

Agenda item:	10
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HRA BOARD COVER SHEET

Date of Meeting:	22 January 2014
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Title of Paper:	Update on EU Clinical Trials Regulation
Purpose of Paper:	To provide the HRA Board with an update of progress with the negotiation of the EU Clinical Trials Regulation, summarise key points and highlight points of particular relevance to the HRA.
Reason for Submission:	For information
Details:	See paper
Suitable for wider circulation?	Yes

Recommendation / Proposed Actions:	To Approve		
	To Note		Yes
	Comments		

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Update on the EU Clinical Trials Regulation

1. Summary

In December 2013, an agreement was reached between the Lithuanian Presidency of the EU and the European Parliament on the European Clinical Trials Regulation that will replace the current European Clinical Trials Directive (EUCTD). This agreement was endorsed by Coreper (the permanent representatives of all Member States) on 20 December 2013. The text, which is now going through legal and linguistic checks, will then need to be formally adopted by the European Parliament and the Council of Ministers before it can be published in the Official Journal of the European Union. The Regulation will apply two years after it is published and so it is anticipated to apply from mid-2016.

Although the current EUCTD was intended to simplify and harmonise the administrative provisions for clinical trials of investigational medicinal products (CTIMPs) across the EU, it did not achieve this objective and it has been the subject of considerable criticism. This is because, as a Directive, it has been implemented differently in Member States and it is blamed for increasing the administrative and regulatory burden. Although it cannot be solely attributed to the EUCTD, the number of clinical trials in Europe has declined, and the costs per trial have increased, since it was implemented. In the UK, we currently review approximately 1,000 CTIMP applications per year.

The new Regulation will introduce:

- A simplified application process - one application will be submitted regardless of the how many Member States will be taking part in the trial. This will replace current situation of individual submissions to each competent authority and ethics committee(s) in each Member State. Additionally, the requirements for the application package, which will be submitted electronically via an “EU portal”, will be harmonised
- A streamlined process for review and authorisation – there will be one authorisation (decision) for the trial in each Member State, replacing the current separate approvals of competent authority and ethics committee(s). Where multiple Member States are involved in a trial the Member States will jointly assess the application, except in respect of defined aspects, such as ethical review. The processes and timelines are defined (up to 60days for decision on an initial application (where no questions), rising to maximum 91 days where questions asked at each stage); tacit approval is assumed where timelines are missed.
- A category of “Low-intervention trials” – where trials fall into this category they are afforded less stringent requirements for monitoring and documentation.
- Rules on the protection of subjects and informed consent – these are intended to harmonise requirements but still allow for national rules in some aspects, such as who may act as a legal representative of a subject or legal age of consent. Additionally provisions have been added for some particular areas of interest to the UK , such as trials in emergency situations and cluster trials.
- Transparency requirements - all clinical trials in the EU will need to be registered and summary of results must be published within one year of the trial ending. Additionally where a clinical study report (CSR) has been submitted in support of a marketing authorisation (MA), it must be made available by the applicant within 30 days of the regulatory decision, on the MA application. Note, the Regulation requires Member States

to have penalties for infringement of Regulation and particular attention is drawn to non-compliance with requirements for information to be made publicly available.

The Regulation has the potential to improve the environment for clinical trials in Europe, through its basis as a EU regulation and in the requirements it sets out. Overall, the text that has been agreed fits well with negotiating objectives, which the UK adopted. The implementation of the Regulation will definitely require changes in the way that CTIMP applications are reviewed and authorised in the UK. However, the UK is well placed for this Regulation as the HRA Assessment & Approval proposal, if approved, will provide the key platform for its implementation; furthermore, there is already a well-established partnership between the Medicines and Healthcare products Regulatory Agency (MHRA) and the HRA that may be readily built upon. The UK has a good record of meeting the timelines set by the current regulatory framework and so the Regulation's timelines are expected to be readily achievable in the UK. Additionally it is expected that, as now, the Standard Operating Procedures (SOPs) for research ethics committees in the UK will apply the requirements of the Regulation to a broader range of studies, where it is appropriate. For example the 60 day approval timeline set by UK clinical trial regulations for CTIMPs is applied to all applications for full ethical review.

2. Background

- 2.1. EU legislation applying to Clinical Trials of Investigational Medicinal Products (CTIMPs) currently includes:
 - 2.1.1. EU Clinical Trials Directive ("EUCTD"; Directive 2001/20/EC)
 - 2.1.2. EU Directive relating to medicinal products for human use 2001/83/EC
 - 2.1.3. EU Good Clinical Practice (GCP) Directive 2005/28/EC.
 - 2.1.4. Note also European Advanced Therapy Medicinal Products (ATMP) Regulation EC 1394/2007
- 2.2. Directives are transposed into legislation in Member States. In the UK this gave rise to the UK's Clinical Trials Regulations:
 - 2.2.1. The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) transposed EUCTD.
 - 2.2.2. The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 (SI 2006/1928) amended the UK Regulation (e.g. added provisions arrangement for payment of fees) and implemented the GCP Directive
 - 2.2.3. The Medicines for Human Use (Clinical Trials) Amendment (No.2) Regulations 2006 (SI 2006/2984) amended the Regulations further to make provision for the inclusion of incapacitated adults in a clinical trial in emergency situations. Specifically provision was made for an incapacitated adult to be entered into a trial prior to consent being obtained if particular conditions are met.
 - 2.2.4. The Medicines for Human Use (Clinical Trials) and Blood Safety and Quality (Amendment) Regulations 2008 (SI 2008/941) then further amended the Regulations to make provisions for trials involving minors in emergency situations. The provisions allowed for a minor to be entered into a trial prior to informed consent being

obtained if particular conditions are met. This revision also took into account amendment of definition of the Gene Therapy Advisory Committee (GTAC).

2.3. The above provided a statutory basis for:

- 2.3.1. Standardisation of procedures for ethical and competent authority review and authorisation
- 2.3.2. GCP standards for commencing and conducting clinical trials
- 2.3.3. Good Manufacturing Practice (GMP) standards for medicines used in clinical trials
- 2.3.4. Inspections against principles and standards of GCP and GMP, which are supported by enforcement powers.

2.4. The Medicines and Healthcare products Regulatory Agency (MHRA) and the National Research Ethics Service (NRES) put in place a memorandum of understanding to summarise the arrangements between them in the implementation of the UK Regulations. This memorandum also fulfilled the requirements of EU Directive on GCP (2005/28/EC) relating to communications between competent authority and ethics committees.

2.5. Whilst the EUCTD was intended to simply and harmonise administrative provisions for CTIMPs across the EU. In practice as it was a Directive and was transposed by Member States into national law, it was implemented differently across the EU. This meant that different standards were applied across the EU and as a result there was considerable criticism of EUCTD. Additionally, the EUCTD was blamed for introducing unnecessary administration, increasing regulatory burden and lacking sufficient clarity. The European Commission have quoted the following data:

- 2.5.1. There were 4,400 clinical trials in Europe in 2010
- 2.5.2. 60% clinical trials are sponsored by industry; 40% are sponsored by other stakeholders including academia
- 2.5.3. Applications for clinical trials fell by 12% between 2007 and 2010 and 25% between 2007 and 2011
- 2.5.4. Cost associated with conducting clinical trials has increased – administrative costs have approximately doubled since implementation of Directive and insurance fees reported to have increased 800% for industry sponsors

2.6. On 17 July 2012, the European Commission published a proposal for a European Clinical Trials Regulation, which would repeal the EUCTD. Refer to Section 7 for link to full text of the proposal. This proposal was preceded by the Commission carrying out two rounds of public consultation (October 2009 – January 2010; February 2011 – May 2011). An EU Regulation was proposed to avoid issues introduced through each Member State transposing into national implementation, such as the introduction of similar but different requirements and/or inclusion of additional national measures.

3. Progress in negotiation of the Regulation

3.1. The MHRA has led the negotiations on behalf of the UK. The HRA has worked closely with the MHRA throughout. The MHRA established the following:

- 3.1.1. Working group – members from MHRA and HRA; met when required to discuss technical detail of proposals and amendments.
 - 3.1.2. Steering group – chaired by MHRA and including members drawn MHRA, HRA, UK Health Departments, and Office of Life Sciences
 - 3.1.3. Stakeholder reference group – this group includes representatives from a range of organisations including pharmaceutical industry, trade associations, Association Medical Research Charities (AMRC), Academy Medical Sciences (AMS), National Institute for Health Research (NIHR), contract research organisations, NHS, clinical trials units and Wellcome Trust. It has met a few times and been used to provide updates on progress and take soundings on particular issues. The MHRA also held a 10 week public stakeholder consultation (ended 31 December 2012) to gather views on several specific issues.
- 3.2. The most recent stage of the negotiation has been the dialogues (Presidency, European Parliament, Commission), which took place during November-December 2013. These were supported by technical working group meetings.
- 3.3. Notification that informal agreement reached between Lithuanian Presidency and European Parliament in December 2013. This was endorsed by Member States in Coreper (Committee of Permanent Representatives of Member States) on 20 December 2013. Refer to Section 7 for link to full text of draft Regulation and the associated press releases.
- 3.4. Next steps in process to finalise the EU Regulation are as follows:
- 3.4.1. Linguistic and legal check of text and corresponding tidying up. It is expected that MHRA will attend these sessions.
 - 3.4.2. Council of Ministers vote
 - 3.4.3. European Parliament vote
 - 3.4.4. Publication in Official Journal of the European Union (OJEU)
- 3.5. Implementation of the Regulation will be two years after publication in OJEU; therefore it is expected to apply from mid-2016, subject to the finalisation steps above and meeting pre-requisites for implementation (e.g. readiness of IT infrastructure).

4. Summary of key points of proposed Regulation

4.1. Comparison between European Commission proposal for Regulation (as published July 2012) and the EUCTD:

- 4.1.1. Scope of proposed Regulation the same as EUCTD (i.e. CTIMPs, refer Article 1 and 2 (1)(2) for detail). Specifically excludes non-interventional studies; this does not change UK practice and should lead to harmonisation of scope in EU. A definition for “low intervention clinical trials” has been added; in this Commission’s proposal these trials were afforded shorter timelines for assessment and less stringent requirements for monitoring and documentation. *Note the definition and timelines were adjusted in negotiation.* Furthermore, as per 2001/83/EC the Regulation will not affect national legislation that prohibits or restricts: use of specific human or animal cells; medicinal

products used as abortifacients; or medicinal products containing narcotics. The Regulation also does not permit gene therapy trials that could result in modification of the subject's germ line (i.e. the Regulation is in line with Article 9(6) of 2001/20/EC.

4.1.2. New initial authorisation procedure set out in the Regulation, including requirements for:

- 4.1.2.1. Single submission for a clinical trial, regardless of the number of Member States taking part in the trial, and harmonised application dossier
- 4.1.2.2. EU Portal linked to EU Database, used for submission of applications and communications between Member State(s) and trial Sponsor.
- 4.1.2.3. Single authorisation (i.e. decision) per Member State to replace current separate approvals from competent authority and ethics committee. However, left to individual Member States how they organise to achieve single authorisation. Additionally stipulated that there is one contact per Member State to ensure efficient communication and cooperation between Member States.
- 4.1.2.4. All Member States involved in trial are involved in assessment process; the process led by a "reporting Member State". Where multiple Member States are involved in the trial then other Member States are designated as "Member States concerned". Distinction of areas where Member States cooperate in assessment and aspects where assessment made by each Member State (i.e. national aspects such as ethical (e.g. consent) or local issues (suitability of site)). Stages in assessment are:
 - Validation
 - Validation– reporting Member State confirms (or not) that it takes this role, whether trial within scope of regulation, whether application complete (as set out in Annex 1), whether low-intervention (if claimed by sponsor). Completion of this activity demarks validation.
 - Part 1 assessment – reporting Member State assesses: compliance with Chapter V (protection of subjects & informed consent) with respect to therapeutic and public health benefits plus risks and inconveniences to subject; compliance with manufacturing and import requirements; compliance with labelling; completeness of investigator brochure. Provision of assessment report to Sponsor and Member States concerned [thus Part 1 requires cooperation competent authority and ethics].
 - Part 2 assessment – each Member State assesses application for own territory (including informed consent, compensation, recruitment, suitability of those conducting trial and trial site, insurance/indemnity
- 4.1.2.5. Set timelines supported by tacit approval (at all stages of assessment)
- 4.1.2.6. Possibility for a Member State to opt-out/refuse authorisation included – rules are set out
- 4.1.2.7. Additional Member States may be added to a trial after the initial assessment decision has been reached (i.e. after the "Notification Date")

4.1.3. Substantial amendments to a trial after the initial assessment decision are now defined as "substantial modification"; the authorisation procedure (also with

reporting Member State and Member State concerned roles set out) is described in the Regulation and includes set timelines.

4.1.4. Ethics Committees and Competent Authorities:

4.1.4.1. Unlike the EUCTD, the proposed EU Regulation does not establish which body or bodies within a Member State approve the clinical trial.

4.1.4.2. Requirement is set for Member States to ensure “an independent high quality assessment within the timelines set out”. Member States are left to organise their decision making within these parameters.

4.1.4.3. Specific considerations are set out for the assessment of trials involving vulnerable populations (incapacitated adults, minors and trials in emergency situations; refer Article 10).

4.1.5. Protection of Subjects and Informed Consent:

4.1.5.1. Requirements for protection of subjects and informed consent as EUCTD;

4.1.5.2. Except that provision added in draft EU Regulation for clinical trials in emergency situations (the UK introduced this in transposition of EUCTD)

4.1.5.3. Protection of personal data follows rules set in EU Data Protection Directive (which will in time is expected to be replaced with a EU Data Protection Regulation).

4.1.6. Safety reporting provisions have been streamlined and provisions included direct reporting of suspected unexpected serious adverse reactions (SUSARs) by Sponsor to EudraVigilance and simplified submission of annual safety report by the sponsor.

4.1.7. Rules for the conduct of the trial that had been codified by GCP Directive and other documents have been brought together in the proposed text

4.1.8. Co-sponsorship provision has been included in the proposed Regulation. Note the UK included this in national regulations when transposing EUCTD.

4.1.9. EU Portal and linked EU Database is stated to provide mechanism for flow of information between Sponsor and Member States, and between Member States. This will be developed and managed by European Commission.

4.2. **Main changes made to the European Commission’s proposed Regulation during negotiation** (i.e. text endorsed by Coreper on 20 December 2013 versus text published by Commission July 2012 – refer to Section 7 for links to full text):

4.2.1. Initial Authorisation process (Chapter II; refer to Annex 1 of this document for an overview) amendments:

4.2.1.1. Process for agreeing reporting Member State is set out (refer Article 5(1))

4.2.1.2. Elements and requirements of authorisation process described in more detail

- 4.2.1.3. Timelines for authorisation extended to 60 days (was 45 days in original Commission proposal); total of 91 days allowed where questions are raised at each stage;
- 4.2.1.4. Tacit approval has remained in text (at each stage of authorisation process); this means that where a reporting Member State or Member State concerned does not submit a response via the EU Portal within required time then presumption is approval. Note this has remained in text although it was controversial amongst Member States.
- 4.2.1.5. Low intervention trials shorter timelines for approval have been removed. Note the definition of low intervention trials has also been amended. These are now classified as trials of IMPs with a marketing authorisation, and where the protocol sets out that the IMP is used in accordance with authorisation or use is evidence based; and where additional risks are minimal (refer Article 2(3) for complete definition).
- 4.2.1.6. Reference to patient involvement in the assessment of trial applications has been removed and replaced with requirement for at least one layperson to participate in the assessment (refer Article 9(8)). Note “layperson” is not defined in the Regulation.
- 4.2.1.7. The clause (Article 6(7)) that allowed a Sponsor to change their application (of their own volition) between validation date and assessment (reporting date) has been deleted.
- 4.2.1.8. Where a Sponsor withdraws an application (may do so up to Reporting Date (i.e. final assessment reports) the trial is withdrawn in all Member States. Furthermore if a Sponsor fails to respond to requests from reporting Member State within required timelines then the application is withdrawn (or lapsed in case of validation) in all Member States (refer Article 12). If the Sponsor fails to respond to requests from Member State concerned within required timeline then the application is withdrawn in that Member State. Where a Sponsor withdraws (or is refused) they may resubmit their application; in these circumstances it will be treated as a new initial application (refer Article 13).
- 4.2.1.9. The possible Member State decisions are defined (refer Article 8) and may be that the trial is: authorised; authorised with conditions; or refused. Authorised with conditions is only allowed when conditions cannot be fulfilled at time of approval. Rules are clarified whereby a Member State may refuse a trial. This includes: where the reporting Member State Part 1 Assessment is acceptable or acceptable with conditions then a Member State may refuse to accept conclusion of Part 1 in defined circumstances; where the Member State concerned Part 2 assessment is not acceptable; or where the ethics committee gives a negative opinion in accordance with that Member State’s national law. Member States must provide this decision and justification via EU Portal. Additionally Member States must put in place appeal processes.
- 4.2.1.10. As per original proposal additional Member States may be added after the Notification Date (decision on initial application); the latest text sets out the process, which is similar to the initial authorisation process, and sets the overall timeline at 52 days (refer Article 14).

- 4.2.1.11. A requirement has been added that the trial must recruit within 2 years of the Notification Date (i.e. date of decision on initial application) otherwise approval is withdrawn (refer Article 8(7)).
- 4.2.1.12. A requirement has also been added for persons assessing the application (Part 1 and Part 2 aspects) within a Member State are required to make an annual declaration of financial interests
- 4.2.2. Substantial modifications (Chapter III):
- 4.2.2.1. Have been clarified to include addition of a trial site or change of a principal investigator at a trial site
- 4.2.2.2. Authorisation process has been clarified; this is very similar to the initial authorisation process. The reporting Member State for authorisation of a substantial modification will be the same as the reporting Member State for the initial application.
- 4.2.2.3. Timelines have been amended:
- Reporting Member State must validate in 6 days – will determine whether Part 1 assessment is affected and whether the application is complete. A 15 day extension is allowed where incomplete (incl 10days for sponsor response and 5 day assessment)
 - Where Part 1 affected (refer Article 18) reporting Member State assessment of substantial modification must complete in 38 days (from Validation Date); where it is a multi-state trial process in line with initial authorisation (timeframe divided to 19days initial assessment, 12 days joint review, 7 days consolidation). Extensions are allowed (31days for questions; 50 days for ATMPs)
 - Where Part 2 affected (refer Article 20) Member State concerned must validate application within 6 days of submission (as above 15 day extension may be allowed); assessment of substantial modification affecting Part 2 must complete in 38 days (as above extension of 31d allowed where questions (12 days for sponsor to respond; 19 days to assess)
 - Decision must be made within 5 days of final assessment report of substantial modification
 - Total timeline for substantial modification process is 49 days (no extensions) or 95 days (if extensions used during validation and assessment).
- 4.2.2.4. Tacit approval applies to substantial modification process.
- 4.2.3. Ethics committees are now explicitly referenced in the text (note: competent authorities remain unreferenced), although membership, operation and functions are not referenced in detail; they are:
- 4.2.3.1. defined (Article 2) as “ (10a) ‘ethics committee’: an independent body in a Member State established in accordance with national law and empowered to give opinions for the purposes of this Regulation, taking into account the views of lay-persons, in particular patients or patients organisations.”
- 4.2.3.2. tasked with undertaking ethical review in accordance with “the Member State national legislation.”; this review may “encompass aspects related to Part I

as per Article 6 and Part II as per Article 7 thereof as appropriate for each Member State concerned.”

4.2.3.3. empowered to be involved in assessment of Suspected Unexpected Serious Adverse Reactions (SUSARs; Article 38) and Annual Reports (Article 39) if empowered by law in Member State (Article 40)

4.2.4. Protection of Subjects and Informed Consent (Chapter V; note text extracted and provided in Annex 2 for ease of reference)

4.2.4.1. This chapter provoked a substantive amount of discussion and proposals for alteration during negotiations.

4.2.4.2. General rules (Article 28) and Informed Consent (Article 29) have been revised with some rearrangement of provisions between these articles. This includes:

- clarifying provisions around withdrawal from participation, in particular consent may be revoked at any time (without providing justification and without detriment) and that this withdrawal will not affect activities carried out or data obtained based on consent up to point of withdrawal.
- adding provision for a Sponsor to ask the subject to consent for use of their data outside the trial protocol when taking informed consent for participating in the trial. It is stated that scientific research making use of data shall be conducted in accordance with applicable data protection legislation.
- replacing original requirement for a member of the investigator or member of the investigating team to carry out the prior interview with subject (or their legally designated representative) to explain trial with “a member of the investigating team who appropriately qualified according to national law of Member State concerned”.
- replacing original requirement for oral consent where a subject is unable to write with a broader provision for “consent may be given and recorded through appropriate alternative means” in these circumstances.

4.2.4.3. Provision included for simplified “informed consent” for cluster trials whereby derogations are provided against some requirements set out in Chapter V, however information must be provided to the subject and the subject may refuse to participate in the trial. Note that text is drafted such that the subject not refusing to participate after receiving information about the trial may be deemed as informed consent. This has led to reactions including from World Medical Association and the Standing Committee of European Doctors (CPME) who issued a press release (refer Section 7 links) . Refer to text provided under Article 29a in Annex 2 of this document for full details of requirements. This provision is limited to where:

- Trial is conducted in one Member State
- No contradiction with national law
- Low intervention trial and IMP is used in accordance with marketing authorisation
- Trial methodology requires groups of subjects (e.g. randomisation by GP practice or hospital) to be allocated to treatment rather than individuals
- No interventions other than standard treatment

- Protocol justifies use of gaining “informed consent by simplified means”.
- 4.2.4.4. Trials in incapacitated adults now allowed where direct benefit or potential for group benefit (except where national rules prevent; refer Article 30, text provided at Annex 2); trials in minors have remained limited to where benefit for subject (refer Article 31, text provided at Annex 2)
- 4.2.4.5. Trials in emergency situations (Article 32, text provided at Annex 2) provisions have been updated, particularly with respect to the conditions. For example the original drafting that required that “no legal representative is available” has been removed and greater reference is made to in being impracticable to provide all information and obtain informed consent within therapeutic window. This is the only group in Chapter V where requirement applied for “grounds to expect ... there is potential to produce a direct clinically relevant benefit for the subject”.
- 4.2.4.6. “Legal representative” of subject has been replaced with “Legally designated representative”, which has now been defined as (refer Article 2(18)) the entity that is empowered by national law to give consent on behalf of the subject.
- 4.2.4.7. Provisions added for further groups (note these have been mirrored in considerations for assessment in vulnerable populations (refer Article 10)):
- Clinical trials on pregnant and breastfeeding women (refer Article 31a, text provided at Annex 2) where specific conditions are met
 - Additional national measures (refer Article 31b, text provided at Annex 2) provision added to allow Member States to retain any measures they may have for those in mandatory military service, prisoners, those in residential institutions or persons for other judicial reasons who cannot participate in trials.
- 4.2.5. EU Portal/IT Infrastructure (Chapter XIV)
- 4.2.5.1. Responsibility for set up and maintenance of EU Portal (Article 77) has been moved from EU Commission to European Medicines Agency (EMA). EMA will also be responsible for maintaining and updating the infrastructure.
- 4.2.5.2. Responsibility for set up and maintenance of EU Database (Article 78), which stores data and information from EU Portal, has also been moved from EU Commission to European Medicines Agency (EMA). Additionally made explicit that the EU Database will identify each trial by a unique EU trial number, which the sponsor must reference. Also added is requirement for data in database to be searchable to “enable citizens of the EU to have access to information about medicinal products” and for it to support recording and submission to EU dictionary of medicinal products.
- 4.2.5.3. The requirement for public accessibility of EU database has been revised to clarify where confidentiality may be justified and to state that application dossiers will not be publicly available until a decision on the clinical trial has been reached.
- 4.2.5.4. Implementation of EU Regulation is conditional on the full functionality of the EU Portal and EU database being in place and having been accepted by Member States and Commission (refer Article 78a and Article 93) Recital 61 explains “... in view of the importance of the extensive IT functionalities required

.... Regulation will only become applicable once it has been verified the EU portal and EU database are fully functional”.

4.2.6. Transparency:

- 4.2.6.1. The text set out that summary of results, layperson summary and clinical study report (where applicable) must be submitted one year of the end of the trial in all Member States. This requirement is irrespective of the outcome of the clinical trial. However, allowance is made for justification for delayed submission (e.g. trial ongoing in third countries)(refer Article 34 and recital 25b). Requirements for the content of the summary of results and summary for lay persons are set out in Annex IIIa and IIIb of the Regulation respectively (for ease of reference Annex 3 of this document contains copy of this text).
- 4.2.6.2. It has also been clarified that the EU Database will contain all information submitted through the EU Portal and that the Database will be publicly accessible and the data searchable (refer recital 52). Related information will be linked by EU trial number and there will be links to data of other trials using the same IMP. No personal data of subjects will be recorded in the Database and allowance is made for justification of confidentiality in particular circumstances. All trials should be registered in the Database prior to recruitment and the start and end dates of recruitment are to be published.
- 4.2.6.3. Furthermore in applications where previous clinical trial data is referenced it must be (refer Article 25(6)):
- In the case of data from clinical trials that are conducted *after* the Regulation is implemented, from clinical trials that registered in a public register (primary or partnered WHO registry) prior to the start of the trial; or
 - In the case of data from clinical trials conducted before the Regulation is implemented, it must be from clinical trials that either registered in a public register (primary or partnered WHO registry) or that published in an independent peer-reviewed scientific publication.
- 4.2.6.4. Note “Clinical Study Report” has been added to the Regulation’s definitions (refer Article 2 (30a)) where it states these are the report on a clinical trial presented in an easily searchable format, prepared in accordance with Annex 1, Part 1 Module 5 of Directive 2001/83/EC. Furthermore it has been agreed that clinical study reports will be published, where available, within 1 month after a regulatory decision has been made on a product. New recital 20a states “For the purposes of this regulation in general the data included into clinical study reports should not be considered commercially confidential once a marketing authorisation has been granted, the decision-making process on the application for a marketing authorisation has been completed, or an application for marketing authorisation has been withdrawn. In addition, the main characteristics of the clinical trial, the conclusion on Part I and the decision on the authorisation of the clinical trial, the substantial modification of the clinical trial, and the clinical trial results including reasons for temporary halt and early termination, in general should not be considered confidential.”

4.2.7. Some other points of note:

- 4.2.7.1. “Principal Investigator” is responsible for compliance with the Regulation of the clinical trial at site (refer Article 69a). Role is defined as “an investigator who is the responsible leader of a team of investigators that conduct a clinical trial at a clinical trial site” (Article 2, definition 14a).
- 4.2.7.2. “contact person” of the Sponsor (Article 70) has been replaced with “Legal representative of sponsor” and clause has been added allowing Member States not to apply this requirement where a trial is only conducted in that Member State.
- 4.2.7.3. National Indemnification Mechanism (Article 73) has been removed
Obligation and requirements for damage compensation redrafted (Article 72).
- 4.2.7.4. Penalties (Article 89a) have been added and require Member States to set down rules on penalties for infringement of the Regulation, particular reference is made to non-compliance with submission of information intended to be made publicly available and non-compliance with provisions for subject safety.
- 4.2.7.5. The regulation will apply 2 years after publication unless the IT is not fully functional (refer points above about EU Portal/Database and Article 93) in which case the application can be delayed. The transitional arrangements, which have been revised, are set out in Article 92.
- 4.2.7.6. A review of the regulation (Article 91a), including its effect on the EU’s competitiveness, has been added to the text and will take place 5 years after date of application of the Regulation

5. Remaining uncertainties

5.1. IT infrastructure (EU Portal and EU Database). Up until recently, the European Commission was tasked with the development of the IT infrastructure. This responsibility now rests with EMA.

- 5.1.1. At present it is not clear exactly what the IT infrastructure will provide, particularly in respect of provision for Member States, for interaction between Member States and for interface with Member State systems (where applicable).
- 5.1.2. The Commission had established a group for informal discussion with Member States about the IT infrastructure. The group had only met a couple of times, however the UK was represented. It will be important for the UK to fully engage with EMA as they take on the responsibility.
- 5.1.3. The Regulation is anticipated to be implemented mid-2016. Reassuringly the agreed text of the Regulation has added a requirement that the implementation of the Regulation will not occur before the IT infrastructure is fully functional and accepted by Member States. Given that responsibility it has just been agreed that responsibility for the IT will be with EMA and there is limited time to the anticipated implementation date, there is uncertainty about whether it will be possible to specify, develop, test and implement fully functional and accepted IT infrastructure in the time available.

5.2. Detailed content of the application dossier for initial application – Annex 1 of the Regulation sets out requirements for the initial application. This includes a brief reference to the EU Application Form. The detailed content of the form is not specified although it

could be expected to be similar to the current EudraCT Annex 1 form. Therefore at this time there is some uncertainty about the full detail of the application dossier. This is flagged as Member States will have to assess and reach decision on application dossier provided and the response to any questions raised. Therefore the NHS REC application form for CTIMPs currently in IRAS will no longer be used for these trials.

- 5.3. Readiness of all Member States. The Regulation will set in place a new authorisation process, which could mean significant changes in working for some Member States. Additionally authorisation processes require greater cooperation between Member States in multi-state clinical trials and there may be issues where Member States are at different levels of readiness for the Regulation. This may also include issues arising from individual Member States interaction with the IT infrastructure that is provided and what national infrastructure they have in place.
- 5.4. Implementation timeline may be uncertain. The text sets out proposed timelines, some of which require addition of detail during next stages for the text. However, the readiness of the IT infrastructure may be ultimate determinant of implementation.
- 5.5. Templates and guidelines. It is not clear what EU templates or guidelines may be implemented as part of the Regulation. For example will requests to Sponsor from reporting/concerned Member States and assessment reports be required to use specific formats or data dictionaries.

6. Comments and next steps

- 6.1. In many respects the UK should be well placed for the implementation of this new Regulation because:
 - 6.1.1. Some provisions brought into Regulation, as compared with EUCTD, are similar to those that were introduced into existing UK Regulations when EUCTD was transposed e.g. rules for trials in emergency situations, co-sponsorship.
 - 6.1.2. We have an established working relationship between the competent authority (MHRA) and research ethics committees.
 - 6.1.3. The UK has a good record in meeting authorisation timelines.
 - 6.1.4. The HRA (and NRES before) are continually working to improve ethical review processes and timelines (for all studies).
 - 6.1.5. The HRA already has projects underway that are likely to provide basis for further improvements to timelines, improved management of applications and increased efficiency overall (for example ethics officer pilot, development of new system for management of ethical review).
 - 6.1.6. The MHRA has successfully negotiated, on behalf of the HRA and UK, a number of amendments to the regulation. Overall, the agreed text is in line with the UK's negotiating objectives.
- 6.2. The implementation of the Regulation will require alterations to current processes, for example:

- 6.2.1. Clinical trial applications (initial applications, substantial modifications, other notifications and reports) will all be according to EU requirements and be received via the EU Portal. Therefore, the current REC application (and supporting document set), which is in IRAS, will not be used for CTIMPs.
 - 6.2.2. This is likely to mean that information provided to RECs for ethical review of CTIMPs will be in a different format and may have different overall content from that used currently.
 - 6.2.3. Systems used for management of ethical review will need to be able to support necessary processes (including timelines) for CTIMPs and non-CTIMPs. These may lead to a variety of requirements depending on study type.
 - 6.2.4. The HRA may need to review how ethical review of CTIMPs is carried out, the Committees that are responsible and the frequency with which they meet.
 - 6.2.5. It is expected that, as now, the Standard Operating Procedures (SOPs) for research ethics committees in the UK will apply the requirements of the Regulation to a broader range of studies, where it is appropriate. For example the 60 day approval timeline set by UK clinical trial regulations for CTIMPs is applied to all applications for full ethical review.
 - 6.2.6. In respect of assessment of clinical trials with specific considerations, the HRA will need to consider how the most appropriate way to organise to ensure that appropriate individuals are included in the assessment process in a sufficiently timely manner (e.g. where a clinical trial involves minors).
- 6.3. The Regulation requires that specific aspects of an application (or substantial modification) are included in either Part 1 or Part 2 of the assessment process. Therefore the UK must organise so that it has in place the processes and mechanisms that distribute responsibility for the various aspects of review in a way that is appropriate and that can work to the timelines set out for the respective parts of the assessment. This will be critical as the overall assessment process takes in aspects that are currently entirely or partly reviewed by the competent authority, ethics committee and NHS R&D. As such it is considered that the HRA Assessment and Approval, which is currently subject to approval by the Department of Health for England, will be critical in delivering the platform for the changes required.
- 6.4. HRA must continue to work closely with the MHRA to ensure that processes are developed, agreed and implemented, which will ensure that the UK is able to meet the requirements of the Regulation, including the timelines.
- 6.5. Timeliness and meeting the set timelines will be critical to avoid authorisation of trials by tacit rather than explicit approval.
- 6.6. It will be critical that the UK (MHRA and HRA) is closely engaged with development of IT infrastructure (EU Portal/Database) in order to ensure that we have the appropriate organisation of systems within the UK to manage review and interact with the EU systems. This is important as it is likely to necessitate new systems and/or enhancements to existing UK systems in order to support the UK in linking with EU IT infrastructure and managing review, communication and authorisation processes within the UK.

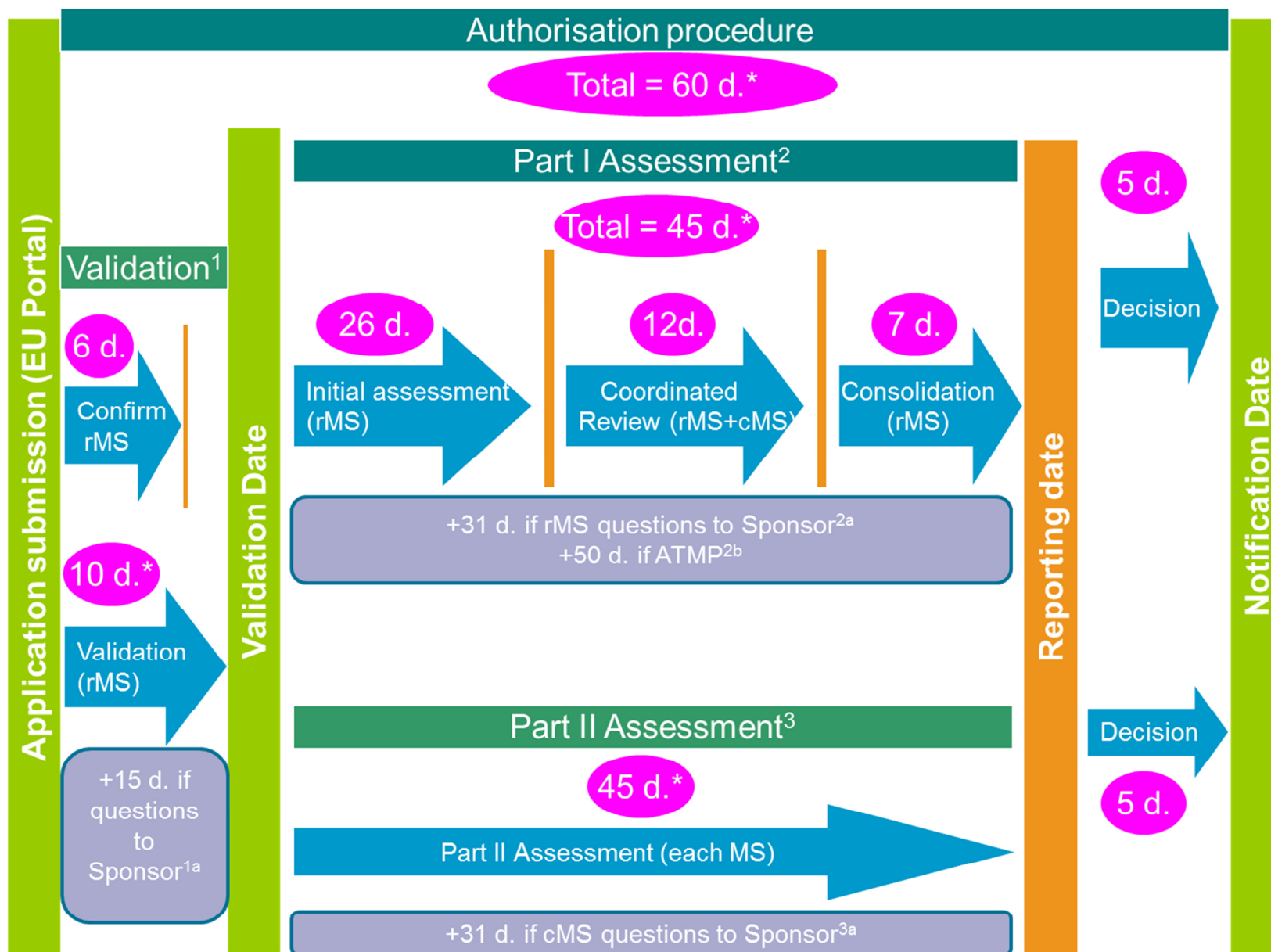
6.7. As the Regulation will replace the existing Directive and thus the UK transposing regulation, there will need to be a programme of work to identify what national legislation will be needed to support the implementation of the Regulation. Some aspects may be clear in that the Regulation stipulates Member States must make national provision (e.g. penalties for non-compliance) but others may be less obvious e.g. where a term or definition in the Regulation will need some foundation in national law and/or where the existing UK regulations provide current legal basis (e.g. legally designated representative of subject, constitution of ethics committees).

7. Links to further information

- 7.1. Consolidated text of the draft regulation as approved Committee of Permanent Representatives (COREPER) on 20 December 2013:
<http://register.consilium.europa.eu/doc/srv?l=EN&t=PDF&gc=true&sc=false&f=ST%2017866%202013%20INIT&r=http%3A%2F%2Fregister.consilium.europa.eu%2Fpd%2Fen%2F13%2Fst17%2Fst17866.en13.pdf>
- 7.2. MHRA News Release, 13 January 2014: <http://www.mhra.gov.uk/NewsCentre/CON363914>
- 7.3. Council of European Union Press Release, 20 December 2013:
http://www.consilium.europa.eu/uedocs/cms_data/docs/pressdata/en/lsa/140241.pdf
- 7.4. European Commission statement, 20 December 2013 : http://ec.europa.eu/commission_2010-2014/borg/docs/statement_20131220_en.pdf
- 7.5. Lithuanian Presidency Press Release following Committee of Permanent Representatives (COREPER) vote, 20 December 2013: <http://www.eu2013.lt/en/news/pressreleases/agreement-on-clinical-trials-major-step-towards-innovative-and-competitive-europe>
- 7.6. EP rapporteur (Glenis Willmott, Labour MEP) Press Release, 16 December 2013:
<http://www.gleniswillmott.eu/labour-mep-brokers-historic-deal-on-clinical-trial-transparency/>
- 7.7. World Medical Association (WMA) and the Standing Committee of European Doctors (CPME) Press Release on the clinical trials regulation “Clinical trials: Not enough safeguards for EU Citizens”, 19 December 2013 [particular reference to cluster trials]:
http://www.wma.net/en/40news/20archives/2013/2013_35/index.html
- 7.8. European Commission Proposal published July 2012:
http://ec.europa.eu/health/files/clinicaltrials/2012_07/proposal/2012_07_proposal_en.pdf

Annex 1- simple diagram of initial authorisation process

The following diagram is adapted from a presentation created by Presidency during trilogues and updated with timelines set out in text informally agreed on 20 December 2013.



Notes:

rMS – designates reporting Member State; cMS designates concerned Member State; MS designates Member State(s)

* highlights timelines where no extensions (refer grey boxes)

1 Validation. This stage includes confirmation via EU Portal of which MS is to be “reporting Member State” (within 6d of submission; refer Article 3 for details of mechanism to agree rMS) and the rMS confirming trial is within the scope of the Regulation and that the application is complete. Concerned Member States (cMS) have 7d from submission date to communicate concerns to rMS; rMS takes these concerns into account. If rMS does not notify Sponsor within 10d then assumed that trial within scope and application complete.

1a Extension of timeline during validation occurs where the application is incomplete or determined that trial not in scope of the Regulation. 15 days is comprised of 10d for Sponsor to reply and 5d for rMS to complete validation following further information from Sponsor. Where the Sponsor does not provide information within timeline the application is considered as lapsed.

2 Part I Assessment (refer Article 6 for detail) includes:

- Confirmation of whether low intervention trial.
- Compliance with Chapter V (Protection of Subjects & Informed Consent) wrt anticipated therapeutic and public health benefits; and risks and inconveniences for subject.
- Compliance with manufacturing and importation of IMP and auxiliary medicinal products set out in Chapter IX
- Compliance with labelling requirements
- Completeness and adequacy of Investigator’s Brochure (IB)

The rMS is responsible for producing an assessment report covering these aspects and have conclusion (broadly: conduct acceptable/conduct acceptable subject to conditions/conduct not acceptable). Timeline is counted from validation date and the rMS provides the final Part I assessment report to cMS and Sponsor via EU Portal.

Where the trial involves multiple MS the Part I assessment has three phases as shown in diagram. A draft Part I assessment report is circulated to cMS during initial assessment.

2a Extension of Part 1 Assessment timeline by rMS to gain additional information from the Sponsor. 31d is comprised of Sponsor submitting additional information within 12d, joint review by rMS and cMS within 12d and further consolidation by rMS within 7d. Where the Sponsor does not provide information within timeline application is considered withdrawn in all MS.

2b Extension of Part 1 Assessment timeline by rMS because trial is an Advanced Therapy Medicinal Product (ATMP) or high-technology medicinal products as defined by (EC) No 726/2004.

3 Part II Assessment (refer Article 7 for detail). Each MS concerned assesses for own territory compliance with:

- informed consent requirements (Chapter V)
- arrangements for rewarding/compensating investigators and subjects (Chapter V)
- recruitment of subjects (Chapter V)
- Directive 95/46/EC [data protection]
- suitability of those conducting trial (Article 46)
- suitability of trial sites (Article 47)
- damage compensation requirements (Article 72)
- applicable rules for collection, storage and future use of biological samples

Each MS creates a report containing assessment wrt Part II and their conclusion; this is submitted to the Sponsor. Timeline is counted from Validation Date.

3a Extension of Part II Assessment timeline for a cMS where that MS has questions for Sponsor in relation to Part II assessment. 31 day extension is comprised of 12d for Sponsor to submit response to questions (via EU Portal) and 19d for cMS to complete their assessment. Where the Sponsor does not provide information within timeline application is considered withdrawn wrt to that MS.

Annex 2- Chapter V (Protection of subjects and informed consent) of EU Clinical Trial Regulation as extracted from text that was endorsed by Coreper on 20 December 2013

Consolidated text of the draft regulation as approved Committee of Permanent Representatives (COREPER) on 20 December 2013:

<http://register.consilium.europa.eu/doc/srv?l=EN&t=PDF&gc=true&sc=false&f=ST%2017866%202013%20INIT&r=http%3A%2F%2Fregister.consilium.europa.eu%2Fpd%2Fen%2F13%2Fst17%2Fst17866.en13.pdf>

Text in ~~strikethrough~~ highlights where deletions made to the Commission's text as proposed in July 2012

Text in **bold underline** highlights where additions have been made to the Commission's text as proposed in July 2012

-----START OF EXTRACT-----

Chapter V Protection of subjects and informed consent

Article 28

General rules

1. A clinical trial may be conducted only where all of the following conditions are met:
 - (a) the anticipated **benefits to the subject or** ~~therapeutic and~~ public health benefits justify the foreseeable risks and inconveniences **and compliance with this condition is permanently monitored;**
 - ~~(b) compliance with point (a) is permanently observed;~~
 - (ba) the subject or, where the subject is not able to give informed consent, his or her legally designated representative has received information in accordance with Article 29(2);**
 - (c) the subject or, where the subject is not able to give informed consent, his or her legally **designated** representative has given informed consent **in accordance with Article 29(1);**
 - ~~(d) the subject or, where the subject is not able to give informed consent, his or her legal representative has had the opportunity, in a prior interview with the investigator or a member of the investigating team, to understand the objectives, risks and inconveniences of the clinical trial, and the conditions under which it is to be conducted and has also been informed of the right to withdraw from the clinical trial at any time without any resulting detriment;~~
 - (e) the rights of the subject to physical and mental integrity, to privacy and to the protection of the data concerning him or her in accordance with Directive 95/46/EC are safeguarded;~~;~~

- (ea) the clinical trial has been designed to involve as little pain, discomfort, fear and any other foreseeable risk as possible for the subject and both the risk threshold and the degree of distress are specially defined in the protocol and constantly monitored;**
- (eb) the medical care given to subjects is the responsibility of an appropriately qualified medical doctor or, where appropriate, of a qualified dental practitioner;**
- (ec) the subject or, where the subject is not able to give informed consent, his or her legally designated representative, has been provided with contact details of an entity where further information can be received in case of need;**
- (ed) no undue influence including that of a financial nature shall be exerted on subjects to participate in the clinical trial.**

2. The rights, safety and well-being of the subjects shall prevail over the interests of science and society.

2a. Without prejudice to Directive 95/46/EC, the sponsor may ask the subject at the time when the subject gives his or her informed consent to participate in the clinical trial to consent to use his or her data outside the protocol of the clinical trial exclusively for scientific purposes. That particular consent may be withdrawn at any time by the subject.

The scientific research making use of the data outside the protocol of the clinical trial shall be conducted in accordance with applicable legislation on data protection.

3. Any subject, **or, where the subject is not able to give informed consent, his or her legally designated representative,** may, without any resulting detriment **and without having to provide any justification,** withdraw from the clinical trial at any time by revoking his or her informed consent. **Without prejudice to Directive 95/46/EC, the** The withdrawal of consent shall not affect the activities carried out **and the use of data obtained** based on consent before its withdrawal.

Article 29

Informed consent

1. Informed consent shall be written, dated and signed ~~and given freely~~ by the **person performing the interview and the** subject or his or her legally **designated** representative after having been duly informed **in accordance with paragraph 2** of the nature, significance, implications and risks of the clinical trial. It shall be appropriately documented. Where the subject is unable to write, oral consent **may be given and recorded through appropriate alternative means** in the presence of at least one impartial witness ~~may be given in exceptional cases.~~ **In that case, the witness shall sign and date the informed consent document.** The subject or his or her legally **designated** representative shall be provided with a copy of the document **(or the record)** by which informed consent has been given. **The informed consent shall be documented. Adequate time shall be given for the subject to consider his or her decision to participate in the trial.**

2. **Information** ~~Written information~~ given to the subject and/or the **legally designated** representative for the purposes of obtaining his or her informed consent shall:
- (a) **enable the subject or his or her legally designated representative to understand:**
 - (i) **the nature, objectives, benefits, implications, risks and inconveniences of the clinical trial;**
 - (ii) **the subject' rights and guarantees regarding his or her protection, in particular his or her right to refuse to participate and the right to withdraw from the trial at any time without any resulting detriment and without having to provide any justification;**
 - (iii) **the conditions under which the clinical trial is to be conducted, including the expected duration of the subjects participation in the clinical trial;**
 - (iv) **the possible treatment alternatives, including the follow-up measures if the participation of the subject in the clinical trial is discontinued; and**
 - (b) be kept **comprehensive**, concise, clear, relevant, and understandable to a lay person **and**; ~~It shall include both medical and legal information. It shall inform the subject about his or her right to revoke his or her informed consent.~~
 - (c) **be provided in a prior interview with a member of the investigating team who is appropriately qualified according to national law of the Member State concerned;**
 - (d) **include information about the applicable damage compensation regime;**
 - (e) **include the EU trial number, and information about the availability of the trial results in accordance with paragraph 4.**
- 2a. **The information referred to in paragraph 2 shall be prepared in writing and be available to the subject or, where the subject is not able to give informed consent, his or her legally designated representative.**
- 2b. *In the interview, special attention shall be paid to the information needs of individual subjects and specific patient populations, as well as to the methods used to give the information.*
- 2c. *In the interview, it shall be verified that the subject has understood the information.*
3. ~~The subject shall be provided with a contact point where he or she may obtain further information.~~
- 3a. **This Regulation is without prejudice to national legislation requiring that both the signature of the incapacitated person and the signature of the legally designated representative may be required on the informed consent form.**

- 3b. This Regulation is without prejudice to national legislation requiring that, in addition to the informed consent given by the legally designated representative, a minor who is capable of forming an opinion and assessing the information given to him or her, shall also assent in order to participate in a clinical trial.**
- 4. The subject shall be informed that the summary of the results of the trial and a summary presented in terms understandable to a layperson will be made available in the EU database pursuant to Article 34(3) irrespective of the trial outcome, and, to the extent possible, when the summaries become available.***

Article 29a

Informed consent in cluster trials

- 1. Where a clinical trial is to be conducted exclusively in one Member State, that Member State may, without prejudice to Article 32, and by way of derogation from Article 28, paragraph 1, points (ba), (c), and (ec), from paragraphs 1, 2(c) and 2a, 2b and 2c of Article 29, and from Article 30 and 31, allow the investigator to obtain informed consent by the simplified means set out in paragraph 2 provided that all of the conditions set out in paragraph 3 are fulfilled.**
- 2. For clinical trials that meet the requirements in paragraph 3, informed consent shall be deemed to have been obtained if:**
- (a) the information required under Article 29(2(a)), 29(2(b)), 29(2(d)) and 29(2(e)) is given in accordance with what is laid down in the protocol prior to the inclusion of the subject in the trial, and this information makes clear, in particular, that the subject can refuse to participate in, or withdraw at any time from, the trial without any resulting detriment;**
 - (b) the potential subject, after being informed, does not object to participating in the trial.**
- 3. Informed consent may be obtained by the simplified means set out in paragraph 2, if all the following conditions are met:**
- (aa) the simplified means for obtaining informed consent do not contradict national law in the Member State concerned;**
 - (a) the methodology of the trial requires that groups of individual subjects rather than individual subjects are allocated to receive different investigational medicinal products in a clinical trial;**
 - (b) the clinical trial is a low-intervention clinical trial and the investigational medicinal products are used in accordance with the terms of the marketing authorisation;**
 - (ba) there are no interventions other than the standard treatment of the subjects concerned;**
 - (c) the protocol justifies the reasons for obtaining informed consent with simplified means and describes the scope of information provided to the subjects, as well as the ways of providing information.**

4. The investigator shall document all refusals and withdrawals and shall ensure that no data for the clinical trial are collected from subjects that refuse to participate in or have withdrawn from the clinical trial.

Article 30

Clinical trials on incapacitated subjects

1. In the case of incapacitated subjects who have not given, or have not refused to give, informed consent before the onset of their incapacity, a clinical trial may be conducted only where, in addition to the conditions set out in Article 28, all of the following conditions are met:
 - (a) the informed consent of the **legally designated** representative has been obtained, ~~whereby consent shall represent the subject's presumed will;~~
 - (b) the incapacitated subject has received ~~adequate~~ **the** information ~~in relation~~ **referred to in Article 29(2) adequate** to his or her capacity ~~to~~ **for** understanding ~~it~~ regarding the trial, the risks and the benefits;
 - (c) the explicit wish of an incapacitated subject who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical trial at any time is **respected** ~~considered~~ by the investigator;
 - (d) no incentives or financial inducements are given **to the subject or his or her legally designated representative** except **for** compensation for **expenses and loss of earnings directly related to the** participation in the clinical trial;
 - (e) ~~such research~~ **the clinical trial** is essential **with respect to incapacitated subjects** ~~to validate~~ **and** data **of comparable validity cannot be** obtained in clinical trials on persons able to give informed consent or by other research methods;
 - (f) ~~such research~~ **the clinical trial** relates directly to a life-threatening or debilitating medical condition from which the subject suffers;
 - (g) ~~the clinical trial has been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and developmental stage and both the risk threshold and the degree of distress are specially defined and constantly observed;~~
 - (h) there are **scientific** grounds for expecting that participation in the clinical trial will produce:
 - (i) a **direct** benefit to the incapacitated subject outweighing the risks **and burdens involved, or**
 - (ii) **some benefit for the population represented by the incapacitated subjects concerned when the clinical trial relates directly to the life-threatening or debilitating medical condition from which the subject suffers and such trial will pose only minimal risk to, and will impose minimal burden on, the incapacitated subject concerned in comparison with the standard treatment of the incapacitated subject's condition** ~~or will produce no risk at all.~~
- 1a. Article 30(1)(h)(ii) shall be without prejudice to more stringent national rules prohibiting the conduct of those clinical trials on incapacitated subjects where there are no scientific grounds to expect that participation in the clinical trial will produce a direct benefit to the subject outweighing the risks and burdens involved.**

2. The subject shall as far as possible take part in the consent procedure.

Article 31

Clinical trials on minors

1. A clinical trial on minors may be conducted only where, in addition to the conditions set out in Article 28, all of the following conditions are met:
 - (a) the informed consent of the **legally designated** representative has been obtained, ~~whereby consent shall represent the minor's presumed will;~~
 - (b) the minor has received ~~all relevant~~ **the** information **referred to in Article 29(2)** in a way adapted to his or her age and **mental** maturity, from ~~professionals~~ **the investigators or members of the investigating team** trained or experienced in working with children, ~~regarding the trial, the risks and the benefits;~~
 - (c) the explicit wish of a minor who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical trial at any time, is ~~duly taken into consideration~~ **respected** by the investigator ~~in accordance with his or her age and maturity;~~
 - (d) no incentives or financial inducements are given **to the subject or his or her legally designated representative** except **for** compensation for **expenses and loss of earnings directly related to the** participation in the clinical trial;
 - (e) ~~such research~~ **the clinical trial is intended to investigate treatments for a medical condition that only occurs in minors or the clinical trial** is essential **with respect to minors** to validate data obtained in clinical trials on persons able to give informed consent or by other research methods;
 - (f) ~~such research~~ **the clinical trial** either relates directly to a medical condition from which the minor concerned suffers or is of such a nature that it can only be carried out on minors;
 - ~~(g) the clinical trial has been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and developmental stage and both the risk threshold and the degree of distress are specially defined and constantly observed;~~
 - (h) **there are scientific grounds for expecting that participation in the clinical trial will produce a direct benefit for the minor concerned outweighing the risks and burdens involved or will produce** some direct benefit for the **population represented by the minor concerned** ~~group of patients is obtained from the clinical trial~~ **and will pose only minimal risk to, and will impose minimal burden on, the minor concerned in comparison with the standard treatment of the minor's condition.**
2. The minor shall take part in the consent procedure in a manner adapted to his or her age and **mental** maturity.
 - 2a. **If during a clinical trial the minor reaches the age of majority as defined in the national law of the Member State concerned, his/her express informed consent shall be obtained before the trial may continue.**

Article 31a

Clinical trials on pregnant and breastfeeding women

A clinical trial on pregnant and breastfeeding women may be conducted only where, in addition to the conditions set out in Article 28, the following conditions are met:

- (a) the clinical trial has the potential to produce a direct benefit for the pregnant or breastfeeding woman concerned, or her embryo, foetus or child after birth outweighing the risks and burdens involved; or**
- (b) if such clinical trial has no direct benefit for the pregnant or breastfeeding woman concerned, or her embryo, foetus or child after birth it can be conducted only if:**
 - (i) a clinical trial of comparable effectiveness cannot be carried out on women who are not pregnant or breastfeeding;**
 - (ii) the clinical trial contributes to the attainment of results capable of benefitting pregnant or breastfeeding women or other women in relation to reproduction or other embryos, foetuses or children; and**
 - (iii) the clinical trial poses a minimal risk to, and imposes a minimal burden on the pregnant or breastfeeding woman concerned, her embryo, foetus or child after birth;**
- (c) where research is undertaken on breastfeeding women, particular care is taken to avoid any adverse impact on the health of the child;**
- (d) no incentives or financial inducements are given to the subject except for compensation for expenses and loss of earnings directly related to the participation in the clinical trial.**

Article 31b

Additional national measures

Member States may maintain additional measures regarding persons performing mandatory military service, persons deprived of liberty, persons who, due to a judicial decision cannot take part in clinical trials, or persons in residential care institutions.

Article 32

Clinical trials in emergency situations

1. By way of derogation from points (c) and (d) of Article 28(1), from points (a) and (b) of Article 30(1) and from points (a) and (b) of Article 31(1), informed consent **to participate in a clinical trial** may be obtained after the **decision to include the subject in the clinical trial provided that this decision is taken at the time of the first intervention in accordance with the protocol for the clinical trial on a subject** start of the clinical trial to continue the clinical trial and information on the clinical trial may be given **accordingly**, after the start of the clinical trial provided that all of the following conditions are fulfilled:
 - (a) due to the urgency of the situation, caused by a sudden life-threatening or other sudden serious medical condition, **the subject is unable** it is impossible to **provide** obtain prior informed consent from the subject and it is impossible to **receive** supply prior information **on the clinical trial** to the subject;

- (aa) there are scientific grounds to expect that participation of the subject in the clinical trial will have the potential to produce a direct clinically relevant benefit for the subject resulting in a measurable health-related improvement alleviating the suffering and/or improving the health of the trial subject, or the diagnosis of their condition;
- (b) ~~no legal representative is available~~ it is not possible within the therapeutic window to supply all prior information and obtain prior informed consent from a legally designated representative of the subject;
- (c) the investigator certifies that he or she is not aware of any objections to participate in the clinical trial ~~the subject has not previously expressed~~ by the subject ~~objections known to the investigator;~~
- (d) the clinical trial ~~research~~ relates directly to the subject's a medical condition because of which ~~causes the impossibility~~ it is not possible within the therapeutic window to obtain prior informed consent from the subject or from a legally designated representative and to supply prior information and is of such a nature that it may be conducted exclusively in emergency situations;
- (e) the clinical trial poses a minimal risk to, and imposes a minimal burden on, the subject in comparison with the standard treatment of the subject's condition.
2. Following an intervention pursuant to paragraph 1, The informed consent in accordance with Article 29 ~~referred to in paragraph 1~~ shall be sought to continue the participation of the subject in the clinical trial ~~obtained~~, and information on the clinical trial shall be given, in accordance with the following requirements:
- (a) regarding incapacitated subjects and minors, the informed consent ~~referred to in paragraph 1~~ shall be ~~obtained as soon as possible~~ sought by the investigator from the legally designated representative without undue delay and the information referred to in Article 29(2) ~~paragraph 1~~ shall be given as soon as possible to the subject and to the legally designated representative;
- (b) regarding other subjects, the informed consent ~~referred to in paragraph 1~~ shall be ~~obtained as soon as possible~~ sought by the investigator without undue delay from the legally designated representative or the subject, whichever is sooner and the information referred to in Article 29(2) ~~paragraph 1~~ shall be given as soon as possible to the legally designated representative or the subject, whichever is sooner.

For the purposes of point (b), where informed consent has been obtained from the legally designated representative, informed consent to continue the participation in the clinical trial shall be obtained from the subject as soon as he or she ~~it~~ is capable of giving informed consent.

- 2a. *If the subject or, where applicable, the legal representative does not give consent, he or she shall be informed of the right to object to the use of data obtained from the trial.*

-----END OF EXTRACT-----

Annex 3- Annex IIIa (content of summary of results of clinical trial) and Annex IIIb (content of summary of results of clinical trial for lay persons) of EU Clinical Trial Regulation as extracted from text that was endorsed by Coreper on 20 December 2013

Consolidated text of the draft regulation as approved Committee of Permanent Representatives (COREPER) on 20 December 2013:

<http://register.consilium.europa.eu/doc/srv?l=EN&t=PDF&gc=true&sc=false&f=ST%2017866%202013%20INIT&r=http%3A%2F%2Fregister.consilium.europa.eu%2Fpd%2Fen%2F13%2Fst17%2Fst17866.en13.pdf>

Text in ~~strikethrough~~ highlights where deletions made to the Commission's text as proposed in July 2012

Text in **bold underline** highlights where additions have been made to the Commission's text as proposed in July 2012

-----START OF EXTRACT-----

ANNEX IIIA

Content of the summary of the results of the clinical trial

The summary of the results of the clinical trial shall contain information on the following elements:

A. CLINICAL TRIAL INFORMATION:

- 1. Clinical trial identification (including title of the trial and protocol number).***
- 2. Identifiers (including EU trial number, other identifiers).***
- 3. Sponsor details (including scientific and public contact points).***
- 4. Paediatric regulatory details (including information whether the trial is a part of a Paediatric Investigation Plan).***
- 5. Result analysis stage (including information about intermediate data analysis date, interim or final analysis stage, date of global end of the trial).***

For trials replicating studies on medicinal product already authorised and used in accordance with the terms of the marketing authorisation, the summary of the result should also indicate identified concerns in the overall results of the trial relating to relevant aspects of the efficacy of the related medicinal product.

- 6. General information about the trial (including information about main objectives of the trial, trial design, scientific background and explanation of rationale for the trial; date of the start of the trial, measures of protection of subjects taken, background therapy; statistical methods used).***
- 7. Population of trial subjects (including information with actual number of subjects included in the trial in the Member State concerned, in EU and third countries; age group breakdown, gender breakdown).***

B. SUBJECT DISPOSITION:

1. *Recruitment (including information with number of subjects screened, recruited and withdrawn; inclusion and exclusion criteria; randomization and blinding details; investigational medicinal products used).*
2. *Pre-assignment Period.*
3. *Post Assignment Periods.*

C. BASELINE CHARACTERISTICS:

1. *Baseline Characteristics (Required) Age.*
2. *Baseline Characteristics (Required) Gender.*
3. *Baseline Characteristics (Optional) Study Specific Characteristic.*

D. END POINTS:

1. *Endpoint definitions.**
2. *End Point #1*
Statistical Analyses
3. *End Point #2*
Statistical Analyses

**Information shall be provided for as many end points as defined in the protocol.*

E. ADVERSE EVENTS:

1. *Adverse events information.*
2. *Adverse event reporting group.*
3. *Serious adverse event.*
4. *Non-serious adverse event.*

F. MORE INFORMATION:

1. *Global Substantial Modifications.*
2. *Global Interruptions and re-starts.*
3. *Limitations, addressing sources of potential bias and imprecisions & Caveats*
4. *A declaration of the submitting party on liability for the accuracy of the submitted information.*

Annex IIIb to the ANNEX

ANNEX IIIB

Content of the summary of the results of the clinical trial for lay persons

The summary of the results of the clinical trial for lay persons shall contain information on the following elements:

- 1. Clinical trial identification (including title of the trial, protocol number, EU trial number and other identifiers).***
- 2. Name and contact details of the sponsor.***
- 3. General information about the clinical trial (including where and when the clinical trial was conducted, main objectives of the trial and explanation of rationale for the trial).***
- 4. Population of trial subject (including information with actual number of subjects included in the trial in the Member State concerned, in EU and third countries; age group breakdown, gender breakdown, inclusion and exclusion criteria).***
- 5. Investigational medicinal products used.***
- 6. Description of adverse reactions and their frequency.***
- 7. Overall results of the trial.***
- 8. Comments on the outcome of the trial.***
- 9. Indication if follow up trials are foreseen.***
- 10. Indication where additional information could be found.***

-----END OF EXTRACT-----