on derogations to orphan market exclusivity expressly recognizes the difficulty in designing and conducting studies to demonstrate clinical superiority and recommends that if an applicant is seeking to rely on the clinical superiority exception that it should seek scientific advice or protocol assistance on the appropriateness of the studies it intends to conduct. Consequently, clinical data relating to the precedent orphan medicine is invaluable to an applicant seeking to demonstrate clinical superiority and challenge the market exclusivity of the authorised orphan product. In particular, as both clinical study reports and clinical summary overviews for orphan medicinal products provide detailed patient level information given the rarity of the condition and the limited number of subjects in trials. Competitors can use such information to inform their study strategies aimed at demonstrating clinical superiority and thereby obtaining access to the market during the traditional market exclusivity period.

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	In addition, allowing access to such information when a marketing authorisation is refused or the application is withdrawn - with the possibility of resubmitting later - increases the chances that a product would no longer qualify for orphan medicine designation under Articles 3 and 5(12)(b) of Regulation No. 141/2000, undermining the purpose of the Regulation, i.e. to encourage development of orphan medicinal products. Predictability on available treatments is crucial for both, patients and pharmaceutical companies. **3) Benefits and Risks Conclusions** The benefits and risks conclusions may provide insights in the likely development plans of the company and how the company makes scientific judgments based on very limited datasets. This is of major importance in light of the market exclusivity attached to the first approved orphan product. In addition, justifications for deviation from regulatory advice outside the EU contain valuable regulatory know-how that can be used by competitors. **4) Biopharmaceutic Studies and Associated Analytical Methods** Biopharmaceutics aspects can be of significant importance for ensuring optimal suitability of the orphan medicines for the specific target patient population, which is often defined in detail in the therapeutic indication. Such biopharmaceutics details can also be specifically relevant for demonstrating significant benefit over existing therapies (to obtain and maintain orphan designation) and for demonstrating clinical superiority (to break the orphan exclusivity of another product). Significant benefit and clinical superiority could, for instance, be based on a new pharmaceutical form that presents important patient benefits and its development will be based in part also on bioequivalence studies. Such biopharmaceutics data could be unfairly used by a third company to support its own claim of significant benefit or clinical superiority. In addition, allowing access to such information also when a marketing authorisation is refused or the application is withdrawn - with the possibility of resubmitting later - increases the chances that a product would no longer qualify for orphan medicine designation under Articles 3 and 5(12)(b) of Regulation No. 141/2000, undermining the purpose of the Regulation, i.e. to encourage development of orphan medicine products. **Clinical Trials on products with a MA** (Phase IV trials and low-intervention trials) Taking into account the above considerations, EUCOPE agrees with EMA's proposal to publish the study and product specific documentation

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	at the time of the decision on the trial, providing that the sponsor will be given the option to defer this publication. **Alignment with EMA policy 0070 – CSRs** EUCOPE welcomes EMA's position to align the requirements for content of Clinical Study Reports (CSR) and redaction of CCI with EMA's policy 0070 on access to clinical study data. However, EMA should stick to internationally harmonised CSR standards and not change the structure of CSR unless agreed at an international level, e.g. through ICH. EUCOPE would like to raise awareness of considering adequate technical provisions for CSR at an early stage of development of the database and portal. As such we propose that the requirement to submit CSR 30 days after MA will be fulfilled by sponsors by hyperlinking to the published CSR made available in a system by EMA under Policy 0070. EMA will publish all CSR that are part of the marketing authorisation application. Hence, this system will include EU and non-EU based CSR and is as such the broadest available source of information. It will by default contain all EU clinical trials intended for obtaining a MA and hence be compliant with the requirements of the Regulation. Such a mechanism would allow streamlining of submissions and avoid any unnecessary operational complexity or duplication. This is of particular importance for SMEs. **Clinical Trials on products without MA (trial I, II, III trials)** EUCOPE appreciates that for Phase I, II, and III trials the study specific and product specific documents (with the exception of the IMPD-Q and the IB section, which should not be made public at any stage) should only be made public at the time of marketing authorisation or nine years after the first summary results are posted as presented by EMA in "6.2. Proposal Two". EUCOPE supports EMA's approach that only validated applications should be made public. Furthermore, EUCOPE strongly agrees and asks EMA to strictly take responsibility and provide technical provisions that no data from the CT application dossier are made public before the decision on the CT has been taken according to Article 81(5) of Regulation 536/2014. **Update of the Database** According to Article 84 of Regulation 536/2014 the Agency shall update the EU portal and the EU database in accordance with the experience acquired during the implementation of the Regulation. EUCOPE strongly suggests that in the beginning, until further experience has been gained, EMA should take a broad approach in relation to

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	accepting CCI defined by the sponsor. EUCOPE asks EMA for close cooperation and involvement of stakeholders concerning experiences gained before further action is taken and that this should be done in a timely manner. **Protection of Personal Data** According to Article 81(7) of Regulation 536/2014, no clinical data of subjects (participating in a clinical trial) shall be publicly available (and only be contained in the database to a limited degree). EUCOPE suggests that in relation to clinical trials with a small number of patients (clinical trials in rare diseases) such data shall not be released in order to avoid identification/traceability of these patients. **Harmonisation with related Databases** As the EMA should avoid unnecessary duplication between EMA systems as per Article 81(2) of Regulation 536/2014 "… and hyperlinks shall be provided to link together related data and documents held on the EU database and other databases managed by the Agency," EUCOPE appreciates a pragmatic approach to avoid unnecessary bureaucratic burden. With regard to streamlining processes for all involved parties EUCOPE appreciates ONE single point of entry of CSR with reference / link to other international databases, e.g. clinicaltrials.gov
36	Faculty of Pharmaceutical Medicine of the Royal Colleges of Physicians of the UK (FPM) is a professional membership organisation and standard-setting body, with over 1,500 members, who are pharmaceutical physicians or those with a professional interest in the specialty. Our mission is to advance the science and practice of pharmaceutical medicine by working to develop and maintain competence, ethics and integrity and the highest professional standards in the specialty for the benefit of the public. The FPM is a registered charity (no. 1130573). The FPM has recently produced two documents of relevance to this consultation. These are *Good Pharmaceutical Medical Practice* (FPM 2014) and the *Report on the Survey on Transparency in Clinical Trials* (FPM 2014). Our responses to the consultation, as set out below, are broadly based on the positions contained within these documents. The Faculty of Pharmaceutical Medicine supports the principle of transparency in clinical trials. All clinical trials should be registered and the summary results made available on completion of the study and before consideration of individual patient data within the program. The EMA will need to increase its staff if it is to fulfil the expectations for full disclosure. For the moment, the EMA seems understaffed for this vital regulatory role. If redaction of material is to be made available, the FPM would strongly advise that the decision to do so resides with

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	the Regulatory Authority. There is a danger in the current proposals that the accessibility of the EMA will not be aligned to the FDA. This could ultimately hamper the progress of R&D and may lead to delays in bringing new medicines to market in the EU.
37	We would like to thank the EMA for this opportunity to express our comments on this highly important issue. Overall, we take the view that the document goes in the right direction. Our more detailed comments are set out below. From a more general viewpoint we would welcome more information on the financial impact that the implementation of this transparency policy is deemed to have on Member States' administrations. We would also like to stress the importance that it becomes crystal clear for stakeholders and the sponsors in particular which information is deemed CCI and which is not in order for them to carry out their tasks and minimize the risk for errors. We are aware that your document "EMA/768628/2014" of 20 January 2015 is currently outside the public consultation, but we would like to inform you of the following. It seems that this draft appendix contains some mistakes as regards phase I studies, as the disclosure should follow the status of the IMP (with or without marketing authorisation) and not the time of publication of the results (this is probably due to "cut and paste" errors).
39	**Foreword** ***Access to clinical data (efficacy and safety data) protects public health from preventable harm*** Public access to full clinical data, including raw data, is particularly important to protect public health as it allows for independent analysis, enhancing knowledge about the real effects of medicines and allowing comparative effectiveness reviews[1]. Yet, the EMA draft proposal for an addendum, on transparency, to "the functional specifications for the EU portal" will prevent the reanalysis of data by independent stakeholders: no access to individual participants' data (raw data) even if they are anonymised, extensive delays in the publication of the information up to 10 years, etc. (read below) This goes against the requirements and objectives of the Regulation (EU) No 536/2014, especially that of increasing the reliability and robustness of clinical data.

[1] Tucker M "How should clinical trial data be shared?" BMJ 2013; 347 doi: http://dx.doi.org/10.1136/bmj.f4465

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39	***Clinical data belongs to the public, not to pharmaceutical companies*** The clinical data held by the new EU Clinical Trial Portal will be related to clinical trials conducted under the auspices of the Declaration of Helsinki. The Declaration of Helsinki explicitly refers to the ethical obligation to disclose the results from research and insists on the completeness and accuracy of the reports (articles 30 and 33)[2]. In fact, patients accept to put themselves at risk, taking part in clinical trials, notably in the hope that their participation will benefit society through the advancement of science. The WHO Informed Consent Form Template for Clinical Studies clearly divides benefits into: "*benefits to the individual, benefits to the community in which the individual resides, and benefits to society as a whole as a result of finding an answer to the research question.*"[3] Yet science is hampered when data from these studies are never made public, which is often the case especially when their results do not favour the sponsor's product- "publication bias"). Since publication bias and the selective reporting of positive study results are widespread practices in biomedical research, failure to make all the data available greatly diminishes the social value of research[4]. Granting public access to detailed clinical data, including raw data, is crucial to minimise dangerous practices of reporting bias, which overrate the benefits of a drug while underestimating its harm[5]. Moreover, industry-funded research often benefits from publicly funded research bodies (access to investigators and research teams at publicly research sites; public funding for basic research through EU grants and Member State funding, etc.). It is therefore more than reasonable to expect that all data from biomedical research is made publicly available. **Outcome (if applicable):** Emphasize in the document that clinical data is scientific data of an overriding public interest and therefore a public good (and adapt CCI definition – read below).
39	***The EMA restrictively misinterprets Regulation (EU) No 536/2014***

[2] Helsinki Declaration available at: www.wma.net/e/policy/b3.htm.
[3] WHO Informed Consent Template Form. Available at: http://www.who.int/rpc/research_ethics/InformedConsent-clinicalstudies.doc
[4] McGauran N, Wieseler B, Kreis J et al ''Reporting bias in medical research- a narrative review'' Trials 11:37 (2010)
[5] Gøtzsche PC. ''Why we need easy access to all data from all clinical trials and how to accomplish it.'' Trials, 12:249 (2011) doi: 10.1186/1745-6215-12-249

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	As soon as the Clinical Trials Regulation was adopted, the European Federation of Pharmaceutical Industries and Associations **(EFPIA) called in particular for "*the Commission and EMA [to] interpret the Clinical Trial Regulation in a manner that respects (...) incentives for companies*** *to make long-term investments in biomedical research*" [i.e to protect what they consider commercially confidential information][6]. Judging by the draft consultation paper, their demands have been widely accommodated. The EMA's interpretation of Regulation (EU) No 536/2014 does little to meet the needs of patients and the public across the European Union but goes a long way to soothe the requests of "clinical trial sponsors" such as the pharmaceutical industry, by **introducing non-disclosure as the norm** and by providing all the wiggle room sponsors need to circumvent their legal obligations to disclose clinical trial data (read below).
43	The *Spanish Association of Pharmacists in Industry* (AEFI), as a representative organism of pharmacists and other professionals that serve in Industry, has NO COMMENTS on the **Public consultation on application of transparency rules of EU Clinical Trial Regulation (EMA /35075/2015).**
44	**The value of sharing clinical trial data to the rare disease patient community:** Many rare diseases are severe and life-limiting. For individuals or families affected by most rare diseases, the day-to-day challenges of managing a severe condition are made worse by the absence of an effective treatment or cure. These patients look to research as the source of new therapies to address their unmet health need. In order for progress to be made, patients recognise the value of transparent data sharing, nationally and internationally. Given the rarity of their conditions, they also recognise that this comes with the inherent risk that they could be identified personally from the information published on clinical trials. Despite this, rare disease patients are generally very willing to share their medical data in order to drive research[7]. It is therefore essential that there are effective systems in place to facilitate the sharing of data for these purposes whilst reassuring those

[6] "EFPIA calls for collaboration in the implementation of clinical trials regulation following vote in the European Parliament" press release, 3 April 2014: 2 pages.
[7] EGAN Patient Charter: 'Genome sequencing: What do patients think?', February 2015, available at: http://www.geneticalliance.org.uk/docs/patient-charter-genome-sequencing-what-do-patients-think.pdf

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	that participate that their data will be stored and shared safely and accountably. EGAN speak on behalf of patients when we welcome greater sharing of clinical trial data throughout the union due to opportunities this will provide to improve our understanding of rare diseases and therefore our ability to develop new treatments.
45	The transparency of clinical trial information should be a welcome step towards increasing public confidence in clinical research.
47	EORTC strongly supports the proposed functional specifications and solutions. EORTC believes proposals in general correspond to the requirements of the regulation and sponsor's needs, at least as far as drug trials are concerned. However, EORTC believes these proposals do not always reflect needs of multimodality trials where confidentiality may not be related to the drug, but to another aspect, such as for instance, companion diagnostics test. EORTC would like to illustrate this comment with the following project that falls under the CT regulation: ***EORTC-10041-BCG*** MINDACT (Microarray In Node-negative and 1 to 3 positive lymph node Disease may Avoid Chemo Therapy): A prospective, randomized study comparing the 70-gene signature with the common clinical and pathological criteria in selecting patients for adjuvant chemotherapy in breast cancer with 0 to 3 positive nodes" This trial uses drugs registered since long time and it aims to validate a gene signature. Though the signature itself is not described in the protocol, it can be anticipated that during the evaluation more information would be asked about the signature and methods used, which information would be considered CCI. Therefore, there would be a need to keep this supplementary information confidential.
47	Questions 1 to 5: EORTC confirms these proposals meet requirements of the regulation 536/2014. Other considerations are specified below.
48	IPFA appreciates EMA to provide Industry the opportunity to express their position on the highly debated transparency issue with the addendum on transparency to the "Functional specifications for the EU portal and EU database". However, this new pathway imposes to the Industry a huge new administrative burden which will impair its competitiveness with clinical trials in Europe. The Regulation (EU) No 536/2014 states that the information described in the Draft proposal should be presented in the database and also defines information that is commercially confidential. It does not state that this means automatic public posting for all information at any

Stakeholder no.	General comment (if any)
	time. Of course, personal data confidentiality rules would be followed by EMA at any stage of the process. If clinical study information were made public at a very early stage, more work load would be needed within the companies to adopt an internal securing system to make sure that the early public disclosure of clinical trial information will not hinder publication of patents. IPFA also supports all and other EFPIA Comments
50	Dear EMA, thank you for asking my view on the “Functional specifications for the EU portal and EU database to be audited”. I am concerned that you seem to subordinate the interests of those humans undergoing experiments and of society to the private interests of sponsors. Experience has shown that all parts of clinical study reports should be made public, without additional anonymisation of those responsible for the trial or for reporting it. From this general statement I would only exempt already anonymized individual listings and phone/fax numbers and email addresses of sponsors, CSR authors and researchers. Any proposal not to disclose investigators brochures and trial meta-documents, as well as full protocols with their amendments are unacceptable. The doscuments are essential for a correct and fair reconstruction of trial programme, pre clinical assessments and the evolution of the trial(s) in question.
51	In general, the BPI appreciates transparency. Transparency as it is currently practiced is already appropriate and sufficient and enables interested parties to extensively access clinical study. The short consultation deadline for this proposal leaves stakeholders insufficient time for response. It is unreasonable to expect stakeholders to provide adequate data, facts and circumstances for the cases mentioned in the draft addendum after verifying legal, scientific and commercial, especially commercial confidentiality aspects of the proposed transparency rules. The proposed publication requirements far exceed the international standards, such as those defined for registries by the World Health Organisation (WHO).
52	From Dr. Giovanni Ghibaudo, Investigator, email: gioghi1@alice.it : • In the "*new clinical trial portal and database*" how the Italian Ethics Committees will be counted?

Stakeholder no.	General comment (if any)
	From Dr. Viviana Mascilongo, Regulatory Affairs Responsible DRN Srl, email: regulatory@drnsrl.it : • On demand a demo of the computer program "*new clinical trial portal and database*" to be downloaded, to be tested for 15 days, to send new pragmatic comments to EMA before its final implementation.
53	SIOPE strongly supported the inclusion of the articles in the Regulation (EU) No. 536/2014 'The Clinical Trial Regulation' that aim to promote transparency in reporting of clinical trials including the registration of all clinical trials within a public registry. We have responded to the specific questions raised in the 'Draft proposal for an addendum, on transparency, to the "Functional specifications for the EU portal and EU database to be audited - EMA/42176/2014' below. In general we are supportive of the proposals as outline and strongly support the principle that the extent of information made public could progressively increase during the development period to the marketing authorisation of a medicine. There are 2 specific points with which we do not agree and that we propose should be amended: 1. **Differentiation of processes for assessing commercially sensitive information (CSI) for phase IV and low-intervention trials:** the proposal to apply a different process of assess the time points for release of data pertaining to a trial for phase IV and low-intervention trials adds unnecessary complexity to the process. A decision of whether the trial has commercially sensitive information should be part of the assessment process and the outcome should follow a simple algorithm with decision points; ie no CSI or CSI and if CSI; the options for time points for release of information defined for each scenario. The division of the trials into simple categories of phase I, II, III, IV will lead to confusion. The innovations in methodology being applied to modern trials; ie randomised phase II, multi-arm, multi-stage (MAMS), Adaptive designs, and Bayesian methodology are blurring the margins between phases of trials. The categories of trials need to be considered more in terms of intended outcome of the trial and whether the trial contributes to the decision to develop a drug towards a marketing application (MA). 2. **Publication of inspection reports and serious breaches**: We have significant reservations regarding the publication of serious breach information and consider that the proposal for the addendum DOES NOT meet the requirements and objectives of the Regulation; as stated in Article 77 but is an excessive public release of trial conduct information which could be inappropriately detrimental. To meet the requirement and objectives of the Regulation, it is suggested that a summary of a serious breach and the measure should be published ONLY IF the actions described in Article 77 1a-c occur: i.e. the member state revokes the authorisation of a trial, suspends

Stakeholder no.	General comment (if any)
	a trial or requires the sponsor to modify any aspect of the trial. All these points would be clear and in the public interest.
54	We would like to thank the EMA for providing us the opportunity to comment on the public consultation on application of transparency rules of EU Clinical Trial Regulation. This is the response from the UK Government and has been agreed cross-government.
55	The consultation relates to implementation of transparency requirements of the European Clinical Trial Regulation. However the title of the consultation document is “Draft proposal for an addendum, on transparency, to the “Functional specifications for the EU portal and EU database to be audited”. The lack of appropriate key words in the title may have significantly limited the reach of the consultation.
57	EuropaBio welcomes the opportunity to submit these comments and observations on the European Medicines Agency’s draft proposal for an addendum, on transparency, to the “Functional specifications for the EU portal and EU database to be audited – EMA/42176/2014”. EuropaBio and its members fully support the EU Clinical Trials Regulation which will streamline the authorisation process and harmonise requirements for the approval and conduct of clinical trials, thus making it easier to develop innovative medicines for patients. We are also supportive of increasing the level of information publicly available for clinical trials conducted in the EU, and the new clinical trial portal and database under development is the key instrument for research transparency. The document issued for consultation sets out proposals and options on the application of exceptions to the transparency requirements provided in Article 81(4) of the EU Clinical Trials Regulation: (a) protecting personal data; (b) protecting commercially confidential information; (c) protecting confidential communication between Member States; and (d) supervision of clinical trials by Member States. It is important to ensure that a balanced approach is taken that respects both the right of patients and public access to information held on the EU database concerning ongoing clinical trials, and the needs of developers and researchers to protect their investments and cutting edge research and development of new, innovative medicines. Making Europe a globally attractive location for clinical research is essential for economic growth, creating highly skilled employment opportunities in the life sciences sector and giving patients the opportunity to participate in clinical trials on innovative medicines. EuropaBio comments in response to the questions posed in the consultation document are outlined below (see specific comments). In addition we wish to highlight the following key issues for further consideration by the EMA, the European Commission and the Member States before finalisation and endorsement of the addendum on transparency:

Stakeholder no.	General comment (if any)
	1. Deferral for disclosure of information and summary results from Phase I trials in healthy volunteers and patients, noting the commercial sensitivity of information on these trials 2. Application of the status of marketing authorisation of the medicinal product 3. Approach to clinical trials on products without a marketing authorisation, noting the need for adequate protection of sensitive and commercially confidential information on new and future indications and pharmaceutical forms included in the study and product specific documents 4. Ensuring alignment of EMA's policies and processes regarding the preparation of clinical study reports (including relevant appendices) and redaction of personal data and commercially confidential information to provide consistency and avoid unnecessary bureaucracy.
58	The Biotechnology Industry Organization (BIO) thanks the European Medicines Agency for the opportunity to submit comments in relation to the *EMA Public consultation on application of transparency rules of the EU Clinical Trial Regulation.* BIO represents more than 1,000 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment. BIO supports and endorses the comments submitted on this public consultation by the European Associations for Bio-Industries (EuropaBIO) to the Agency.
60	Regeneron welcomes the detailed guidance provided by the agency on the operation of transparency rules under the new Clinical Trial Regulation 536/2014, and the opportunity for stakeholder comment on these important considerations.
61	LEO Pharma welcomes this addendum and is generally in agreement with the proposals. Detailed comments can be found below. In the document it is stated that rules for public access to the EU database should operate automatically (line 293-303). LEO Pharma would like to submit that, due to the variety of trials, it could be wise to have an ad hoc review procedure when needed on specific points. In addition, it may be considered to have a recall system in place in order to withdraw information which have been put into the database by mistake.

Stakeholder no.	General comment (if any)
62	The guideline relates to 'clinical trials conducted in the EU'. Please clarify what this means, especially in the context of global clinical trials (e.g. with patients recruited from Europe, US, Asia). Does this mean clinical trials with at least one patient recruited from Europe? Or does this mean the Clinical Trial Application need to be submitted in Europe?
64	**In reply to the EMA consultation:** 1. **The main problem,the lack of homogeneity of the quality with which a clinical trial is conducted in the different European countries and member states remains.** a) Indeed, the crucial aspects of performing a clinical trial are still under the national legislation of the member states. "determine the appropriate bodies …" As long as this rule holds, Europe will not be able to compete with other countries such as the USA. Example: The radiation safety authorities delay trials in certain European member states by more than year, whereas other countries grant permission in a few weeks – for example if you have to perform a chest x-ray as part of the screening program or as part of the endpoint assessment. In some countries the honorarium for the work done by the study physician is payed to the private account of the PI – thus there is a bias in the motivation to enter patients into a trial by PIs in certain countries. In some countries patients entering a clinical trial receive a clear advantage as they have access to doctors and facilities not covered by the national health system. b) The diagnostic certainty of physicians in different member states for a given disease is different. 2. Another aspect is the hurdle for academician (investigator) to initiate and to conduct clinical investigated driven research (so called IIT trials) has increased over the last years. Thus the opposite is the case: EMA regulations do not facilitate IIT trials – one of the key projects which contain innovations.

Stakeholder no.	General comment (if any)
	3. Last but not least, financial issues represent significant barriers: The financial support from the national research agencies and the European research programs for company-independent clinical trials is low – at least in most of the Member states – thus this makes it nearly impossible to perform a multinational clinical trial without support of a company. In fact the financial support even in programs such as Horizon 2020 or JPND is very low when compared to similar programs in the USA. This fact reduces the competitiveness of European clinical trial consortia – in comparison to The financial support from the national research agencies and the European research programs for company-independent clinical trials is low – at least in most of the Member states – thus this makes it nearly impossible to perform a multinational clinical trial without support of a company. In fact the financial support even in programs such as Horizon 2020 or JPND is very very low compared to similar programs in the USA. This fact reduces the competitiveness of European clinical trial consortia – in comparison to the USA.
65	**Introduction** EFPIA, EBE and VE welcome the opportunity afforded to comment on the EMA's *Draft proposal for an addendum, on transparency, to the "Functional specifications for the EU portal and EU database to be audited – EMA/42176/2014"* (referenced as 'draft Addendum' in these comments). EFPIA brings together 33 European national pharmaceutical industry associations as well as 40 leading companies undertaking research, development and the manufacture in Europe of medicinal products for human use. EFPIA and its member companies, as the largest contributors to clinical research in Europe, offer our perspectives on approaches intended to optimally balance public access to clinical trial information whilst ensuring more efficient patient access to new innovative treatments. EBE represents the developers of biological medicines and includes European based multi-national and small and medium-sized enterprise (SME) companies. VE represents innovative research–based global vaccine companies as well as SMEs operating in Europe. Biopharmaceutical companies are indeed committed to advancing public health goals through responsible sharing of their clinical trial data in a manner which is consistent with the following imperatives: • Safeguarding the privacy of patients; • Preserving scientific rigor and the trust in the regulatory systems; and

Stakeholder no.	General comment (if any)
	• Maintaining incentives for investments in biomedical research. Building upon the foundation of these imperatives, in 2013, EFPIA (along with the Pharmaceutical Research and Manufacturers of America) adopted Principles for Responsible Clinical Trial Data Sharing. These set out industry's commitments to: (i) enhance data sharing with researchers; (ii) enhance public access to clinical study information; (iii) share results with patients who participate in clinical trials; (iv) certify procedures for sharing clinical trial information; and (v) reaffirm commitments to publish clinical trial results[8]. Inherently, we fully support the provisions in the Clinical Trial Regulation that allow EU citizens to have access to information about clinical trials (Ref: Article 81(2))[9]. We regard a main benefit will be to enable patients and healthcare professionals to more quickly identify clinical trials and evaluate the relevance of these to an individual patient's condition. Access to information and enrolment in clinical trials should be key considerations together with establishing the right balance between openness and protection of personal and commercially confidential information when implementing Article 81. Over the last several years, EFPIA has contributed ideas and commentary to the EMA on this topic during its public workshops and draft consultations attempting to achieve a balanced approach to the transparency of clinical trial information. We fully support EMA's aim expressed here that a "balanced approach is needed to protect public health and also foster the innovation capacity of European medical research, thus supporting the EU as a location for innovative, cutting edge research that results in development of novel products and research into new and better uses of existing products"[10]. Indeed, following our review, EFPIA believes that the proposals from the EMA, for the most part, support this aim. EFPIA, whose views in this response are supported by EBE and VE, appreciates that the Agency has outlined important options for stakeholder consultation and we therefore offer these constructive comments to assist the EMA in achieving its essential intent to "strike the right balance"3. Within our specific comments we have addressed those EMA questions that EFPIA believes have a substantial impact on the innovative pharmaceutical industry. In addition, EFPIA, EBE and VE look forward to future opportunities to continue this dialogue with EMA to realise optimal solutions for these complex issues. **Major Comments**

[8] http://transparency.efpia.eu/uploads/Modules/Documents/data-sharing-prin-final.pdf [accessed 26 January 2015]
[9] REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC.
[10] 'Draft proposal for an addendum, on transparency, to the "Functional specifications for the EU portal and EU database to be audited – EMA/42176/2014'

Stakeholder no.	General comment (if any)
	Proposed Timeline for Disclosure of Phase I Information and Results EFPIA appreciates EMA's acknowledgement of the particular commercial sensitivity of Phase I trials (as outlined in lines 345-346) and the possibility to defer the disclosure of protocol-related information to be made public at the time of decision on the trial. However, EFPIA remains concerned that this acknowledgement does not extend to the commercial sensitivity of publishing summary results of Phase I trials and the potential for release of commercially confidential information (CCI). EFPIA recognises and supports the requirement for results of all clinical trials to be made publically available. However, EFPIA remains concerned that the disclosure of Phase I trial results[11] within 12 months after completion of the trial may compromise CCI. Release of information regarding Phase I results within 12 months after trial completion would significantly narrow the window for filing and securing patents for new inventions. Therefore, even though the CT Regulation does not make an explicit exclusion for Phase I trial results as CCI, release of Phase I trial results within 12 months should be considered CCI and could compromise the EU's competitive balance. For example, at the time of Phase I, companies may not have enough information to secure all of the patents that will eventually be obtained since the support of clinical evidence may be necessary to file. In such circumstances a company (or researcher) may require longer than 12 months to prepare and file appropriate patent applications for innovative approaches or uses discovered during Phase I, as the results of the study may be needed to support these applications. It should also be noted that there might be prolonged development duration post completion of Phase I for a particular aspect of a product. There might also be practical challenges to preparing a summary report within 12 months (e.g. for vaccines, where there are delays in serology), which would entail the need for more time to prepare and file patents. As another example, the Phase I results of exploratory objectives may include biomarkers that could be used as 'hypothesis generating' for future studies. Disclosing the results of these exploratory objectives within 12 months of end of trial may preclude obtaining patents that would cover biomarkers and/or diagnostics themselves, as well as method of use patents directed to patient subpopulations[12]. EFPIA also believes that Phase I studies would not be expected to significantly benefit from the various improvements provided by the CT Regulation (such as a coordinated assessment). These studies are on the other hand subject to the new disclosure requirements according the EMA's draft consultation. In sum, disclosing results of Phase I trials within 12 months of the end of the trial would put the EU at a

[11] In these comments, Phase I results refers to the publication of summary results of these trials in the Database. Phase I results may also routinely be included in documents such as the Investigators Brochure (IB), clinical and preclinical IMPD sections and the protocols for Phase II/III. By evident extension, this timeline should also apply similarly to the Lay Language Summary. As with the Phase I summary results, the Phase I results presented within these additional documents should be similarly and accordingly deferred.

[12] Regardless of development Phase, since exploratory outcome measures may be CCI, results for these studies should not be disclosable publically. This would be consistent with the approach currently applied under Commission Guideline 2012/C 302/03, Point 5, para 1 and with that of other regulators worldwide.

Stakeholder no.	General comment (if any)
	competitive disadvantage given that there is no equivalent disclosure in other jurisdictions. Therefore, EFPIA believes that more deliberation and discussion is necessary regarding an acceptable mechanism and deferral period for release of Phase I trial summary results. Here EFPIA describes three potential approaches for the deferral of Phase I results that should be fully considered given their level of merit: • ***Deferred until the granting, refusal, or the withdrawal of the marketing authorisation application (MAA) or at least 10 years after the end of the trial***. EFPIA believes that this approach would provide consistency with the '*Triggers for timing of publication'* proposed by the EMA in the draft Addendum (6.5). Given its uniformity, this approach would aid in resource conservation for sponsors and EMA. It would also standardise the release of information for products discontinued during development. Finally, this approach would minimise the potential for unintentional release of CCI. • ***Where the trial is not to be used as part of a marketing authorisation application (MAA), release of information should be deferred until an established, finite period of time has lapsed following completion of the trial, at a minimum of 6 years***. This approach could be consistently applied and enable simplification of the Database operation. • ***In any case, postpone a final policy decision until it is possible to align EU's deferral approach with international standards***. In the US, there are ongoing deliberations on the possibilities for release of Phase I trial summary results. Alignment of EMA's final determination would then establish one global ('gold') standard, minimise the possibility for confusion, and ultimately conserve resources. EFPIA proposes further discussion with EMA and other involved stakeholders such as a workshop to agree to an optimal deferral approach. In addition, it is unclear why the EMA draft proposal focuses on Phase I trials in healthy volunteers. Under specific circumstances, mainly based on ethical arguments, Phase I trials might have to be conducted in a patient population with the target disease and/or a combination of healthy volunteers and patients. Phase I is defined in doc EMA/641479/2014 p. 4 (footnote) as trials that" usually involve healthy volunteers or sometime patients". The same definition should apply consistently throughout both documents EMA/641479/2014 and EMA/768628/2014. For the reasons described, EFPIA believes that Phase I results from trials conducted in patients should be considered similarly sensitive as with Phase I trials conducted in healthy volunteers. If Phase I trials in patients would have the same transparency requirements as later phase studies, it would be a disincentive for sponsors to conduct these studies in the EU. Unless carefully accounted for, this outcome could contradict the original objectives of the legislation – boosting the EU's competitiveness as a place to conduct

Stakeholder no.	General comment (if any)
	research and ensuring more efficient patient access to new innovative treatments. **Approach to Clinical Trials on Products without a Marketing Authorisation** EFPIA strongly supports efforts to share the results of clinical trials involving products that have achieved marketing authorisation as well as the results of trials for investigational products with discontinued development programs, regardless of outcome. EFPIA also strongly supports the EMA's position that particularly for trials on medicines without a marketing authorisation, certain documents should be considered to contain significant CCI. In the draft Addendum, EMA has proposed four options for the disclosure of clinical trial information for products without a marketing authorisation (MA). EFPIA believes that from the four options presented, the optimal proposed approach is a version of option "6.2 Proposal Two: The study specific and product specific documents (with the exception of the IMPD-Q section, which would not be made public at any stage) should only be made public after the earlier of the conditions set out in paragraph 6.5 below are met."[10], [13] Proposal 6.2 establishes clear milestones (i.e., at the time of MA or 9 years after the first summary results for the trial should have been published) for the disclosure of study specific and product specific documents (and therefore at least 10 years after the end of the trial). However, Section 4.4.1.2 acknowledges that product specific documentation (in particular the IB and IMPD S & E) contain CCI but does not provide an opportunity for identifying and redacting CCI which may remain after approval. This potentially compromises CCI in relation to indications under development i.e. outside of the particular indication and /or pharmaceutical form of the marketing authorisation and does not meet the requirements or objectives of the Regulation. EFPIA considers that the details in the IB which can be commercially confidential are not confined to a particular part but may be entered in many different sections and changes over the lifecycle of the product. Thus, the IB (like the protocol) should be treated as one entity for transparency purposes and should not be made public at any time, as detailed in our response to Question 7. It is proposed that Proposal Two, as referenced above, includes a sponsor-led redaction process of product specific documentation, particularly IMPD S&E, prior to release from the EU database. The proposal described in 6.1 to release these documents at the time of **decision on the trial** may undermine the protection of commercial interests. As such, if this option were implemented, it would likely result in extensive rounds of redaction to remove CCI at this **early stage** thus burdening constrained agency and researcher resources without resultant added public value. This point is of particular importance since the Regulation already includes provisions for a summary of the protocol and the results for most trials to be made publicly available at the time of decision on the trial and within 12 months of last patient visit respectively.

[13] The exception for IMPD-Q should likewise extend to answers and assessment report sections.

Stakeholder no.	General comment (if any)
	The options listed under 6.3 and 6.4 would be unnecessarily complex to implement requiring a level of system sophistication that could actually delay Database availability. The complexity would only be exacerbated by the increasing number of clinical trials with adaptive design that are often viewed as dual Phase I/II, Phase II/III or Phase III/IV. It could also be anticipated that advances in regulatory science such as use of adaptive pathways could add a further level of complexity for options 6.3 and 6.4. There are transformational changes in science and technology, in general, and it is important that EMA "future proof" the system. Furthermore, EFPIA is concerned that the approaches presented in 6.3 and 6.4 would result in public availability of detailed results information while the regulatory decision making is ongoing. This release of information could, interfere with the regulatory review process. In summary, EFPIA supports option 6.2 as the most reasonable and pragmatic approach. **Determining Marketing Authorisation Status** EMA also proposes three options for consideration on how the status of marketing authorisation of the medicinal product should be applied since it must be taken into account in deciding which information/documents within the Database should be publicly accessible. EFPIA believes that proposal 1.3 (i.e., "once a marketing authorisation has been issued, by at least one Member State, for a medicinal product using that active substance and for the indication and formulation/route of administration under study"3) is the only approach that would adequately protect CCI or guard against unintended consequences (e.g. breaches of intellectual property rights that might disincentivise future investment in R&D). Indeed, information to be released after the MA decision should relate to the authorised indication and/or authorised pharmaceutical form that was studied during the concerned clinical trials. CTA information related to extensions of indication and/or line extensions could be released after the MA decision for this particular indication and/or pharmaceutical form has been rendered. Of note and in direct support of option 1.3, individual indications and particular formulations can be protected by patents that are separate to the composition of matter patent. Early disclosure of information relating to these innovations could adversely impact the ability for a sponsor or researcher to obtain such protection. **User-friendly and Harmonised with International Standards** To facilitate patient access to clinical trial information in a simple and user-friendly manner, EFPIA supports that the information is published through a single EU repository, harmonised with international standards (e.g., ClinicalTrials.gov). Since clinical trial researchers are often required to submit information on clinical trials in both the EU and United States, EFPIA requests

Stakeholder no.	General comment (if any)
	that EMA continues to collaborate and co-ordinate with U.S. regulators as it develops the set of data fields and standards. Developing a system with a set of data fields that will allow for information entry and validation from either database (i.e., EU Portal/Database or ClinicalTrials.gov) to be accepted by the other database will lead to substantial efficiencies for regulators, sponsors and researchers. Finally, it is unclear if there are intentions to update CSR guidance in the near-term. If this is the intention, given that the content and format for CSRs is covered by ICH guidance, any adjustment would be accomplished through international agreement. Ideally similar harmonisation efforts could also be made in the case of the summary for laypersons. **Alignment of EMA's Policies and Processes** EFPIA believes that the policy for the management of clinical study reports (CSRs) submitted to the EU Database should be consistent with EMA's approach in its Policy 70 and the interaction between the two processes should be clarified. In particular, the draft Addendum does not appear to include any requirements for access registration or terms of use (ToU) of the information within the Database. The draft Addendum remains silent about "how" and under which terms and conditions, if any, the information, data and documentation, which will be included in the EU Database, shall be rendered publically accessible. These aspects seem in contrast to EMA's recently released Policy 70 on publication of clinical data. Policy 70 requires that all users who access clinical data pursuant to the EMA's new policy agree, essentially, to restrict their use of the data to non-commercial research purposes. The legal rationale for imposing these ToU as explained by the EMA in Policy 70 is to provide protection for sponsors who have generated and submitted the data against unfair commercial use of that data, which necessarily applies equally to disclosures of CSRs and regulatory documents via the EU Database. Likewise, the agreed principles for redaction of clinical reports/regulatory documents as defined in Policy 70, the legal rationale for which is protection of CCI, should be consistently applied to regulatory submissions under the Clinical Trial Regulation. Indeed, we believe that the applicant/MAH/sponsor is best placed to determine whether the publication of such information may undermine the protection of its commercial interests, including intellectual property. Finally, the management and release of documents submitted to the EU Database should indeed be consistent with the EMA Policy 70, not only in relation to CSRs, but also for publication of other parts of a CTA dossier such as the IMPD E+S sections and IB (e.g. redaction of CCI like certain methods, watermark on downloaded documents), if applicable. **Enable an Efficient System, Balancing Automation with Direct Sponsor Involvement** In keeping with the aim of the new Regulation to simplify processes, the identification of CCI and the process to maintain confidentiality

Stakeholder no.	General comment (if any)
	throughout the lifecycle of the product should be simple, proportionate, predictable, clearly communicated, and involve the stakeholder who submitted the data. In the future as CSRs are submitted to the new EU Database, duplication of submissions (full or simplified CSR) at the national level must be avoided consistent with the overall objective of the Regulation to streamline provisions. We agree with the statements in Section 4.4.1 (LL493 – 500), that clinical trial-related documents contain a mixture of commercially confidential and non-confidential information. This point underscores the need for sponsor involvement. **Assess the Overall Value of the System** Based on experiences in enhanced disclosure of information (e.g., EU Clinical Trial Register, Pharmacovigilance information such as PRAC minutes, lay summaries for Risk Management Plans, and added detail in EPARS), all stakeholders should systematically and collectively reflect on the level of impact the disclosed information has on the public and more specifically on patients and HCPs. A thorough assessment should occur within 5 years to help balance the level of detail, complexity and methods of disclosure.
66	General Comments: It is to thank this consultation and we would afford some general comments, as follows: 1. - We understand that the functional specifications submitted to consultation have the objective of better informing the citizens on what is going with clinical trials. So as they have been drawn the specifications are too reiterative and difficult to understand without electronic tools because excessive details. The direct reading of registers would be very difficult, and as a consequence the utility of the data base impaired. 2. - The commercial rights of sponsors may be already protected by the patent claims and patent legislation. It is no sense setting delays for publication of ten years for so many variables as it is proposed. So long delays transform the data base in a kind of “museum” or a repository of old experiences. It is to think whether it is worth to spend so much money in an obsolete database. 3. - The personal data of investigators have an excessive granularity, and so it is proposed the data base does not preserve the personal confidentiality. All personal data should follow Good Clinical Practice norms, be approved by RECs and by Regulatory Agencies but not made public in an indiscriminate way and in a so great detail. The previous informed consent of data owners should be considered.
67	The Regulation states that the EU database “shall be publicly available unless one or more exceptions apply”. These are: • to protect personal data;

Stakeholder no.	General comment (if any)
	• to protect commercially confidential information, in particular taking into account the marketing authorisation status of the medicinal product, unless there is an overriding public interest; • to protect confidential communication between Member States in preparing their assessment; • to protect the supervision of clinical trials by Member States. In general the EFPC is in favour of the protection of personal data and understand the value to protect the supervision of clinical trials by member states. On the other hand we do see the need that member states should be transparent about their findings and make this as a priority in order to provide consumers and professionals to stay informed as good as possible. For the protection of commercial confidential information we are clearly in favour of a maximum of transparency to the public. We ask for very strong argumentation of the drug industry before confidentiality can be accepted (and not the opposite : that it is necessary to prove 'overriding public interest' before study data are made available). In addition it is needed to make sure that all results of clinical trials are made public in a pro-active manner in order to avoid the currently widely accepted procedure of publishing only research results which are in favour of medicinal product and to hide any negative results by not publishing (ref All Clinical Trials)
68	In general, we believe that the attempt to automate considerations of confidential commercial information based on broad principles is dangerous and that these assessments should be made on a case by case basis. What one sponsor feels would not undermine its legitimate economic interest might not work for another sponsor. We propose the documents will be sent for Sponsors review, deletion of confidential information prior to posting it, as for example is done for EPARs. In general we would like to know if bioequivalence studies against a RLD are also considered to be clinical trials in the scope of the document. If bioequivalence studies are considered to be a clinical trial, this would give disclosure of a generic company's product pipeline to direct competitors in a very early stage, especially if several studies have to be performed sequentially. In case of a global development where study start is triggered by US market timelines, this would mean a disclosure years before submission of a file in Europe.

Stakeholder no.	General comment (if any)
	If bioequivalence studies are covered, as what type of studies will they be handled; phase I? Will only pivotal studies fall within the scope of this regulation or are early pilot studies included as well? Especially as not all pilot studies have to be submitted, e.g. failed pilot studies that caused a re-formulation during development. These studies would also disclose the companies generic pipeline to direct competitors in a very early stage of generic development. We don't see how disclosing information on bioequivalence study as soon as the study is approved would benefit patient, doctors and researchers and if it does to what extent it outweighs the inconvenience resulting from the loss of secrecy of product pipeline. In that respect we have noticed that the big majority of request to access to documents are currently made by competitors. We believe that the more information is published before grant of the marketing authorization, the more likely it is that third party companies will interfere in the decision making process of the regulatory agencies.
69	I. BEUC welcomes the opportunity to contribute to the EMA public consultation on the application of transparency rules to the EU Clinical Trials Regulation. However we regret that the consultation runs for less than one month and that EMA didn't comply with the European Commission guidelines for public consultations that foresee a minimum consultation period of 12 weeks. This is particularly difficult to understand taking into account that the Clinical Trials Regulation will not be in operation before 28 May 2016. Such a tight deadline on a highly technical document is likely to generate an imbalance in the input gathered via the consultation in favour of more resourced stakeholders. II. Overall we consider that the EMA interpretation of what constitutes commercially confidential information is too broad. Some of the specific provisions outlined in the draft proposal for an Addendum will hinder the proper access to clinical trials data as intended by legislators when they adopted the new European Clinical Trials Regulation (EU) No 536/2014. III. According to the Helsinki Declaration, all authors have a duty to make the results of their research on human subjects publicly available and are accountable for the completeness and accuracy of their reports. Making clinical trial data available is necessary to ensure competent authorities have complete and reliable information to carry out safety and cost/effectiveness analyses, avoid exposing patients to unnecessary risks and waste of public resources on ineffective medicines. Disclosure of trial data empowers patients, promotes a better quality of healthcare and contributes to a restoration of public confidence in regulators following recent scandals which have affected the medical sector.

Stakeholder no.	General comment (if any)
	BEUC calls for these principles to be better reflected in the Addendum.
70	The European CRO Federation appreciates the opportunity to submit these comments and observations on the European Medicines Agency's ''Draft proposal for an addendum, on transparency, to the "Functional specifications for the EU portal and EU database to be audited' (EMA/42176/2014) issued for public consultation. EUCROF represents members from 16 EU countries: It speaks for 300 member Contract Research Organisations and their over 15,000 employees. EUCROF's aims and objectives are - amongst others - to promote clinical research of high quality in Europe/the European Union, and to represent its members in interactions with regulatory bodies, the pharmaceutical-biotechnology industry and the medical research community. EUCROF support's the EMA and Member States' efforts to balance transparency and availability of information on clinical trials with the aim of fostering research innovation in Europe. We support the EMA's acknowledgement of the particular commercial sensitivities of Phase 1 trials. Furthermore we support the EMA's proposal that information on clinical trials should be made available in stages: *"Thus, the extent of information made public could progressively increase during the development period to the marketing authorisation of a medicine from first in human Phase I trials to post-authorisation Phase IV and low-intervention trials."* **Overview General Comments Section** Our specific comments will be dealing with the EMA's questions. In the general comment section we would like to present our views on two specific points which relate to the proposal in general, rather than the EMA's proposals and questions: • **The definition of what constitutes a "Phase 1" trial** • **The publication of (lay) summary reports** **How should a "Phase 1" trial be defined?** We strongly advocate defining a "Phase 1" trial for the purpose of applying transparency rules as follows: **Phase 1 trials** are clinical trials using IMP, device & IMP/device combinations, performed in **healthy volunteers and/or patients without therapeutic (or prophylactic) intent** This is in accordance with Belgian and UK law and the current application of this term within Europe and globally.

Stakeholder no.	General comment (if any)
	Belgian law states in Article 2, 12: "Phase 1 study: "*study performed on healthy volunteers or on certain types of patients without therapeutic objectives which covers one or more of the following aspects: estimation of initial safety and tolerability, pharmacokinetics, pharmacodynamics, early measurement of drug activity*". **UK law (Statutory Instrument 2004 No. 1031) states under "Interpretation":** *"Phase 1 trial means a clinical trial to study the pharmacology of an investigational medicinal product when administered to humans, where the sponsor and investigator have no knowledge of any evidence that the product has effects likely to be beneficial to the subjects of the trial;"* **21 CFR Part 312.21 states** *"Phase 1 (1) Phase 1 includes the initial introduction of an investigational new drug into humans. Phase 1 studies are typically closely monitored and may be conducted in patients or normal volunteer subjects. These studies are designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. During Phase 1, sufficient information about the drug's pharmacokinetics and pharmacological effects should be obtained to permit the design of well-controlled, scientifically valid, Phase 2 studies.* *(2) Phase 1 studies also include studies of drug metabolism, structure-activity relationships, and mechanism of action in humans, as well as studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes.* **ICH E8 states:** *"Phase I starts with the initial administration of an investigational new drug to humans. […] Studies in this phase of development usually have non-therapeutic objectives and may be conducted in healthy volunteer subjects or certain types of patients […]."* Rationale: A limitation of "Phase 1" trials to healthy volunteers would be inappropriate for an innovative research environment in the EU. In fact, such a limited definition has not been used in the EU or globally for many years and would be a significant step back, which is against the objectives of the EU CTR.

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	Therapeutic intent is an intent to treat and/or to cure. Prophylactic intent is an intent to prevent disease. If a trial is designed with therapeutic/prophylactic intent (i.e. a Phase II and higher trial), then it is understandably in the interest of all parties that relevant information is shared with the public. Patients can reasonably expect that the product used within the terms of the trial protocol has effects likely to be beneficial to them. Patients will be recruited and consented on that basis. Such expectations should not be raised lightly e.g. for the purpose of recruiting patients into trials, especially when life-threatening diseases or rare chronic diseases are concerned. A first-time-in-human trial in patients (including oncology patients) would only in extremely rare circumstances be designed with therapeutic intent. There are too many uncertainties at that stage of development, even if the trial design was to include methods to gain early evidence of efficacy (such as biomarkers). For a study without therapeutic/prophylactic intent, patients must be recruited and consented on the basis that they cannot expect that the product used within the terms of the trial protocol will have effects likely to be beneficial to them. This is to ensure that no false hopes and unrealistic expectations are raised. Clearly, trials in patients who do not have the target disease, such as pharmacokinetic studies in patients with renal or hepatic impairment are also included into the current global and our proposed continued definition of “Phase 1” trials in the EU. During early phase drug development there is particular sensitivity about the commercial confidentiality of information on clinical trials. For studies without therapeutic or prophylactic intent, the need to inform the public about the study should be limited to the extent that applies for trials in healthy volunteers. With regards to the draft proposal on transparency, the definition of “Phase 1” impacts on whether or not sponsors will have the possibility to opt to have only very minimal public information at the time of decision on the trial. Potential benefits of public access to information at the time of decision on a trial are not applicable to trials without therapeutic/prophylactic intent, whether in adult healthy volunteers or patients. A limitation of “Phase 1” transparency rules to healthy volunteers would inevitably lead to a decrease in innovative early phase clinical trial designs being conducted in the EU. Innovative, non-therapeutic/prophylactic early phase (including first-time-in human) trials in healthy volunteers *and* patients are the future of early phase research in the EU. It is key to the future of clinical research in Europe that we can continue to perform these trials in patients. Moreover, an increase of such trials being conducted in Europe will lead to faster development of new medicines and thereby faster access to these new treatments for patients. **When should (lay) summary reports be published?** The draft proposal sets the publication time point for (lay) summary reports at 12 months after the end of a trial for all stages of drug development, including Phase 1. Whereas throughout the proposal a staged publication approach in relation to the development of the

Stakeholder no.	General comment (if any)
	product (phases of clinical research, therapeutic/non-therapeutic trials) or marketing authorisation status is advocated, this approach is not applied for summary reports. The draft proposal acknowledges that the subject information sheet and protocol can "contain extensive detail of a commercially confidential nature". In relation to summary reports, where the same applies, there is uncertainty how the EMA envisages the concept of CCI to be applied. In relation to the risks of early publication of summary reports for non-therapeutic/prophylactic (Phase 1) trials, this is a particular issue as Phase 1 studies are usually short and completed within months rather than years. This would lead to very early publication of potentially commercially confidential information. We refer to our position paper dated 31 October 2014 which was also submitted as part of our response to the first consultation on the EU portal (http://www.eucrof.eu/images/EUCROF_Position_Paper_Public_Access_to_Early_Phase_EU_database_information_31_OCT_2014.pdf). Following a detailed risk/benefit assessment, *"with regards to the potential benefits of publicly accessible (lay) summary results of Phase 1 studies, we found that the benefits stated by [ClinicalTrials.gov, the WHO/International Clinical Trials Registry Platform (ICTRP) and the CTR] will not necessarily affect patients or ongoing clinical research at the time. Benefits will become relevant at various time points during drug or drug/device combination development. This may be earlier or later than one year from the end of a trial."* And: *"The potential risks of early publication and disclosure of Phase 1 studies' […] results may outweigh its benefits for patients, health professionals and the public. During early drug development much of this information is considered commercially confidential. Regulation outside Europe does not require publication of Phase 1 studies, except after FDA approval in the US. Sponsors would therefore likely manage perceived risks by performing Phase 1 studies outside Europe. This would have a detrimental effect for European early and late phase clinical research, which would ultimately translate into disadvantages for patients and the public."* **We therefore suggest the following in relation to the publication of summary reports:** (1) If summary reports are to be published 12 months after the end of a trial, then the information provided should be limited to non-CCI. In case of Phase 1 clinical trials, this would further limit the benefits of publication, whilst at the same time increasing the administrative burden of providing redacted/abbreviated reports. (2) An alternative would be to set an automatic trigger to publish Phase 1 summary reports when the first therapeutic study's summary

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	report for that same IMP (indication, formulation, route of administration) is published.
71	The EGA welcomes the opportunity to comment on the “Draft proposal for an addendum, on transparency, to the 'Functional specifications for the European Union portal and EU database to be audited” and would like to highlight 3 key points. (1) While the EGA acknowledges the need for information disclosure, it is important that all aspects (e.g. nature of data, timing) are carefully assessed in order to balance on the one hand the information provision and on the other hand the possible consequence on the applicant (e.g. competitive disadvantage) (2) The EGA would like to stress the importance of the appropriate timing of the publication of data and documents in order to protect CCI in an adequate way. (3) In order to protect personal information identifying sponsor staff or staff acting on behalf of the sponsor, the EGA supports the general principle that this information should not be included in the database. To the extent that information is included, it should not be made public except for those persons with certain legal roles. In the light of this general principle, the EGA highlights the need for the EMA to reconsider the the inclusion of the personal information of the signatories of the clinical study report in the database. This would be coherent with the protection of personal information that is applied to Member State experts.
73	Overall, the European Association of Hospital Pharmacists (EAHP) supports the direction of transparency indicated within this consultation document. However, we consider the period of consultation (4 weeks) to be well below best practice (12 weeks being a general standard by the Commission and many governments), especially in view of both the technical nature of the matters under consideration, and their high level of importance for the future medical and pharmaceutical research environment in Europe. Such short periods of consultation, especially without clear prior notice, can provide difficulties for resource-strained NGOs in coordinating expert submissions (e.g. contacting and eliciting responses from experts in the field), and is likely to consequently bias the levels of response the Agency will receive. In our own case, it has meant leaving some questions unanswered in our response as the time available has not permitted full reflection on the matters. In cases where the EMA consults in periods shorter than 12 weeks a reasoning provided for the shorter period would be helpful in promoting understanding of the Agency’s perspective. Nevertheless, the importance of transparent reporting of clinical trial results appears well described and understood by the Agency in the

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	early parts of the document, including: • Reinforcing public trust in clinical trial outcomes and the decisions taken by regulators based on those outcomes; and, • Acting as a knowledge management resource to foster innovation and stimulate and accelerate further research by building on accumulated knowledge and technical ability. From the strong levels of response received to past EMA consultations and consultative exercises by the EMA on this topic, as well as highly publicised court cases, we are sure the Agency appreciates the level of public interest that is at stake in relation to clinical trial transparency. The continuing growth of the AllTrials campaign, of which EAHP and many of its member associations are signatory supporters, also serves to underline the spotlight of public scrutiny in getting trial transparency in Europe right. EAHP supports suggestions that any deferrals to making information public must be justified and those justifications should be subject to periodic audit.
74	First we would like to congratulate EMA for its proactive transparency policy and urge EMA to take transparency of clinical trial data as the main principle of the EU portal and database and restrict it only if compelling reasons arising out of EU Charter of Fundamental Rights, such as data protection of individual patient level data, so require. Transparency of clinical trial data is vital for ensuring continuous public trust in research and in safety of medicines. Data from concluded and discontinued trials provide valuable information for further medical research and innovation. Therefore it is of utmost importance that the principles and terminology in this addendum is precise and unambiguous and in harmony with other EU legislation. The most difficult issue relates to defining how sponsor's eventual commercially confidential information (CCI) is defined in the addendum. The term CCI refers to company's trade secret which are defined in the addendum as any information contained in the data or documents submitted to the database that is not in the public domain or publicly available and where disclosure may undermine the legitimate economic interest of the sponsor. This definition is broader and more vague than the standard international definition given in the Art. 39.2 of the TRIPS Agreement according to which information may be regarded as a trade secret if it is secret and has commercial value because of secrecy and it has been subject to reasonable steps to keep it secret. Moreover, the TRIPS Agreement requires Member States to protect undisclosed pharmaceutical test data against unfair commercial use except where necessary to protect the public or unless steps are taken to ensure that the data is protected against unfair commercial use. This means that under international law regulatory test data is not to be regarded as a trade secret and is not subject to intellectual

Stakeholder no.	General comment (if any)
	property rights as such. Compelling public safety or other requirements of public interest can justify the publicaton of regulatory test data. The EU has also proposed a directive for the protection of undisclosed know-how and business information (trade secrets) against their unlawful acquisition, use and disclosure. In the proposal it is explicitly stated that disclosure by Union's institutions and bodies or national public authorities of business-related information they hold pursuant to the obligations of Regulation (EC) No 1049/2001 or to other rules on the access to documents should not be considered unlawful disclosure of a trade secret. (Recital 9) This means that regulatory data should not be regarded as a trade secret and should be available under freedom of information law. This has been recently confirmed by the European Ombudsman in her inquiry to EMA's practices under Regulation (EC) 1049/2001. We emphasize the importance of prompt implementation of the EU portal and EU database together with the transparency addendum, no later than May 2016.
75	The Leeds Institute of Clinical Trials Research is an academic clinical trials unit and a registered member of the UKCRC Registered Clinical Trials Units Network. We support the international campaign to improve the transparency and unbiased reporting of clinical trials and welcome the inclusion in Regulation (EU) No. 536/2014 'The Clinical Trial Regulation' of the requirement to register all clinical trials within a public registry. We favour a simpler approach for timing of release of commercially confidential information, possibly linked to the release of Study Results and consider the proposed tiered approach to be too complex; potentially leading to errors in implementation and interpretation. Protection of commercially confidential information in our Phase IV and low intervention trials is of particular concern in regard to this proposal and we would consider these to be important in protection of current and future funding relationships. For example, many of our trials fall into the phase IV or low intervention category, they may include an Investigational Medicinal Product with a marketing authorisation but in a new indication or at a lower dose which is being provided free of charge by a pharmaceutical collaborator. We are concerned that we may be required to make public commercially confidential information owned by that third party which may put future funding relationships at risk. The publication of inspection reports and serious breaches is strongly opposed. Specifically in the UK, where serious breach reporting has already been included in the national laws pertaining to clinical trials, this relies on self-reporting, monitoring and audit by the sponsor. We are concerned that this proposal will drive forward a continuing culture of fear and risk aversion to the conduct of clinical trials, driving up costs for sponsors and researchers who will be forced to implement more resource intensive methods to protect them from the reputational risk of a publically available negative report. The EU Portal must allow time delays for release of other sensitive information such as Urgent Safety Measures and early trial closure, in

Stakeholder no.	General comment (if any)
	order to allow the sponsor time to communicate relevant information to patients on the trial. It would not be acceptable for first communication to be made via media reports following publication on the EU Portal. The current documentation does not describe the technical functionality of the portal; this is critically important in considering minimising the administrative burden on Sponsors in the formatting of information to be uploaded and keeping this up to date. For example, clinical study reports (as per the ICH template) are not produced for all trials; also it would be concerning if specific formats such as CDISK are adopted. The definition of 'dataset' remains unclear and the specific administrative burden for uploading datasets vs inputting individual data points must be fully considered.
76	The UKCRC Registered Clinical Trials Units support the international campaign to improve the transparency and unbiased reporting of clinical trials and welcome the inclusion in Regulation (EU) No. 536/2014 'The Clinical Trial Regulation' of the requirement to register all clinical trials within a public registry. Further to our statement made in 2013 which recommended this key step forward, our current response relates to the detailed plans regarding transparency of the conduct of clinical trials within the EU. We would favour a simpler, single approach for timing of release of commercially confidential information linked to the release of Study Results and consider the proposed tiered approach to be too complex; potentially leading to errors in implementation and interpretation. The current proposed tiered approach will result in the greatest level of up front transparency and scrutiny being linked to trials of potentially the lowest risk (low interventional and post marketing trials). Protection of commercially confidential information is important; reassurance is required that academic sponsors could consider contractual obligations to protect commercially confidential information of 3rd parties such as pharmaceutical collaborators as a legitimate economic interest in relevant trials in order to protect current and future funding relationships. The publication of inspection reports and serious breaches is strongly opposed. Specifically in the UK, where serious breach reporting has already been included in the national laws pertaining to clinical trials, this relies on self-reporting, monitoring and audit by the sponsor. We are concerned that this proposal will drive forward a continuing culture of fear and risk aversion to the conduct of clinical trials, driving up costs for sponsors and researchers who will be forced to implement more resource intensive methods to protect them from the reputational risk of a publically available negative report. The EU Portal must allow time delays for release of other sensitive information such as Urgent Safety Measures and early trial closure, in order to allow the sponsor time to communicate relevant information to patients on the trial. It would not be acceptable for first communication to be made via media reports following publication on the EU Portal.

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77	The CCMO has respond on an earlier version of the transparency document on January 8, 2015. We like to refer to this document for their general comments. ***Comments as provided 8 January 2015:*** The Netherlands supports the need to have the best possible balance between public access and the protection of commercially confidential information (CCI). We also support that the public disclosure of data fields and/or documents is done on the basis of automatically applied rules in the EU Portal and Database, rather than on a case by case basis which require extensive resources. This asks for a critical assessment whose interest is served. What is in the public interest and what is in the sponsor's interest when it comes to the protection of commercial confidential information. The system should be designed in such a way that sponsors will not take up a defensive position which might have a negative impact on the quality of the data. In that respect, it might be more efficient to include information in the EU application form instead off splitting documents in two or three documents, for instance the summary of the protocol and information about the principle investigator (including his/her financial and/or economic interests). This approach will also result in a more uniform way of presentation of data. The document is primarily focused on industry-driven clinical trials aimed at the authorisation of a medicinal product. Rules and proposals are often related to the marketing authorisation of the medicinal product. Little or no attention is paid to so-called investigator initiated trials. In this situation industry is not involved or only to a limited extent. Sometimes these trials are very early development trials, in other situations they are at best described as phase IV trials. In principle transparency is agreed, however, investigators would be very unhappy with too early transparency. In the first situation, early development trials, economical confidential issues are relevant as these trials could lead to new promising drugs. In the second, academic investigators will be reluctant to early transparency as this could hamper publication in official journals. Authors have to confirm that the proposed data are not yet already in the public domain. The document should address investigator initiated trials. In this respect it is also important to clarify more what is meant by commercial intent (see comment question 7 (2nd). Furthermore, the document does not give sufficient information on how to handle data on phase 1 trials, which are often seen as very confidential by industry. These trials give little information on clinical effectiveness or safety. The objective of these phase 1 trials is to generate kinetic information, to determine maximal tolerated dosage, and/or to determine interaction or bioequivalence. Early development of biosimilars is a confidential issue, with competition between companies. Most of those studies are performed in volunteers except for risky oncology products. But even in the latter situation no efficacy data will be generated in these phase 1 trials. So public interest in those

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	trials is very limited. The risk is that industry will move to countries outside the EU for those trials. These trials are of high economical interest in some EU member states. There are several proposals to delay the public disclosure of study specific and product specific documents depending on the phase of the study. However, many fields in the EU application form will be made public at the time of decision for each trial in all of the four proposals. Combination of fields, like full title of the trial and and the objectives of the trial (main and secondary objectives/endpoints, principle in- and exclusion criteria) can reveal some commercial confidential information. Therefore, the Netherlands propose to delay the public disclosure of this information with six months after the decision of the trial. This will give the sponsor enough time to take the necessary actions to protect the confidentiality of this information. This procedure is current practice in the Netherlands and is an accepted procedure. The document should say something about the process of transparency (quality assurance and harmonization between MSs). Also, it should be clear what the procedure is if confidential information or a confidential document is made public by mistake? Who is responsible?
78	1. It is strongly supported that rules for making public access to the database have to be as simple as possible, predictable and applicable in an automatic way. In order to do that, it is proposed to define a structured set of CT data that will include all information that should be sequentially published in relation to the relevant CT characteristics for all clinical trials. Having this structured CT data set could also simplify the assessment of substantial modifications related to the protocol, and ensure keeping easily traceability of changes. Also this could be a sufficient description of the protocol for certain simple low intervention CT. 1. Fostering innovation and simplifying the CT application process requires setting the principle of requesting sponsors every piece of information only once. The information already in the system should be used to automatically populate the necessary templates (e.g. Assessment report or summary of trial results) to minimize work for sponsors and MS and to ensure consistency of such information. This will make easier to apply transparency criteria. In relation to information already in the system, in subsequent CT applications only updates of such information should be requested. The system should present MS the complete information (cross-referenced plus new, showing which is new). Redundant information in the IMPD with respect to IB (non clinical and clinical information) should also be avoided. <u>Other minor comments</u> In all CT and not only in those phase IV the sponsor should be given the opportunity to advance the publication of the complete CT dossier.

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	With respect to publication of results: a. For integrated protocols, including two different parts in such a way that the results of the first part are used to further define certain characteristics of the second part, it should be clarified what is expected with respect to publication of both parts. b. All journal publications related to a certain clinical trial should also be referenced or accessible in the results section of the trial in the EU database, at least on a voluntary basis. c. With respect to resubmissions it should be clarified if the last CT application will replace for the previous application already published or if both will persist in the public domain. d. It should be clarified if the complete dossier of CT ended without any patient included, and of withdrawn or rejected CT applications will be published the same as for authorised CT.
81	AESGP represents the manufacturers of non-prescription medicines in Europe. We appreciate the opportunity to review the 'draft proposal for an addendum, on transparency, to the Functional specifications for the EU portal and EU database to be audited' and would like to submit the following comments. It should be clarified that the sponsor's request for deferral will be documented publicly.