

The Implementation of Directive 2001/20/EC in Europe

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1 Introduction

The Act on medical research involving human subjects (WMO) is not an exclusively Dutch piece of legislation, but is part of a 'multi-layered legislation'.¹ Aside from the effect of international agreements, the paragraph in the WMO (par. 5a) on clinical research with pharmaceutical products is a direct consequence of the implementation of Directive 2001/20/EC,² also known as the 'Clinical Trials Directive' (hereafter referred to as: the directive).³ Even though this type of clinical research only accounts for around 30%⁴ of the research dealt with by the WMO, it is this research that carries the greatest risks and provides the Medical Ethics Boards with the greatest challenge. Reason enough to devote attention to the regulation of research with pharmaceutical products.

The bulk of this article is a comparison of the Dutch solutions to the implementation of the directive with those of other EU countries. Unlike most other European countries the Netherlands had an instrument for reviewing and oversight of clinical medical research, namely mentioned WMO. With the implementation of the directive in the Netherlands, the amendment of the WMO was kept as

¹ E.M. van Veldhuizen-Polman & M.J.H. Kenter, 'Veellagigheid van wet- en regelgeving bij medisch-wetenschappelijk onderzoek met mensen', in: A.C. Hendriks & H.-M.Th.D. Ten Napel (ed.), *Volksgezondheid in een veellagige rechtsorde. Eenheid en verscheidenheid van norm en praktijk*, Alphen aan den Rijn: Kluwer 2007, p. 229-243.

² Directive 2001/20/EC of the European Parliament and the Council of 4th April 2001 (PbEG 2001, L121/34).

³ Where, below, this directive is referred to, unless the text states otherwise, it encompasses Directive 2005/28/EC from the European Commission which sets down the specific Good Clinical Practice (GCP) conditions.

⁴ CCMO, *Annual Report 2008*, Den Haag: CCMO 2009, p. 10.

minimal as possible.⁵ Other countries either had to come up with a totally new review system or completely overhaul their existing one. During the last two years at a number of congresses and in a few reports, it has been maintained that little of the harmonisation intended by the directive has come about. These reports show that in many countries, the opportunities for non-commercial clinical research⁶ in particular have declined. These reports are discussed in this article. This discussion inevitably prompts the question as to how much further European harmonisation is desirable. On that vexing question only a few opinions will be offered since a thorough discussion would exceed the scope of this article.

For a proper understanding, first the main points of the directive are mentioned inasmuch as they depart from the existing Dutch system before the implementation of the Directive (see the text box at the end). Then the implementation in the Netherlands is dealt with. Next come the reports in which the effect of the directive is examined. This paper concludes with some final remarks.

2. Directive 2001/20/EC c.a.

The launching of and trade in medicines has been subject to harmonising European legislation for some time.⁷ The reason behind this is that without such harmonisation, the free movement of goods, in casu medicines, would be drastically hampered. The clinical trials directive should be seen in the same light. The idea was that without the harmonisation of the conditions for clinical scientific research, industry would still be confronted with national impediments to the sales of medicines. If the EU strives for such harmonisation on the basis of article 95 of the EU Treaty, a high level of protection can be maintained (art. 95 par. 3 EU).⁸

Compared to the WMO system prior to 2006, the directive brought the following changes: a system of double review, namely alongside a Medical Ethics Committee, a 'competent authority', deadlines before which such review should be completed, a European database (EurdraCT) in which details of the proposed research are registered,⁹ detailed rules for the submission of substantial amendments and their consequences, stipulations on the research dossier to be submitted, rules for the reporting of side-effects and serious side-effects,¹⁰ their registration in an European database (Eudravigilance)¹¹ and their consequences.

⁵ *Kamerstukken II* 2003/04, 28 804, m.n. nr. 3.

⁶ I use the terms 'non-commercial', 'investigator initiated' research and 'academic research' to refer to the same thing, namely: researchers and sponsor are the same, are involved with patient treatment in publicly financed health care and do not have the intention to bring a medicine onto the market. Their research could, however, lead to an alternative indication for a medicine which is already on the market.

⁷ C.f.: L. Lisman, 'De toelating van geneesmiddelen, hoe effectief is ons systeem', in: *Geneesmiddelen en Recht. Preadvies 2006*, Den Haag: Sdu Uitgevers 2006, p. 13-133.

⁸ Court of Justice, EC 12th December 2006, nr. C-380/03.

⁹ <eudract.emea.europa.eu> (last visited June 2009). Originally access to this database was restricted to certain parties, such as the national competent authorities. Recently it has become possible for the general public to obtain an extract, see European Commission ENTR/F/2/SF D (2009) 3687. That has turned this part of EudraCT into a clinical trials register.

¹⁰ Better known under the English term: SUSARS, serious adverse reactions.

¹¹ <eudravigilance.emea.europa.eu/human/index.asp>. This site has two modules. Alongside the reports of SUSARS in scientific research, also serious side effects after the drug has come onto the market.

The directive further contains detailed regulations on scientific research with children and those with diminished competency (articles 4 and 5 respect.). Should a protocol of this sort be under review, the Medical Ethics Committee is required to have an expert present in the field of the target group in question. The rules for medicinal research among adults with diminished competency appear not to allow non-therapeutic research even though this research can only be done with subjects suffering that condition and might lead to better treatment for other patients with condition later. (art. 5.1 directive). This question will not be gone into further.

The directive is followed by implementation directives and guidelines from the European Commission. All European documents are readily accessible through a website.¹²

3. The implementation in the Netherlands

The directive was translated into a bill Scientific research with medicines. As has been said, this bill added on nicely to the existing WMO. The main point was a new paragraph (5a) in the WMO with new rules for scientific research with medicines.¹³ Amendments were also made to the first articles of the WMO (see art. 2a and 3a WMO). The WMO already dealt with a number of important elements from the directive such as the distinction between - in WMO terms - the instigator and the expeditor. In terms of the directive, this is the distinction between 'sponsor' and researcher. The directive makes review by a Medical Ethics Committee mandatory, and this was already the case here. The composition of the Medical Ethics Committees needed some alteration. The Central Commission for Human Research (CCMO) became the competent body for medicinal research where the CCMO was not the principal reviewer¹⁴ and the Ministry of Health for research where the CCMO was the principal reviewer.

The passing of this bill is interesting from the point of view of constitutional law but also in the context of this article, namely the problems the directive posed for non-commercial research.¹⁵ The Upper Chamber, as voiced by Helene Dupuis (professor emeritus in medical ethics), found the conditions for this type of research to be too restrictive, despite the concession that certain issues could be dealt with subsequently by administrative order. This led to an amending order of the Bill which implied the following for research with already-registered medicines:¹⁶

- the dossier is only required to contain a summary of the product information. If the protocol contains a different method of administering the medicine or for different indication et cetera, the product information must be augmented with information relevant to that particular research (art. 13h WMO). That is an exception to the situation for non-registered medicines. In

¹² <ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10_en.htm> (last visited June 2009).

¹³ *Kamerstukken II* 2003/04, 28 804, nr. 1.

¹⁴ See WMO art. 2 and the Decree of 3rd January 2006, *Stb.* 2006, 39.

¹⁵ Whereby the instigator and the performer are one.

¹⁶ *Kamerstukken II* 2004/05, 30 194, nr. 2.

that case, de facto, the so-called 'Investigational Medical Product Dossier' (IMPD) must be included;^{17 18}

- these medicines – contrary to the non-registered ones – do not have to be provided by the researcher free of charge.

In addition, the period within which the competent authority can voice any objection to the proposed research was reduced to the present fourteen days. It was stressed that the review by the competent authority was a marginal one, namely a search in the Eudravigilance database for any reported unacceptable side effects.

Apart from that, during the bill's passage, another small amendment was made to the WMO.¹⁹ That made it possible, for example, that an administrative order could direct that the initial review of other kinds of research than were already mentioned in the WMO could be consigned to the CCMO (art. 2 para. 2 under b 4 WMO), and that the CCMO could impose demands on the qualifications and experience of the METC members (art. 16 para. 2 under c WMO). This came into force in April 2005.²⁰ Both of the bills (the original and the amending order) implementing the directive came into force in January 2006.²¹

For the sake of completeness I should point out that the Lower Chamber is dealing with a new and limited amendment to the WMO.²² This entails:

- that the minister can prescribe further rules on the information to be given to potential test subjects. The question is how necessary such rules are with research that leans more towards observational research than invasive research and whether this distinction will be reflected enough in these rules;²³
- the possibility of an administrative appeal against a negative decision of an METC – an independent body²⁴ – on a judgement over medicinal research is restored. This had been scrapped because it had been deemed undesirable that the competent authority should also be an appeals body. Considering their marginal role, and despite objections from the Council of State,²⁵ this appeals possibility is considered differently.

The handling of this bill was deferred in March 2009 in anticipation of the outcome of the investigations by the CCMO and the Health Care Inspectorate into the 'probiotica' affair.^{26 27}

¹⁷ C.f. also: *Clinical Research with medicinal products in the Netherlands. Instruction Manual*, Den Haag: Ministerie van VWS 2005, o.a. p. 16.

¹⁸ This is not written directly in the Dutch implementation decree. They refer, however, to the Directives on Good Clinical Practice from the Commission (see note 3) where this is mentioned.

¹⁹ *Kamerstukken II* 2003/04, 29 748, nr. 2.

²⁰ Decree of 13th April 2005, *Stb.* 2005, 205.

²¹ Decree of 31st January 2006, *Stb.* 2006, 57.

²² *Kamerstukken II* 2007/08, 31 452, nr. 2.

²³ E.B. van Veen & I. Janssen, *Toetsing op maat. Een onderzoek naar de beoordeling van wetenschappelijk onderzoek op de grens van de Wet medisch-wetenschappelijk onderzoek met mensen*, Den Haag: MedLawconsult 2008.

²⁴ K.M. Breuker, 'De Wmwo en de EG-Richtlijn: winst of verlies?', *TvGR* 2005, p. 634-649.

²⁵ *Kamerstukken II* 2007/08, 31 452, nr. 4.

²⁶ *Kamerstukken II* 2007/08, 31 452, nr. 9.

²⁷ M.G.H. Besselink e.a., 'Probioticaprofylaxe bij voorspeld ernstige acute pancreatitis: een gerandomiseerde, dubbelblinde, placebogecontroleerde trial', *NTvG* 2008, p. 685-696; M.C. de Vries & E. van Leeuwen, 'Ethiek van

4. The implementation of the directive at a European level: problems and suggested solutions

Already before the directive came into effect, problems were envisaged for non-commercial, 'investigator initiated' medicinal research.²⁸ In addition, there was opposition to the limitations on medicinal research among adults unable to give informed consent.²⁹ The non-achievement of the intended harmonisation had not yet come up.

These were first addressed fully at a conference of the European Medicines Agency together with the European Commission in October 2007. The closing report is clear on the varying implementation of the directive and the problems partly, though not exclusively, resulting from it.³⁰ It was the overture to an extensive investigation into the implementation of the directive by the so-called ICREL group.³¹ Their final report appeared in February 2009.³² A related research group, called ECRIN,³³ also investigated the working of the directive and presented suggestions in November 2008.³⁴ The sizeable ICREL report makes no mention of these suggestions. Under the banner of the European Science Foundation (ESF) a 'forward look' on investigator-driven clinical trials was developed in which the results of ICREL and ECRIN are included in an original way and also contains suggestions on amending the (implementation of) the directive.³⁵

Below, I will discuss the acknowledged problems with the directive (para. 4.1). Then I deal with the suggested solutions (para. 4.2) At the close of this section I make a number of comments (para. 4.3). The sheer quantity of text in the different reports compel a limitation to the main points without going into the differences between the reports.

medisch-wetenschappelijk onderzoek: informed consent en de therapeutische misconceptie', *NTvG* 2008, p. 679-683.

²⁸ A.J. Baeyens, 'Implementation of the Clinical Trials Directive: Pitfalls and Benefits', *European Journal of Health Law* 2002, p. 31-47.

²⁹ H.K.A. Visser, 'Europese regelgeving voor klinisch geneesmiddelenonderzoek bij minderjarigen en meerderjarige wilsonbekwamen', *NTvG* 2001, p. 942-945; K. Liddell e.a., 'The European Clinical Trials Directive revisited: The VISEAR recommendations', *European Journal of Cancer* 2006, p. 9-14; E.J.O. Kompagne, A.I.R. Maas & D.W. Dippel, 'Klinisch geneesmiddelenonderzoek bij acuut beslissingsonbekwame patiënten in de neurologie en de neurochirurgie; implicaties van nieuwe Europese regelgeving', *NTvG* 2003, p. 1585-1589.

³⁰ EMEA/565466/2007. This report is a breath of fresh air if you are accustomed to the newspeak on the blessings of the work of the Commission which is normally found in these documents.

³¹ ICREL stands for Impact on Clinical Research of European Legislation.

³² See: <www.efgcp.be/icrel/?L1=6&L2=0>.

³³ ECRIN stands for European Clinical Research Infrastructures Network.

³⁴ <www.ecrin.org/index.php?option=com_content&task=view&id=80&Itemid=107>. The final report I make use of in this article is not on the website. I can provide a copy if required.

³⁵ *Investigator Driven Clinical Trials*, Straatsburg: European Science Foundation March 2009 <www.esf.org/publications.html>.

4.1 Acknowledged problems with the directive

- Although the directive relates to clinical medicinal research, in some countries, the whole regime of the directive has been applied to all research involving patients, for example, to research with medical devices or even observational research with human tissue and data.
- Regarding medicinal research: in a large number of countries, no distinction is made between the conditions for submitting or carrying out research with non-registered or registered medicines.
- There are also variations in the definition of medicinal research. For example, in a number of countries medicinal research in the sense of the directive is taken to mean translational research whereby the working mechanism is investigated using blood samples. Of course these are usually the countries where the distinction referred to in the previous point is not made.
- Most countries require a multinational study to have a single sponsor, even when it is 'investigator initiated' research whereby a number of researchers from different countries work together on equal footing.
- The administrative procedures in the individual member states vary, both with the Medical Ethics Committees and with the competent bodies, definitions of 'Suspected Unexpected Serious Adverse Reactions' (SUSARs) differ, et cetera.
- The conditions and coverage for the insurance of the trial subject also vary greatly between the member states.

On the practical effects of the directive, measured over all the member states:

- The number of protocols set-up and approved by and for industry have apparently not decreased.³⁶ There has, however, been a shift in the countries where such protocols are submitted. Industry also reports that these are costing more time and money. The amount of paperwork has increased sharply.³⁷
- A decrease of around 25% has been discovered in the number of 'investigator initiated' protocols. It is also reported that in certain countries, no more of such protocols are being submitted. That means an increase in other countries. A large non-commercial research organisation as the European Organisation for Research and Treatment of Cancer (EORTC)³⁸ reports just as industry a much heavier load in terms of time and means to get protocols off the ground in a sufficient number of countries.

³⁶ M.J. Brown, 'The impact of clinical trials legislation on clinical pharmacology: problems and solutions', *British Journal of Clinical Pharmacology* 2009, p. 487-493.

³⁷ Also apparent from the summary on p. 9 of *Toetsing en toezicht in de toekomst* (toekomstvisie CCMO), Den Haag: CCMO juni 2009.

³⁸ European Organisation for Research and Treatment of Cancer, zie <www.eortc.be>. This foundation instigates a lot of 'investigator initiated' research, especially in the Netherlands.

4.2 Suggested solutions

Part of the solution is obvious, namely a distinction between registered and unregistered medicines, such as the Netherlands has introduced. Within the European discussion this is referred to as a 'risk based approach'. In themselves, the weightier procedures are being accepted as long as it is for the benefit of the patient. The application of all conditions on all research, as is the case in some countries, is regarded as disproportional.

In the framework of this 'risk based approach', a categorical distinction between 'commercial' and 'investigator initiated' research is rejected. A certain distinction between such sponsors is regarded as acceptable. Non-commercial sponsors should receive special facilities. In particular, the ESF report was full of the support such 'sponsors' should receive in various areas. To a small extent, this is also the case in the Netherlands. The 'Future Strategy' by the Central Committee on Research with Human Subjects (CCMO) mentions that a module is being developed whereby side effects can be reported electronically via 'toetsing online' (review online). Since a three-day training course is required for this module (!), this reporting could be done by the CCMO on behalf of non-commercial researchers.³⁹ This Dutch module would also be available to Medical Ethics Committees. At present, Medical Ethics Committees do not have access to the Eurovigilance database. This is regarded as a serious omission in all the reports.

With regards to the term sponsor by 'investigator initiated' research, more flexibility is argued for. This is already the case in the Netherlands. It is sufficient that there is one principal investigator that carries the responsibility *that* the conditions are complied with. The trial-subject insurance can that of each of the participating centres, only covering the patients included there.⁴⁰

The general trend in all the reports is towards more harmonisation. The ECRIN report argues for a single European law to cover all patient-related⁴¹ research. The European Medicines Agency (EMA)/European Commission report is a little more qualified and suggests that 'soft law'⁴² initiated by the Commission could also offer a solution.

The ESF report highlights an interesting point, namely the access to results and 'data sharing' by both academic and commercial medicinal research. It must be pointed out that in commercial trials, the data is the property of the commercial sponsor. An increase in knowledge demands, according to the report, that this data is also shared. It suggests a two-part solution:

- more support from researchers in respect of (knowledge of) intellectual property rights, contracts and the like;

³⁹ CCMO 2009, p. 27 (see note 37).

⁴⁰ For example: Instruction Manual, Ministerie van VWS 2005 (see note 17)

⁴¹ This is my translation of 'clinical research'. In all the discussions, the comparability of terms plays a large role and is sometimes very inadequate. Under the term 'interventional' I count research that in the Netherlands is invasive but wouldn't be intrusive (such as the drawing of extra blood). That is why the most broad term 'clinical research' is used. For that matter, the (in)comparability of terms was a big problem in the empirical research into the effect of the directive. Personal comment from Jaques Demotes, contact person for the ECRIN study at the ESF symposium on 29th September 2008.

⁴² Such as directives, recommendations, benchmarking and the like. Over soft law in the EU in general, see among others: L. Senden, *Soft law in the European Community law. It's relationship to legislation*, Oxford: Hart Publishing 2003.

- a trial register in which the results of the study are published. As I understand it, this would concern the 'raw' data, just as they are received by the sponsor on the so-called 'case record forms' kept by the researcher on each participating patient. That goes much further than the publication of processed results in literature.⁴³

4.3 Discussion

Let's assume that not all problems for 'investigator initiated' research in a given country can be explained by the unqualified application of the directive. This kind of research has more or less come to a standstill in England.⁴⁴ In my opinion, this also has a lot to do with the 'Good research governance' conditions for research carried out in National Health Service financed institutions.^{45 46} However, as is apparent from the "Future Strategy" by the CCMO the protection of healthy test subjects in England has not increased.⁴⁷

Indeed, in the first place, this is all about patient safety. The interests of society⁴⁸ or, to be more concrete, of the patients who can profit from the results of the research in the future, are secondary to this. In that sense, it is right that 'investigator initiated' *research* as such should not qualify for a lighter regime. The Dutch probiotica affair was an example of such research. Clearly the Good Clinical Practice conditions (see note 3) should also apply to such research. It is essential that such researchers are accommodated and that this research can hitch a lift with a qualified, risk-based regime. As such research will normally concern research with already registered medicines, translational research into the working mechanisms of biomarkers, et cetera. Hence, research with lesser or even no risks. The necessity of good and much medicinal research not driven by commercial motives seems to be self apparent.⁴⁹

The first, and from a European legal point of view, most interesting question is whether more harmonisation, in whatever form, is desirable. One could embrace the unorthodox opinion that the Dutch implementation promotes a competitive advantage. Other countries would either have to forgo such research or adapt their legislation or create an extensive support bureaucracy for researchers.⁵⁰

⁴³ ESF 2009, p. 11 (zie noot 35). The trial register referred to there is the initiative of a commercial publisher and does not deal with registering results in the sense of raw data from the study.

⁴⁴ G.E. Griffin e.a., 'UK research trials are on the verge of extinction', *The Times* 14 januari 2009.

⁴⁵ Editorial, 'Research governance: a barrier to ethical research?' *QJMed* 2004, p. 113-114; Editorial, 'Meeting the challenges of research governance', *Rheumatology* 2005, p. 571-572; R.A. Salman, T.M. Brock & M.S. Dennis, 'Research governance impediments to clinical trials: a retrospective survey', *Journal of the Royal Society of Medicine* 2007, p. 101-104.

⁴⁶ In 'Obstacles to European research projects with data and tissue: Solutions and further challenges', *European Journal of Cancer* 2008, p. 1438-1450, I argue for a good research governance code but from the bottom up, developed by researchers and patients.

⁴⁷ De TGN1412 affair, dealt with in CCMO 2009, p. 13 (see note 37).

⁴⁸ World Medical Association (WMA) Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects, June 1964, latest amendment October 2008.

⁴⁹ But for those that want arguments, the ESF report from 2009 is very clear on this, especially p. 5 en 8 (see note 35).

⁵⁰ Such as in France, the Inserm, to which several lawyers are associated.

This approach does not offer a solution for non-commercial researchers who want to cooperate internationally now. And that is essential, particularly when it is research into medicines for rare diseases. In such cases it is not possible to recruit enough participants in a single country for a study which has enough 'power' to provide valid results. For translational biomarker research, it is essential to have very large datasets available to be able to distinguish the effect of an intervention, in whatever form,⁵¹ from pure chance.

Something needs to happen. The question is whether this should be by amending the directive or by soft law. It is not easy to answer that. The current Commission guidelines have contributed little to a rational, risk-based interpretation. It also would not really be in the nature of the Commission to announce that its 'own' directive should be interpreted restrictively. For example, the comment on the 'sponsor' in the Questions and Answers⁵² do not exactly lead to the Dutch interpretation. Fortunately, these answers are not the law. If a number of academic researchers work together with each other internationally, it would be quite feasible to arrange for SUSAR reports to be collected centrally. It is virtually impossible for a single centre or international scientific organisation that has drawn up a protocol to shoulder the liability and trial-subject insurance for all the participating centres in Europe. An amendment is required in line with the Dutch approach, but in itself, this would be quite possible through a new interpretive announcement or possibly a new Commission guideline or directive.

That applies to many of the suggestions. Not however for the as yet unmentioned suggestion of a single submission of a protocol for all the European countries where the study would be carried out. I ask myself however if this idea is either realistic or desirable. In any event, such a suggestion could only be realised if the scope of the directive at the very least is harmonised much further.⁵³ At the same time, the risk-based approach needs to be realised for the documents to be submitted. Theoretically this is possible through Commission directive and soft law, but not if such a drastic consequence is attached.

I have doubts as to whether the European Parliament (EP), which would obviously be involved in the amendment of the directive, would be equal to the task. The stipulation on the impossibility of non-therapeutic medicinal research with adults unable to give informed consent is, in my opinion, an example that the EP sometimes overshoots in its effort to protect the European citizen. This does not bode well for a 'risk-based approach'. Lobby groups sometimes offer a counterbalance. Apart from the fact that that result is not always a success, academic researchers don't have the time or the money for it. The EORTC tried at the inception of the directive but as a small club, not particularly specialised in this matter, they didn't make much headway.⁵⁴

⁵¹ This refers to research which is translational to medicinal research. The participants are already ill. It does not refer to research with healthy participants which investigates the chance of an illness developing on the basis of biomarkers.

⁵² Brussels, 16-12-2008, ENTR/F/2/SF D (2008) 41047, see ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10_en.htm (last visited June 2009).

⁵³ For example, that a translational, or add-on study into the working of a medicine which already conforms to the professional standard and would also be given without the study, would not be regarded as medicinal research in the sense of the directive.

⁵⁴ Personal anecdote from Ann Bayens and Françoise Meunier

For that reason I am an opponent of a much broader directive for all patient-related research. Most directives do not lead to actual harmonisation⁵⁵ but usually they do lead to more bureaucracy. From a legal standpoint, such a directive would have to be based on the free movement of services. Only medical devices, which would also then be covered, would be goods just like medicines. For the rest, and certainly for observational research, it is about services. It is questionable if this research would be limited by diverse national regulations. They would if they imply that, as soon as a medicine is involved, it would fall under Directive 2001/20. This is where a more limited interpretation of the scope of the directive would help. In any case, this research would be about obtaining patient data and human tissue. In Europe, data for research are treated in different ways despite Directive 95/46 EC.⁵⁶ The conditions for the use of human tissue for scientific research in Europe vary even more. There is the recommendation of the Council of Europe.⁵⁷ A number of countries, however have a stricter regime⁵⁸ for 'further use',⁵⁹ a larger number of countries a lighter one, varying from blanco consent from the start⁶⁰ to no objection.⁶¹ In the Netherlands, we are awaiting the law on the authority over human tissue and function, in practice, despite criticism in scientific literature,⁶² according to the Code of Good Use, which equally follows this latter course.⁶³ For the exchange of human tissue, these different regimes make no difference. Together with others I developed the rule of mutual recognition.⁶⁴ This is based on primary EC law: if human tissue becomes available in a country and can be used for scientific research in that country according to that country's regulations, that tissue can be used under the same conditions for scientific research in another country even if that other country applies different conditions for the use of human tissue for research from its 'own' patients. Any other solution would in principle be an undue hindrance of the free exchange of services. The provider of the first country still has to retain enough authority over the human tissue comparable to

⁵⁵ In E.B. van Veen e.a., 'TuBaFrost 3: Regulatory and ethical issues on the exchange of residual tissue for research across Europe', *European Journal of Cancer* 2006, p. 2914-2923. examples are given of how the Directive 95/46 has not harmonised the conditions for doing research with patient data.

⁵⁶ See Van Veen e.a. 2006 (see note 55) and also D. Beyleveld, D. Townend, S. Rouillé-Mirza & J. Wright (ed.), *Implementation of the Data Protection Directive in Relation to Medical Research in Europe*, Aldershot/Burlington: Ashgate 2004.

⁵⁷ Recommendation of the Committee of Ministers to member states on research on biological materials of human origin, adopted on 15 March 2006 at the 958th meeting of Ministers' Deputies, 2006, 4.

⁵⁸ Particularly France (see note 55) and Germany, see Beschlusse der Gesundheitsministerkonferenz der Länder, 20-04-2007 (<www.gmkonline.de/?&nav=beschluesse_80>).

⁵⁹ Refers to anonymously coded use of human tissue made available for use other than for scientific research. For an explanation of the terms, see Van Veen e.a. 2006 (see note 55).

⁶⁰ England (see note 55); Sweden, Biobanks in Medical Care Act (2002:297). An amendment to the previously stricter Norwegian legislation towards the Swedish model is being dealt with at the moment (announcement at congress in Stockholm, 26th May 2009).

⁶¹ Denmark (see note 55), recently Belgium, Wet van 19 december 2008 inzake het verkrijgen en het gebruik van lichaamsmateriaal met het oog op de geneeskundige toepassing bij de mens of het wetenschappelijk onderzoek, art. 20 paragraaf 2.

⁶² E. Olsthoorn-Heim & C. De Klerk, 'Juridische analyse', in: I. Geesink & C. Steegers, *Nader gebruik nader onderzocht. Zeggenschap over lichaamsmateriaal*, Den Haag: Rathenau Instituut, 2009, p. 53-92; H.J.J. Leenen/J.C.J. Dute & W.R. Kastelein, *Handboek gezondheidsrecht. Deel II: Gezondheidszorg en recht*, Houten: Bohn Stafleu van Loghum 2008, p. 231; J. Somsen, J.A. Bovenberg & B.C. van Beers, *Humane Biotechnologie en Recht*, Deventer: Kluwer 2009, in particular, the preliminary advice from Somson.

⁶³ <www.federa.org/?s=1&m=68>.

⁶⁴ Van Veen e.a. 2006 (see note 55).

the responsible-processor construction⁶⁵ applicable to the transfer of personal data between member states.⁶⁶

Hence, in my opinion, an encompassing European Directive or even Regulation covering all medical or health research in which directly or indirectly human subjects are involved is not necessary to collaborate in the context of European research projects. If it is not necessary it would also be 'ultra vires' for the EU to act with legislation. And, as argued, the side effects of such legislation are usually considerable. If European research would be a patient and the encompassing legislation the proposed treatment, it would be unethical to apply it.

Finally, a short discussion on whether European legislation should prescribe 'data sharing' of the results of clinical medicinal research as the ESF report argues. 'Data sharing' a hot issue at the moment, nationally and internationally. The National Institutes of Health (NIH) in the United States requires a 'data sharing'-plan as a condition of funding. The Dutch Council for Health Research (RGO)⁶⁷ suggested a Code of Conduct. Recently, at a well attended session of the Dutch Epidemiology Congress,⁶⁸ this was discussed further.⁶⁹ Around the same time as the RGO advice, an international Code of Conduct for 'data sharing' for observational research appeared: the Bamako Code.⁷⁰

For 'investigator initiated' medicinal research, it would seem to me that de facto a lot of data exchange takes place already. The EORTC is, all things considered, one giant 'data sharing' for non-commercial cancer research. Specialised groups work closely together via the European scientific foundations. The protocols are usually a joint undertaking and this assures 'data sharing'. It could probably be done better but that would require an infrastructure and a 'data broker'.⁷¹ It would seem to me pie in the sky that commercial sponsors would share raw research data and it is questionable whether one should expect that. This is not about publicly financed research, which immediately invalidates one argument in favour of sharing data.

With clinical research there are other arguments. However, they do not point at sharing of all raw research data. These arguments concern patient safety and the need not to burden potential trial-subjects unnecessarily. Validated research should not be repeated. Apart from the rules already contained in the GCP, there should be a specific duty to publish the results of the research. A condition of this sort, such as applies in the Netherlands via the model conditions for the research agreement from the CCMO,⁷² has not, according to the reports, been brought in everywhere. The GCP pays a lot of attention to the technical aspects of the preparations and execution of the research, not

⁶⁵ C.f. art. 1 Dutch Personal Data Protection Act.

⁶⁶ And with human tissue it is always also about data, since human tissue without data on the donors is of no use for scientific research. This does not, however, always need to be personal data, although this does depend on how this is defined. See for example Van Veen, note 55.

⁶⁷ Raad voor Gezondheidsonderzoek, *Van gegevens verzekerd. Kennis over de volksgezondheid in Nederland nu en in de toekomst*, Den Haag: RGO, nr. 58, 2008.

⁶⁸ <www.weon.nl>.

⁶⁹ The presentations are available on <www.federa.org/?s=1&m=191>.

⁷⁰ <www.casimir.org.uk/storyfiles/64.0.data_sharing_code_bamako.pdf>.

⁷¹ See the presentation by Bot-Essink on WEON 2009 (see note 69). See also J. Kaiser, 'Making Clinical Data Widely Available', *Science* 2008, p. 217-218.

⁷² CCMO-Richtlijn 'Beoordeling onderzoekscontract', *Stcrt.* 2008, 905.

to the aftermath. There needs to be a solution for the gap in the phase between the end of a clinical research protocol and the submission (or not) of a drug dossier to a body responsible for deciding on its market approval. In my opinion this issue could be adequately dealt by amending Commission Directive 2005/28/EC.

5 Final remarks

At the inception of the directive, there were warnings in literature against the too strict conditions it would contain for non-commercial research with medicine.⁷³ However, the Dutch Secretary of State maintained, in line with the official European point of view, that the directive would simplify research with medicine in Europe, because now the same conditions would apply everywhere.⁷⁴ As has been shown, this expectation has not been realised.

Medicinal research is undergoing important developments. Big Pharma is looking intensely for new blockbusters now that many patents are expiring. There are the promises of personalised medicines for which a far more precise knowledge of the working mechanisms is required. There are an increasing number of biotechnological medicines and therapies.⁷⁵ In order to review such studies, some very specialised expertise is required. The concept of 'generic' products will probably not apply where biotechnological medicines are concerned. Each applicant with a method already tested for clinical working will need to provide new bio-equivalence studies to show whether his method of preparation does the same as that of the competitor. Then there is the necessity of cost control which require academically good but also large phase IV studies. Big Pharma will, in the context of cost control, partly forgo their guarded approach to 'personalised medicines'. Of course industry wants as broad a field of (medical) indication as possible. However, if that means that the medicine wouldn't be included in the public health insurance cover, because the larger group of patients doesn't show enough improvement across the board as expressed in 'Qualities' of whatever other yardstick is chosen, then rather the (much) smaller identified group for which that is the case. This leads to all kinds of 'add-on' studies which Medical Ethics Committees regularly have to tackle. Ageing populations mean the necessity of suitable medication, or at least a better knowledge of the working of existing medicines for the elderly. Finally, I would mention the patient groups that press for prompt availability of medicines suitable for them.⁷⁶

On the one hand, this calls for a European or even global approach. It is certainly undesirable that the lightest regime is invoked for medicinal research. Think of a third world country where medicines are tested on a population that could never obtain them within the framework of an insured health care.⁷⁷

⁷³ See Baeyens 2002 (see note 28).

⁷⁴ *Kamerstukken I* 2003-2004, 28 804, nr. C, p. 7.

⁷⁵ C.f. also EC Decree on medicines for advanced therapy (1394/2007).

⁷⁶ C.f. S.A. Danner, 'AIDS, interventiestudies en patiëntendruk', *NTvG* 1990, p. 1835-1836 with the presentation by C. Smits at the ICRIL congress on 2nd December 2008, unpublished, obtainable from the author.

⁷⁷ The GCP standards also have to be complied with, otherwise the drug would never be approved.

⁷⁸ At the same time, it appears that a European directive on harmonisation hasn't had the required effect and even has even been counterproductive for 'investigator initiated' research. There is no simple solution.

It begins, in my opinion, with modesty. Modesty about what you hope to achieve with regulating, also at a European level. Modesty from national regulators, too, in whatever capacity. Furthermore, trust in, and support for 'investigator initiated' research as being the real motor behind innovation in medicinal research and health care research in general. Expanding on the last two points would exceed the scope of this article however.

As far as regulating research is concerned, enough points have been referred to in the forgoing. It should be limited to the risks that actually need to be addressed by the directive. Those risks come up in considerably fewer scientific research situations than have been covered in many countries in their 'implementation' of the directive. There should be room for flexibility as dealt with above when discussing the concept of the 'sponsors'. I have argued that a substantial amendment of the directive is, in my opinion, unnecessary and that much could be achieved with implementing directives from the Commission and with 'soft law'. The limited (guarded) and flexible application of the directive in the Netherlands could be seen as an example. If it would come to a substantial revision, this could be better achieved through a Regulation than a directive, in my opinion. Then it would be clear what the European regulation requires and, more importantly, does not require. The Regulation should be limited to clinical medicinal research. Other health (care) research shouldn't not come in its ambit. As has been argued, European collaboration in this other research is quite possible without detailed European harmonisation.⁷⁹ The lesson to be drawn from the directive is that such attempts are counterproductive for non-commercial research.

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⁷⁸ C.f. Declaration of Helsinki, paragraph B7 (see note 48).

⁷⁹ The formulation of principles as was done, for example, in the 'Convention of the Council of Europe on Human Rights and Biomedicine' and its additional protocol is quite another case. That is a quite different form of regulation than EC legislation. I will not go any further into the meaning of, and criticism on non-binding declarations of international organisations. See in this regard Van Veen e.a. 2006 (see note 55) and A. Follesdal, R.A. Wessel & J. Wouters, *Multilevel Regulation and the EU*, Leiden/Boston: Martinus Nijhoff Publishers 2008, particularly part 1, which mention a tendency to 'a race to the top' with such declarations. In my article (footnote 55) I referred to this tendency as 'rhetorically keeping up with the Joneses'.

WMO before the implementation of the Directive (insofar as not following from the text)

The scope of the Act is medical research in which persons are subjected to acts* or are required to behave in a certain manner.

The WMO contains material and procedural conditions for such research. Material conditions are, amongst other things, that the research must be scientifically sound and that it can be reasonably expected that the risk and burden of the research will not outweigh the potential benefit for the patient and its scientific value. It contains detailed provisions on the possible participation of incompetent persons or minors in medical research. Written informed consent based on a PIF should be given.

The possible participant should be able to consult an independent doctor (now independent professional qualified in the field of that research) before giving consent.

The protocol should be approved by an accredited medical research ethics committee (REC).

Accreditation is done by the Central Committee on Research with Human Subjects (CCMO). Certain protocols are exempt from the ambit of these decentralised REC's, like interventional non-therapeutic research with incompetent persons and minors. Here the CCMO is the competent REC.

The Act contains provisions on the liability severally of the sponsor, researcher and the institution where the research takes place and on a compulsory trial-subjects insurance. This is a third party insurance, based on the no-fault principle.

* The translation on the CCMO website says 'treatment' instead of 'acts'. Treatment is too restrictive given the Dutch literal text and its application.