Comments on 'Assessment of the Functioning of the "Clinical Trials Directive" 2001/20/EC – Public Consultation Paper'

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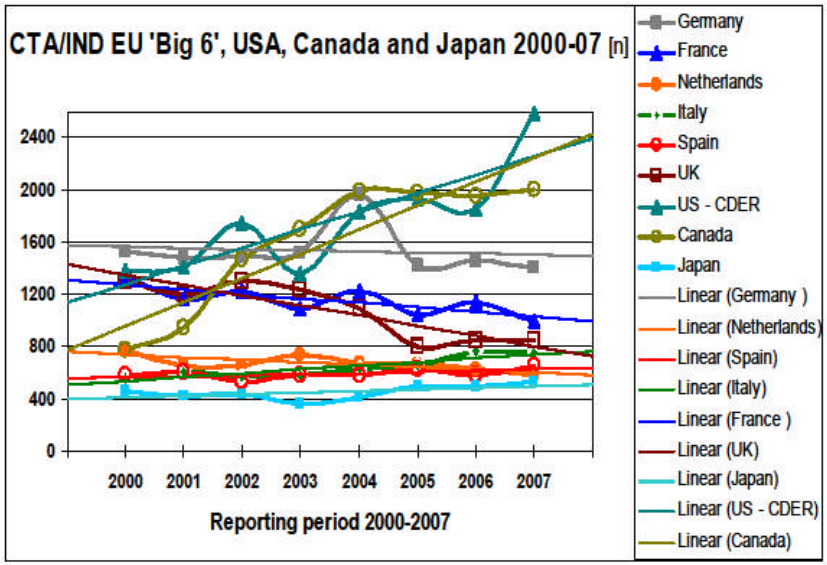
	General Comments on Consultation
	The consultation paper states correctly that "*the long term consequence* (of the current functioning of the CTD 2001/20/EC) *is that patients are deprived of innovative treatments and competitiveness of European clinical research is reduced*" (p. 22, l. 37-38). Any revision of the current trial legislation should meet these major concerns. Both issues – the one of **access** as well as the one of **competiveness** – are linked to the central benchmarks 'time' and 'costs'- the success of a revised trial legislation will directly depend on the EU Commission's ability to reduce the administrative burden generated by EU's current clinical trial legislation.
	Although the Consultation paper constitutes a very far-reaching and ample reflection, some conceptual limitations are still discernible: • The document – generated under the auspices of DG Enterprise and Industry – is still focusing, like the CTD 2001/20/EC, on the role of clinical trials as vehicles to obtain marketing authorisations for medicinal products. The relevance of clinical trials to contribute (i) to the continued benefit-risk assessment of commercially available therapies in comparison to other products and/or other therapy forms, and (ii) to the medical evidence building in daily medical practice should find more emphasis in the revised, future legislative texts. • The data on clinical trial authorisations in the EU in Ch. 2 – taken from EudraCT database - are of limited significance: they neither allow (i) to assess the legislative outcome of the CTD 2001/20/EC compared to the situation before the Directive entered into force, nor (ii) to compare the trial metrics in the EU against the situation in other areas world-wide. Due to these limitations, some of the statements made in Ch. 2.5 might be discussed controversially. With regard to the cited ICREL data, additional metrics are incorporated into this contribution (see below), to allow the EU Commission to get a more comprehensive picture of the decline of clinical trial activities in several EU countries over the last decade and to better assess the Directive's outcome in comparison to other regions world-wide.
	Over the last decade, Europe's **competitiveness** in clinical drug research has decreased. Clinical trial activities – measured in terms of CTA authorisations - in those EU Member States which might be considered as the European 'heavyweights' in clinical research (i.e. those which decide in average per year on more than 500 clinical trial applications with medicinal products ('EU big six')), were regressive over the last eight years (2000-2007), compared to North America. Only Italy with an average annual growth rate of around 5% keeps pace with the US (+8%) and Canada (+13%). All five other analysed EU Member States experienced growth rates even below the average growth rate in Japan (+3%) – in case of Spain the rate is still positive (+2%); for Germany (-1%), France, the Netherlands (both -3%) and the UK (-7% per annum over the period from 2000 to 2007!), the average annual growth rates are negative. The figures shown below are based on official clinical trial applications (CTA) statistics from National Competent Authorities which are published by the respective authorities on their websites pages.

Comparison of drug agencies' official clinical trial **application authorisation statistics (drug trials)**



	Determination Coefficient (Lin. Regr.)	Average growth rates (Annualized)
Germany	R^2=0.01	- 1%
France	R^2=0,60	- 3%
Netherlands	R^2=0.55	- 3%
Italy	R^2=0.78	+ 5%
Spain	R^2=0.35	+ 2%
UK	R^2=0.79	- 7%
US - CDER	R^2=0.71	+ 8%
Canada	R^2=0.83	+ 13%
Japan	R^2=0.33	+ 3%

US: Data for original Investigational New Drug (IND) applications (Data from Center for Drug Evaluation and Research only)
Italy: Clinical trial authorisations phase II-IV only
UK: Clinical trial authorisations phase II-IV only (Phase I trials were exempted from notification/authorisation prior to May 2004)

Reference : http://www.ctmconference.com/PPT/Markus%20HARTMANN_The%20Impact%20of%20the%20EU%20Clinical%20Trial%20Directive%202001_20_EC.pdf (plus sources / references cited therein)

The reported average growth rates might be considered as adequate benchmarks to assess the relative change over time per country (average growth rates) with view to the authorities' rather unbiased accounting; the trend lines were determined by linear regression analysis (method of least-squares). The listed numbers are compiled from publicly accessible websites of the competent drug agencies (annual reports, application statistics); UK MHRA provided on request additional data (trial authorisations per calendar year).

	Clinical trials play an important role to allow patients across Europe to get **rapid access** to innovative and/or state-of-the art medicinal products, i.e. in phase-III trials for line extensions. In addition, clinical trials and especially non-commercial clinical trials, play a very important role for patients to get **equal access** to medicinal products **within members states** (i.e. in those MS who have salary-financed health systems with horizontal disharmonies granting specific professions privileged access to medicinal services and products) and **between member states** (i.e. offering access to approved (high-price) innovative medicinal products in EU accession countries). These highly beneficial effects clinical trials, especially when conducted in rare diseases or paediatric oncology in order to meet completely 'unmet medical needs', are not adequately reflected neither in the Clinical Trials Directive (Recital 14), nor in the Commission Directive 2005/28/EC (Recital 11). The revised legal text should therefore explain in more detail both Directives' notion of '"great benefit to the patients concerned" in terms of the access issue, referencing to the respective initiatives of the EU Commission to improve citizen's health, access to medicines and health care protection (as laid down e.g. by EU Commission Communications COM(2003) 383 final, COM(2004) 301 final, COM(2005) 115 final) and COM(2007) 630 final)	
	Specific Comments on Chapters / Consultation items	**Proposed change**
Key issue °2 **Ch. 4.1.3**	'Scope of the Clinical Trials Directive' • 'Interventional' versus 'Non-interventional' The CTD 2001/20/EC has introduced the concept of interventional versus non-interventional clinical drug trials, defining the latter, rather bureaucratically, as "*studies where the medicinal product is described in the usual manner in accordance with the marketing authorization. The assignment of the patient to a particular therapeutic strategy is* ***not decided in advance*** *by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study*" (Article 2 of CTD 2001/20/EC) As a consequence of this definition, any prospective, conceptual thinking of a medical practitioner, to improve (e.g. his own) daily medical provision of care to patients, has been considered since 2004 by legislators in most EU Member States to constitute a prospectively planned (non-randomised) clinical trial. Today, publication of results/outcomes of such case series which aim to contribute to evidence-based medicine and constitute some kind of quality assurance in daily medical care, bear considerable legal risk to become retrospectively classified by third parties to be of prospective, hence interventional character therefore infringing legislation due to the non-notification/authorization of the trial. The problem of the present definition of a clinical trial must be seen in the fact that virtually any attempt to gain medical knowledge and to build therapeutic evidence becomes a subject of public supervision. These rules apply even in cases in which study participants' risk is migrating, due to the raised attention of the treating clinician and meticulous documentation, below the risk level of usual medical care.	To revise the definition and the concept of interventional versus non-interventional trials in terms of a more risk-oriented approach of clinical trial notification and authorisation. In addition, the EU Commission should incorporate provisions into revised legislation allowing physicians more flexibility in defined areas of patient oriented clinical research. Examples exist e.g. in the USA, where FDA allows for exceptions from the IND process in defined

	Following case study aims to highlight the problem/issue: Case Study: Reducing therapy-relating side effects in patients with metastatic transitional cell cancer by application of a slightly changed, not-approved dose regimen Background: The MVAC regimen has been the standard treatment for locally advanced and metastatic urothelial cancer for the past 15 years. In a pivotal, randomised phase III study with 400 patients, the combination of Gemcitabine and Cisplatin has shown to be equally efficient in terms of survival and progression-free survival, but less toxic (von der Maase, JCO 2000). Based on this favourable risk-benefit ratio, the regimen has been approved in the EU and became a widely accepted regimen in bladder carcinoma. Some investigators have modified the four-weekly dose regimen (GEM 1000 mg/m² d1,8,15; CIS 70 mg/m²d2) in order to improve compliance whilst maintaining dose intensity, because 50% of patients require a dose reduction on days 8 and 15 (Soto Parra, JCO 2002). In other platinum sensitive tumours like NSCLC or Ovarian cancer, splitting of the cisplatin dose has shown to be an adequate measure to reduce toxicities in combination regimen and to avoid extensive hydration and co-medication aid too. Concept: A physician would like to test split-course cisplatin (40 mg/m² on two consecutive days in combination with the favourable dosage of GEM on d1+8 (q3w)) in a cohort of 46 patients. The doctor used the q4w regimen routinely but liked to reduce the percentage of patients (40%) with grade III/IV toxicity. Drugs' legal status: Both drugs are authorised in the indication, (Cisplatin is labelled for "mono-/ combination-chemotherapy in bladder carcinoma"; Gemcitabine for: "locally advanced or metastatic bladder carcinoma in combination with other cytostatics"). Prospective thinking: A case series (i.e. non-randomised Phase II), based on the Fleming design*, (α=0.01, β=0.20), could answer the question, if in daily practice such a split-course regimen could result into a reduced serious event rate (i.e. grade III/IV thrombocytopenia, neutropenia & nausea(. To test this question)i.e. the primary objective: Reduction of event rate by 50%(, a maximum of 9 toxicity events in 46 patients should be observed. In case, the number of events is below, a change of daily medical practice could be considered beneficial for patients. The issue: Both drugs are used within their labelling. No additional monitoring or diagnostic procedures are required, no assignment (i.e. randomisation) in advance to a particular therapy strategy is necessary. Is this 'trial' interventional due to the fact that the changed therapeutic use is observed systematically in 46 patients in order to get a statistically interpretable result? Should physicians stop such attempts to improve daily medical care, as the formal set-up of a clinical study would result into an inappropriate high burden of administrative work, costs and time for a practitioner? * Biometrics calculation done using: Machin D, Campbell MJ et al. Sample Size Tables for Clinical Studies. 2nd Ed., Blackwell Science, London, 1998 Source/Reference: http://www.dgra.de/studiengang/pdf/master_hartmann_m.pdf (p. 28)	therapeutic areas (HIV, Cancer[1]) Such an approach would offer clinicians more choice in patient-focused research and could contribute to improved care.

[1] An example for such an approach is FDA's Guidance for Industry on 'IND Exemptions for Studies of Lawfully Marketed Drug or Biological Products for the Treatment of Cancer', exempting several types of Phase I and II Therapy-Optimization Studies from the IND process. http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126837.pdf

	• The scope of the CTD 2001/20/EC is covering primarily, but not exclusively trials with medicinal products. The situation of trials investigating multimodal treatment regimen or whole therapy sequences has been considered neither in the CTD 2001/20 /EC nor in the public consultation. Following the transposition of the CTD 2001/20/EC into national law, the assessment of such therapy strategy trials has been handled differently by EU Member States. (Reference: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1488897/figure/pctr-0010013-g001/ PLoS Clin Trials. 2006 1(2): e13.(	To consider the situation of the complex therapeutic strategy trials in revised legislation, to incorporate a definition of 'therapy strategy trials' and to allow for a specific statute for such trials similar to the provisions incorporated since 2003 into Italian law (Decreto Legislativo 24 giugno 2003, N° 211')
Key issue °3 **Ch. 5.4**	Review of existing guidelines *versus* Review of existing Directive *versus* Review of Directive and/or excluding clinical trials of "academic" sponsors from the scope of the Directive *versus* Adopting the text of the Directive in the form of a Regulation (Consultation items n° 11, 12 & n° 13, plus Consultation item n° 8) Regarding these central issues, the EU Commission should follow an approach to establish at long-term a unique, simplified regulatory framework for clinical trials in Europe. To achieve this objective, the change of the legal instrument, i.e. the set-up of an EU-wide applicable **Regulation**, bears the greatest potential of administrative simplification and improvement of Europe's competiveness (for industry, SMEs as well as for medical research infrastructures!). Annexed to this contribution is an Opinion paper, issued in September 2008 by F. Hartmann-Vareilles and M. Hartmann that discusses legal issues regarding the - Set-up sponsor of sponsor-specific legislation (Consultation item n° 13) - Suitability of a 'one-fits-it-all' legislative approach (translational plus clinical drug/non-drug research) - Switch/change of legislative instrument (Consultation items n° 8, t 1 and t 2) This Opinion paper had been issued following discussions taking place at the EORTC-Conticanet-ICREL-ECRIN Workshop: „Biomedical Research in Europe: Which Challenges and Solutions for Academic Sponsors?", Brussels, May 2008) (Reference: http://www.eortc.be/services/doc/EUCTD/EORTC_BiomedicalWorkshop.pdf) and had been forwarded on 2 Sept 2008 to representatives of the organisations/associations organising the workshop.	The EU Commission should timely review the Directive, incorporate simplified provisions adapted to practical necessities, and should prepare in parallel the switch of the legal instrument in order to pave the way towards an EU-wide centralised trial approval procedure on the basis of a community-wide applicable Regulation.

Annex:

Opinion paper (issued 1 September 2008):

A legal point of view regarding the revision of the Clinical Trial Directive and the idea to set-up a harmonised framework for academic biomedical research in Europe

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1st issue: Sponsor-specific legislation – an option for the future legal framework for biomedical research?

The Clinical Trial Directive 2001/20/EC has (indirectly) introduced the notion of 'commercial' and 'non-commercial' sponsors into EU law[2]. By transposing the Clinical Trial Directive into national legislation, some Member States have set aside this concept. Today, some EU Member States pay specific attention to clinical trials carried out by academic sponsors, whereas other ones do not. One outcome of this non-harmonised transposition of the Directive is that almost all requirements for 'commercial' drug research (set-up for risky investigations with innovative, unapproved medicinal products awaiting commercialisation) are applicable for patient-orientated therapeutic drug research too.

The current situation offers the two following possible (general) options:
- To opt for a revision of the existing framework with its present definition for sponsor status (or even to omit any separation within the future framework, as proposed by different contributors to the European Commission-EMEA conference held in October 2007 in London), or
- To opt for an independent legal framework applicable for academic sponsors only.

From our point of view, the latter option is not a real option any longer as:
- GCP and the protection of patient rights are universal principles (an argument also used by several national policy-makers and authorities opposing to the concept of different sponsor types and sponsor-type related trial requirements),
- Stakeholders do not agree to the perception of two levels of quality in clinical research,
- The Clinical Trial Directive itself is not providing a formal distinctive status of 'commercial' and 'non-commercial' sponsors of clinical trials with medicinal products,
- The time slot to ask for a specific framework has probably closed at the London conference held in October 2007 [the academic community did not expressly ask for an own legal framework and Ms. Georgette Lalis from the (EU Commission) expressed at the conference's end her happiness that "it (the community) does not request a specific framework"[3]].

We conclude that most likely any revision (or extension) of the legal framework for biomedical research at EU level will continue to be drafted and adopted in form of legislative acts that will **consider the nature of the sponsor as not relevant/predominant**. This might not exclude the possibility that subsidiary legal acts (ordinances etc) will be issued in specific situations, addressing sponsor-specific needs.

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[2] The CTD 2001/20/EC only refers once (in Recital 14) to this terminology: "***Non-commercial*** *clinical trials conducted by researchers without the participation of the pharmaceuticals industry may be of great benefit to the patients concerned*". The only existing definition – the one for commercial sponsors – is provided in form of a footnote in Annex 1 of EU Commission's '*Detailed guidance for the request for authorisation of a clinical trial on a medicinal product on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial*'. (Annex 1 = Application form for request of a clinical trial). This type of EU Commission guidance called 'soft-law' is not legally binding on EU Member States.

[3] See '*Report on the EC-EMEA conference on clinical trials*' (EMEA/565466/2007, 30 Nov 2007) http://www.emea.europa.eu/pdfs/conferenceflyers/clinicaltrials/report.pdf

2nd issue: Check for suitability of an 'one-**fits-it**-all' legislative approach

The European pharmaceutical legislation is characterised today by the set-up of different and divergent regulatory frameworks for different classes of 'medicinal products' in the last 10 years: human (as well as veterinary) medicinal products, herbal medicinal products, blood products, biologicals (vaccines etc.), advanced therapy medicinal products (ATMP) as well as combined products composed of medicinal products and medical devices. Complementary regulatory systems exist for so-called 'orphan drugs' and for 'paediatric medicines' too. Any cross-acting legal act (as e.g. the Clinical Trial Directive, applicable for different classes of products) must comply with a growing number of specificities laid down for the specific classes of pharmaceutical products and the myriad of subsequently issued methodological and procedural guidance documents. This applies to each revision or extension of such cross-acting act too. Hence today policy-makers and stakeholders have to check thoroughly any proposed change of one component of the legal framework for feasibility and impact on the whole body of co-existing legislation.

Therefore, before being adopted, any new EU legislation is intensively checked for consistency as well as for legitimacy by the EU legislative bodies – but also by any opponent of new pieces of Community legislation. In this context, the pro and con of a 'one fits-it-all' legislation must be discussed.

The Clinical Trial Directive has been legitimated on basis of Article 95 of the EU Treaty[4], i.e. the need for "approximation of laws", which is a rather weak legal source. Without entering into the details of the discussion, Article 95 has been 'accepted' because there was a common agreement that the aim of the Directive is to facilitate the development and later commercialisation of products intended for commerce in the single market, which covers free movement of goods, services, persons, capitals.

> **Article 95** of EU Treaty – Approximation of laws:
> "(1.) (…) The Council shall, acting in accordance with the procedure referred to in Article 251 and after consulting the Economic and Social Committee, adopt the measures for the approximation of the provisions laid down by law, regulation or administrative action in Member States which have as their object the establishment and functioning of the internal market."

The question is as follows: would the legitimacy of the Clinical Trial Directive during the revision process be maintained, reinforced or weakened, if the scope of the directive is enlarged and include some areas not directly related to medicinal products (non-drug trials, translational research, etc.)?
Said otherwise: under which circumstances and how far can the competences of the European Parliament and the European Commission go to regulate additional areas – borderline areas – which might fall under the competences of EU Member States?

Therefore, the legitimacy criterion should be applied to each matter under discussion (and proposed to be linked to the current Clinical Trials Directive) as for example:
- Non-drug trials: Has the EU competence to regulate medical/clinical research intended to improve radiotherapy or surgery – research carried out in order to improve 'best medical practice'? (The subject of this research is no longer related to a 'product' intended for (later) 'free movement' on the internal market)
- Translational research / tissue research / biobanking: As biological materials/tissues are expressly being excluded from commercialisation and trade, Article 28 ("principle of free movement of goods"), which has been the basis to legitimate any EU legislation applicable for pharmaceutical products, cannot be used.

Regarding Article 95, the legitimacy to extend the scope of the Clinical Trial Directive optionally, is rather limited. Therefore, the next question is whether for this type of research, **other legal sources** exist in EU community law that could serve as a vehicle to justify the adoption of an act at EU level?

Two potential options can be deduced from the EU Treaty.

➢First: could a pan-European harmonisation (of different areas) of clinical research can be obtained on basis of Article 152 ("public health"), arguing that current obstacles to and fragmentation of biomedical research does not contribute to the political aim of 'improvement of public health'? Could a common legal

[4] European Union – Consolidated Versions of the Treaty on European Union and of the Treaty establishing the European Community: OJEU C321 E/1 of 29.12.2006 http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2006:321E:0001:0331:EN:PDF

framework for biomedical research contribute to ameliorate 'public health' or at least maintain it at a high level? Does the EU have competency in this issue?

Article 152 of EU Treaty – Public health: "Community action, which shall complement national policies, shall be directed towards improving public health, preventing human illness and diseases, and obviating sources of danger to human health. Such action shall cover the fight against the major health scourges, by promoting research into their causes, their transmission and their prevention, as well as health information and education. The Community shall complement the Member States' action in reducing drugs-related health damage, including information and prevention.
(…)
The Council, (...) shall contribute to the achievement of the objectives referred to in this Article through adopting:
(a) Measures setting high standards of quality and safety of organs and substances of human origin, blood and blood derivatives; these measures shall not prevent any Member State from maintaining or introducing more stringent protective measures;
(b) (…)
(c) Incentive measures designed to protect and improve human health, excluding any harmonization of the laws and regulations of the Member States.
The Council, acting by a qualified majority on a proposal from the Commission, may also adopt recommendations for the purposes set out in this Article. Community action in the field of public health shall fully respect the responsibilities of the Member States for the organisation and delivery of health services and medical care. In particular, measures referred to in paragraph 4(a) shall not affect national provisions on the donation or medical use of organs and blood. "

The answer provided in reading Article 152 is clear: the primary competence for action in the field of public health remains a national one.

➢Second: are there sufficient EU competences in the field of 'research', to adopt additional legislation?

In the area of research (Articles 163-173), the European competences are limited to coordination and financing of research and technology programmes ('Framework programmes').

Title XVIII (Articles 163-173) of EU Treaty: Research and Technological Development –
Article 163: "The Community shall have the objective of strengthening the scientific and technological bases of Community industry and encouraging it to become more competitive at international level, while promoting all the research activities deemed necessary by virtue of other Chapters of this Treaty.
For this purpose the Community shall (...), encourage (…) research centers and universities in their research and technological development activities of high quality; it shall support their efforts to cooperate with one another, aiming, notably, at enabling undertakings to exploit the internal market potential to the full, in particular through the opening-up of national public contracts, the definition of common standards and the removal of legal and fiscal obstacles to that cooperation."
Art. 166-170: Legal basis for DG Research's 'Framework programmes'
Art. 171-172: Legal basis for EU Commission 'Joint undertakings' as e.g. IMI

We hence conclude that the European Commission as well as the European Parliament have rather limited competences to extend the scope of the Directive – explicit opposition from some/many EU Member States (manifested through the Council) can be expected for any respective legislative proposal.

3rd issue: The legal instruments: directive versus regulation

From the previous paragraphs of this opinion paper, it is obvious that any proposal for revision of the Clinical Trial Directive should focus primarily on trials with medicinal products. The last question to be discussed is therefore, whether other legal instruments than the one of a directive could be considered as suitable to revise the Clinical Trial Directive.

Any modification of the existing Clinical Trial Directive would bear the risk that provisions intended to improve the current situation (e.g. for academic sponsors) would again be subject to discussions with the danger of possible drawbacks and be implemented in different ways by the Members States. The change of the legal form (i.e. to a regulation) would therefore be an attractive option to avoid these pitfalls. Indeed, whereas a directive only imposes Member States to obtain a result (letting them choosing the means to achieve them), a regulation does not let any possibility of interpretation to the Member States.

The directive must be transposed into national law through national legal instruments. The regulation once adopted is on the contrary immediately applicable in the Member States.

Is it realistic to consider this option?

A regulation could certainly solve some problems of diverging interpretation in the Member States, but it could not lead to a complete harmonisation of all complex issues of clinical trials as many issues linked to the conduct of clinical trials remain in the competences of the Member States as e.g. definition of incapacitated adults, insurance provisions, any provision related to the reimbursement of investigation medicinal products and many others.[5]

Legally, the European Commission has some competence to consider a change in the form of the legal instrument. Again, this argumentation can only be applicable in the context of Article 28, the achievement of free movement of medicinal products. In addition, the consideration of clinical trials as 'services' (creating a market) and clinical trial data as 'commercial goods' could strengthen this approach[6].

To avoid potential opposition from EU Member States, the attempt to change the legal instrument would require intensive and long-term talks between the European Commission and the Member States in order to clear the way for a successful ratification procedure. Without going into details, there are procedures in place as the 'Open Method for Coordination' by which the EU Commission could enter into (forced) negotiations with Member States in order to prepare a change.

A very last option[7], though relatively weak at least in the short term, could be also the use of Article 152 ("public health") as a tool for the Commission to take some non-binding measures in order to foster/enhance more cooperation between the Member States and find (at least) some solutions to the major problems of diverging interpretation of the Clinical Trial Directive.

We therefore believe that a change in the legal instrument could be beneficial to solve the known and bemoaned problems for clinical (drug) research in Europe. However, as a regulation is much more detailed than a directive, the option of a change of the legal instrument would result into a much longer institutional revision and consensus process. Moreover, any revision of an existing piece of legislation like the Clinical Trial Directive bears the risk that some issues formerly agreed between the Member States be subject to new discussion and changes.

[5] It is not the intention of this opinion paper to discuss in detail all the areas of division of competences between EU and Member States that touch many practical aspects of research in human beings.

[6] Such consideration would apply to any cases where research institutions (as well as any 'medical institution') carry out (remunerated) clinical research tasks – as service providers on request of another party. But is such a consideration also applicable to 'independent' research, intended e.g. for verification of clinical results or simple hypothesis testing – with the central intention of publication in a (high-level) research journal?

[7] To be considered apart from the issue 'directive' or 'regulation'