COUNCIL OF THE EUROPEAN UNION

Brussels, 19 July 2012

12751/12 ADD 3

Interinstitutional File: 2012/0192 (COD)

PHARM 60
SAN 176
MI 508
COMPET 513
CODEC 1946

COVER NOTE

from:	Secretary-General of the European Commission, signed by Mr Jordi AYET PUIGARNAU, Director
date of receipt:	17 July 2012
to:	Mr Uwe CORSEPIUS, Secretary-General of the Council of the European Union
Subject:	COMMISSION STAFF WORKING DOCUMENT Impact assessment report on the revision of the "Clinical Trials Directive" 2001/20/EC Accompanying the document Proposal for a Regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC

Delegations will find attached Commission document SWD(2012) 200 final VOLUME II.

Encl.: SWD(2012) 200 final VOLUME II

EUROPEAN COMMISSION

Brussels, 17.7.2012
SWD(2012) 200 final

VOLUME II (Annexes)

COMMISSION STAFF WORKING DOCUMENT

Impact assessment report on the revision of the "Clinical Trials Directive" 2001/20/EC

Accompanying the document

Proposal for a Regulation of the European Parliament and of the Council

on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC

{COM(2012) 369 final}
{SWD(2012) 201 final}

EN

ANNEX 1: CLINICAL TRIALS AND THE CLINICAL TRIALS DIRECTIVE

(1) Clinical trials

Clinical trials are performed in many different contexts. Traditionally, these are referred to as 'phases'. While there is no universally agreed terminology, the phases can be defined as follows:[1]

- Phase I (human pharmacology): Initial trials provide an early evaluation of short-term safety and tolerability and can provide pharmacodynamic and pharmacokinetic information needed to choose a suitable dosage range and administration schedule for initial exploratory therapeutic trials.

- Phase II (therapeutic exploratory): Phase II is usually considered to begin with the start of studies in which the primary objective is to explore therapeutic efficiency in patients. In addition, additional information on the safety profile of a compound is gathered.

- Phase III (therapeutic confirmatory): Phase III is usually considered to begin with the start of studies in which the primary objective is to demonstrate or confirm therapeutic benefits. In addition, additional information on the safety profile of a compound is gathered.

- Phase IV (therapeutic use): Phase IV begins after authorisation of the medicinal product. Therapeutic use studies go beyond the prior demonstration of the safety and efficacy of the medicine and dose definition. Phase IV covers all studies (other than routine surveillance) performed after drug approval and related to the approved indication. They are studies that were not considered necessary for approval but are often important for optimising use of the medicinal product. They may be of any type, but should have valid scientific objectives. They commonly include additional drug-drug interaction, dose-response or safety studies and studies to support use for the approved indication, e.g. mortality/morbidity studies.

(2) The Clinical Trials Directive

Prior to the entry into force of the Clinical Trials Directive, the rules for performing clinical trials varied significantly in the Union. Since 2004, clinical trials performed in the EU are regulated by the Clinical Trials Directive. The primary purpose of this Directive is to:

- Protect the health and safety of participants in clinical trials;

- Ensure the reliability and robustness of data generated in clinical trials; and

- Simplify and harmonise the administrative provisions governing clinical trials in order to allow cost-efficient clinical research.[2]

---

1 Report of Working Group VI of the Council for International Organisations of Medical Sciences (CIOMS), 'Management of safety information from clinical trials', 2005, p. 232. A more detailed overview, with examples, is contained in ICH Guideline E8, 'Note for guidance on general considerations for clinical trials' (CPMP/ICH/291/95).

2 Cf. recital 10 of the Clinical Trials Directive.

Since the Clinical Trials Directive entered into force, it has been supplemented by a Commission Directive[3] setting out the principles of good clinical practice (GCP). A multitude of other guidance documents have been published in EudraLex, Volume 10,[4] including the Guideline on 'Good Clinical Practice — ICH E6'. This guideline was agreed under the auspices of the ICH and is, *de facto,* recognised worldwide as *the* standard applicable to GCP.

In terms of substance, these Union rules aim at establishing, *inter alia*:

- Procedures for applications to conduct a clinical trial and authorisation of a clinical trial by the national competent authority (NCA) and Ethics Committee;
- Requirements for a clinical trial, including rules for protection of participants;[5]
- Rules on reporting adverse events, in particular 'suspected unexpected serious adverse reactions' (SUSARs), during the clinical trial;
- Rules on the manufacturing, importation and labelling of the 'investigational medicinal product' (IMP); and
- Rules on inspection of clinical trial sites.

As a result of this harmonisation, today, clinical data generated anywhere in the EU is accepted, as regards subject rights and safety, as well as data robustness and reliability.

The Clinical Trials Directive does not address the question of whether and how the result of a clinical trial can be used, for example in an application for a marketing authorisation for a medicinal product. Instead, this is regulated in Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use[6] (the 'Community Code'). The Community Code stipulates that all clinical trials performed in the EU and submitted as part of an application for marketing authorisation must comply with the Clinical Trials Directive. If the clinical trials are performed in non-EU countries, they must comply with rules and principles equivalent to those laid down by the Directive.

The Clinical Trials Directive applies only to 'interventional trials', but not to 'non-interventional' studies.[7] Non-interventional studies are trials where the medicinal product is prescribed in the usual manner in accordance with the terms of the marketing authorisation, the assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice, prescription of the medicine is clearly separated from the decision to include the

---

3 Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products (OJ L 91, 9.4.2005, p. 13).

4 http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10_en.htm.

5 Article 2(i) of the Clinical Trials Directive refers to participants in clinical trials as 'subjects'. In this document, the term 'participants' is used.

6 OJ L 311, 28.11.2001, p. 67.

7 Also referred to as 'non-interventional studies' or 'observational studies'.

patient in the study, no additional diagnostic or monitoring procedures are applied to the patients and epidemiological methods are used to analyse the data collected.

The reason for excluding non-interventional trials from the scope of the Directive is that they typically pose a lower risk than interventional trials. In addition, this restriction is meant to exclude medical activities which are normal clinical practice and, as such, part of the general medical surveillance of a patient.

The results of observational trials cannot be taken as the basis for an application for marketing authorisation.

The Clinical Trials Directive provides for a database — EudraCT — which contains protocol-related information on clinical trials performed in the EU or contained in a 'paediatrics investigation plan' (PIP). The sponsor submits this information on a specially designed form, together with the application for authorisation of a clinical trial, to the NCA of the Member State concerned, which forwards this information to EudraCT. EudraCT is managed by the Agency.

(3) Criticism of the Clinical Trials Directive

The Clinical Trials Directive is **the most heavily criticised piece of legislation of the entire EU acquis for pharmaceuticals**. The severe criticism is voiced by all stakeholders and political actors - patients, industry, and academic research, Member States, Union institutions - and has been re-iterated and stressed during the various consultations referred to in point **Error! Reference source not found.**. Examples are:

- Patient organisations: The European Cancer Patient Coalition, in its response to the 2009/10 public consultation stressed that "[The Clinical Trials Directive] *has severely hampered cancer research in Europe, and threatens to further destruct existing multi-national research networks which have been established prior to the Clinical Trials Directive. […] The Clinical Trials Directive has created many additional burdens for the conduction of trials, while it did not meet the primary objective of harmonizing and simplifying the legislation in the Member States."*[8]

- Industry: The European Federation of pharmaceutical industries and associations (EFPIA) considers that "the European Clinical Trials Directive has added administrative and regulatory constraints in some EU countries where there weren't any such measures or where these were set a lower level without - until now - bringing the tangible benefits of a real harmonisation of the framework conditions to conduct clinical trials across Europe (despite the fact that this initially was the intended goal). In this context, large-scale multi-centred clinical trials are very difficult and cumbersome to operate in Europe, whatever the disease area or medical indication, which may translate into long delays and higher costs."[9] Regarding SMEs, the European Confederation of Pharmaceutical Entrepreneurs (EUCOPE), who has a large membership of SMEs, has stressed during the 2009/10 public consultation that 'Difficulties for SMEs are in parts similar to those of larger companies. However, there is a higher burden for SMEs due to the increased need of staff for preparation and management of clinical trials […]. This leads to an overall increase in resources required for the performance of clinical trials in the new

[8] Response of the European Cancer Patients Coalition (ECPC) to the 2009/10 public consultation, page 5.
[9] EFPIA statement at: http://www.efpia.eu/content/default.asp?PageID=507.

regulatory framework which is especially burdensome for SMEs.[10] This was also highlighted by other respondents, stressing that the Clinical Trials Directive poses 'a specific challenge [for] SME companies when developing new products for rare disorders that affect a limited number of patients. […] Typically, SMEs do not have in-house resources to track and manage national regulatory documentation, translations and approval processes.'[11]

- Non-commercial research: The Federation of the European Academies of Medicines, in its response to the 2009/10 public consultation highlighted that '*The Clinical Trials Directive has not solved the problems it was designed to do, but has dramatically increased administrative burden and costs for academia, resulting in a deterrent effect on new clinical research. […] In consequence of the Clinical Trials Directive, the EU has become a less attractive location of such research*.'[12] The European Science Foundation (ESF), together with the European Medical Research Councils (EMRC), have highlighted that "*current EU legislation represents a major hurdle to improving medical treatment due to the straight-jacket of EU legislation that the 2001 Clinical Trials Directive imposes*".[13] The severe criticism of the Clinical Trials Directive has also led to a high number of academic publications painting a picture of increased bureaucracy and costs, accompanied by a reduction in important research activities.[14] These publications highlight the '*Regulatory impediments* [which] *jeopardize the conduct of clinical trials in Europe funded by the National Institutes of Health*', [15] the '*Harmful impact of EU clinical trials directive*',[16] leading to '*the death of academic clinical trials*'.[17]

- Member States: The Heads of Medicines Agencies (HMA), an intergovernmental body bringing together the heads of all Medicines Agencies of the EU, has, in its 'Strategy for the Heads of Medicines Agencies 2011-2014'[18] called for "*the creation of an efficient and unified regulatory environment for clinical trials in Europe that encourages innovation and high quality clinical research, by improving efficiency and reducing duplication, focussing assessment and inspections for clinical trials on a risk-based approach and promoting harmonised interpretation and implementation of guidelines and legislation related to clinical trials*". This confirms the viewpoint of Member States who, in a statement made in Council in 2010, called upon the Commission to treat revision of the Clinical Trials Directive '*as a matter of*

---

10 Response of the European Confederation of Pharmaceutical Entrepreneurs (EUCOPE) to the 2009/10 public consultation, p. 4.

11 Response of the European biopharmaceutical enterprises asociation (EBE) to the 2009/10 public consultation, p. 1.

12 Response of the Federation of the European Academies of Medicines (FEAM) to the 2009/10 public consultation, page. 1.

13 Press release of the ESF and the EMRC, 30 January 2012; http://www.esf.org/media-centre/ext-single-news/article/improving-medical-treatment-requires-a-risk-based-approach-to-the-regulation-of-clinical-trials-799.html.

14 Cf. the literature review in ICREL (pp. 25-43). However, there are also publications which take a less black-and-white approach when discussing the negative impact of the Clinical Trials Directive (cf. Berendt *et al.*, 'Effect of the European Clinical Trials Directive on academic drug trials in Denmark: retrospective study of applications to the Danish Medicines Agency 1993-2006', BMJ, published online on 6 December 2007).

15 Clin Trials, 20 August 2010, p. 1.

16 BMJ 2006; 332 doi: 10.1136/bmj.332.7540.501 (Published 2 March 2006)

17 Morice AH, Lancet 361:1568 (2003).

18 http://www.hma.eu/fileadmin/dateien/HMA_joint/HMA_Strategy_Paper_II/HMA_Strategy_final_version__2_.pdf.

urgency'.[19] Apart from joint statements, there have been statements by individual Member States. For example the UK government, in its reply to the 2011 public consultation stressed that "*the forthcoming review of the Directive provides an important opportunity to ensure that the EU maintains its position as an attractive place for the conduct of clinical trials necessary to the development of new medicines*."[20]

- Union institutions: The European Parliament and the Council had also called repeatedly for revision of the Clinical Trials Directive. Examples include the Council Conclusions of 9 December 2010 on innovation and solidarity in pharmaceuticals, which call upon the Commission to '*give priority to revising the Clinical Trials Directive*'[21] and the European Parliament Resolution of 10 April 2008 on combating cancer in the enlarged European Union, which '*calls on the Commission to revise* [the Clinical Trials] Directive […] *to encourage more academic research on cancer*'.[22]

The criticism of the Clinical Trials Directive has also found its way into non-scientific publications stressing for example the bureaucracy created by the Clinical Trials Directive ('*Les experts passent de plus en plus de temps à faire de la bureaucratie, aux dépens de la recherche clinique*'),[23] its negative impact on public health ('*British patients may be denied access to the latest drugs and treatments as a result of EU rules on clinical trials*'),[24] and its negative impact on innovation and research ('*EU Regulations hindering drug development, say charities*').[25]

(4) Globally applicable principles of GCP

A range of internationally agreed documents set out universally applicable principles on protection of participants in clinical trials, no matter where the trial is performed. Studies suggest that, between 1947 and 2000, almost 400 international codes on the conduct of biomedical research have been adopted by various international bodies.[26] Of these, there are some key documents, such as:

- The revised version of the World Medical Association Declaration of Helsinki — Ethical Principles for Medical Research Involving Human Subjects;[27] and

- The Guideline E6 on Good Clinical Practice of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use ('ICH').[28]

---

19 'Statement' of the governments of the Netherlands, Belgium, Bulgaria, Ireland, Spain, Finland and Sweden, annexed to the EU pharmacovigilance legislation adopted in 2010, Document 10779/10, 22 June 2010 ADD1 (http://register.consilium.europa.eu/pdf/en/10/st10/st10779-ad01.en10.pdf).

20 P. 1. See also the open letter, in July 2008, from the UK Secretary of State for Business, Enterprise and Regulatory Reform on '25 ideas for simplifying EU law': http://www.administrative-burdens.com/filesystem/2008/07/25_ideas_for_simplifying_eu_law_517.pdf.

21 Page 9 (http://www.consilium.europa.eu/uedocs/cms_data/docs/pressdata/en/lsa/118278.pdf).

22 http://www.europarl.europa.eu/sides/getDoc.do?type=TA&reference=P6-TA-2008-0121&language=EN.

23 Le Soir, Belgium, 4 Septembre 2010, p. 8: 'Les essais cliniques belges en crise'.

24 The Daily Telegraph, 13 January 2012, p. 20.

25 The Telegraph, 26 September 2011.

26 Tröhler, Ulrich; The long road of moral concern: Doctors' Ethos and Statue Law relating to Human Research in Europe; History and theory of Human Experimentation (Eds. Schmidt, Ulf; Frewer, Andreas), 2007, p. 36.

27 http://www.wma.net/e/.

Moreover, at a more detailed level, international guidelines have been agreed on a variety of matters, such as the structure and content of clinical trial reports,[29] choice of control groups, statistical principles, etc.[30]

Finally, there are conventions on this matter which have been concluded under binding international law such as

- The Council of Europe (CoE) Convention for the Protection of Human Rights and Fundamental Freedoms;[31] and

- The CoE Convention on Human Rights and Biomedicine ('Oviedo Convention').[32]

(5) Sponsors involved in clinical trials

Clinical trials are performed under the responsibility of a sponsor. The sponsor is the person responsible for the trial. The notion of 'sponsoring' in this context must not be confused with the 'funding' of a clinical trial. The types of sponsors vary widely, from large multinational pharmaceutical companies and large research organisations with well-organised structures to small, fragmented cooperative structures with a far lower level of dedicated resources. However, these structures are often interlinked: for example, research organisations may carry out clinical trials for pharmaceutical companies and clinical research and their publications may influence the development of medicinal products.

(6) Authorisation by national competent authorities and Ethics Committees, inspections and surveillance

Clinical trials are subject to authorisation by the NCA and the EC of the Member State where the clinical trial is performed (the 'Member State concerned').

The Clinical Trials Directive is based on the concept of one EC opinion per Member State concerned. However, several Member States have a decentralised system where the single EC opinion is based on the opinions of several local committees. As a consequence, in the EU approximately 2 000 ECs are involved in assessment of clinical trials (see Annex 2).

Apart from this *ex-ante* control, regulatory compliance is verified by means of inspections of clinical trial sites by NCAs. According to information uploaded in EudraCT, since May 2004, approximately 3 150 inspections have been performed in the EU by NCAs. Clinical trials in non-EU countries are inspected only in the course of marketing authorisation procedures.

---

28 http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/3cc1aen.pdf.

29 http://www.emea.europa.eu/pdfs/human/ich/013795en.pdf.

30 See, for example, http://www.emea.europa.eu/htms/human/ich/ichefficacy.htm.

31 http://conventions.coe.int/treaty/Commun/ChercheSig.asp?NT=005&CM=&DF=&CL=ENG.

32 http://conventions.coe.int/treaty/en/treaties/html/164.htm.

ANNEX 2: KEY FIGURES

1. Introduction

This annex sets out the key figures used in the calculations of the costs of the various policy options discussed.

Unless indicated otherwise, the sources are:

- The EU database for clinical trials 'EudraCT'[33]; or
- The Agency report 'Clinical trials submitted in marketing authorisation applications to the EMA — Overview of patient recruitment and the geographical location of investigator sites'.[34]

All figures on the duration of action or costs per man-hour were checked with stakeholders in the 2011 public consultation and the related workshops (see point **Error! Reference source not found.**).

2. Number of clinical trials in the EU

Table 1: Clinical trials by year, by phase and by sponsor status[35]

	Sponsor status	2005	2006	2007	2008	2009	2010
Phase I	Commercial	1217	1271	1324	1348	1240	1190
	Non-commercial	124	158	173	184	212	187
	Unspecified	9	8	6	4	4	7
Phase I total		**1350**	**1437**	**1503**	**1536**	**1456**	**1384**
Phase II	Commercial	622	647	806	696	685	597
	Non-commercial	310	489	682	601	663	585
	Unspecified	7	5	4	9	6	4
Phase II total		**939**	**1141**	**1492**	**1306**	**1354**	**1186**
Phase III	Commercial	686	673	704	603	564	620
	Non-commercial	187	272	426	331	346	296
	Unspecified	6	6	6	3	4	1
Phase III total		**879**	**951**	**1136**	**937**	**914**	**917**
Phase IV	Commercial	243	207	214	165	142	136
	Non-commercial	514	538	664	637	618	552
	Unspecified	7	11	7	4	13	19
Phase IV total		**764**	**756**	**885**	**806**	**773**	**707**

[33] It should be noted that EudraCT data is supplied by the NCAs of MSs. The data submitted prior to 2007 has some flaws. This is due to the fact that – despite the transposition date of 1 May 2004 – the Clinical Trials Directive (and the corresponding reporting requirements to EudraCT) was fully applied only in 2006 or later.

[34] EMA/INS/GCP/154352/2010, 5 November 2010.

[35] The sponsor status 'commercial' or 'non-commerical' is self-declared by the sponsor. In the absence of a EU-definition of these terms, usually a formal criteria (company or not) applies.

Table 2: Number of clinical trials applied for in the EU per year since 2007[36]

2007	*2008*	*2009*	*2010*	*2011*
5028	*4'627*	*4619*	*4'400*	*3490*

Table 3: Number of applications to conduct clinical trials in the EU[37]

Sponsor status	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**
Commercial	5865	6714	7686	7993	7655	7672
Non-commercial	1303	1677	2216	2039	2161	2037
Unspecified	62	73	47	56	53	68
Total	**7218**	**8446**	**9949**	**10008**	**9869**	**9763**

[36] These numbers do not match the total of the entries in table 1. The reason is that the (self-declared) phase is sometimes missing. The data for 2011 is a forecast on the basis of EudraCT data available on 18 October 2011.

[37] The same clinical trial can be applied for in several MS, i.e. one clinical trial can mean up to 27 clinical trial applications.

3. Number of multinational clinical trials (EU)

Approximately 25% of EU clinical trials are performed in more than one EU Member State (see Table 4). This is equal to approximately 60% of all applications to conduct clinical trials in the Member States.

Table 4: Number of Member States/NCAs involved per clinical trial per year[38]

	Number of Member States Involved																								
Year	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
2005	2,972	280	196	115	95	71	73	50	31	23	24	16	6	7	7	3	5	1							
2006	3,292	274	162	121	101	86	74	53	31	33	24	14	22	12	12	5	5	5	4	2	2	1		1	
2007	3,840	297	183	153	95	88	75	67	49	41	32	29	21	22	13	7	2	7	1	2	2	1		1	
2008	3,520	259	175	130	102	96	67	58	49	33	32	32	18	13	11	6	6	6	2	4		3	2	3	
2009	3,573	228	194	128	96	91	63	59	44	26	25	17	26	11	17	4	6	2	3	4	1				1
2010	3,357	227	166	99	124	89	70	58	54	40	32	15	17	11	11	4	7	4	4	6	2	2			1

4. Number of clinical trials in each Member State

Table 5: Clinical trials by year, by Member State and by phase[39]

[38] The total per year is not absolutely identical with the figures in table 3. This can be explained by the fact that data in EudraCT is self-declared by the sponsors and as such not always fully stable.

[39] For the terminology, see point **Error! Reference source not found.** of the impact assessment report. On the detailed terminology see ICH Topic E8 – General Considerations for Clinical Trials (CPMP/ICH/291/95).

	Trial type: Human pharmacology (Phase						Trial type: First administration to						Trial type: Bioequivalence						Trial type: Other						Trial type: Therapeutic exploratory (Phase						Trial type: Therapeutic confirmatory (Phase						Trial type: Therapeutic use (Phase					
YEAR:	**05**	**06**	**07**	**08**	**09**	**10**	**05**	**06**	**07**	**08**	**09**	**10**	**05**	**06**	**07**	**08**	**09**	**10**	**05**	**06**	**07**	**08**	**09**	**10**	**05**	**06**	**07**	**08**	**09**	**10**	**05**	**06**	**07**	**08**	**09**	**10**	**05**	**06**	**07**	**08**	**09**	**10**
AT	29	32	24	42	45	44	3	12	4	12	9	11	3	5	3	5	3	2	20	16	19	29	27	26	78	96	96	120	101	107	157	164	152	186	125	156	53	42	54	64	38	52
BE	134	140	136	147	134	148	35	39	35	54	44	47	10	9	5	5	8	6	71	59	66	63	66	74	166	160	166	182	175	138	257	217	203	221	216	222	63	64	67	54	50	47
BG			14	24	18	33			1	1	1	4			11	14	9	23			2	2	6	7			14	61	48	45			22	126	91	96			0	10	9	8
CY		0	0	0	0	0		0	0	0	0	0		0	0	0	0	0		0	1	0	0	0		1	1	0	0	1		5	2	3	2	0		1	1	0	0	0
CZ	21	31	37	41	37	39	1	5	3	3	12	8	25	31	33	29	25	28	11	11	12	12	7	13	76	84	116	93	128	91	157	220	210	190	175	204	22	23	26	26	18	28
DK	21	39	26	32	17	20	6	11	11	12	6	5	1	4	1	0	2	1	18	24	15	24	13	17	74	94	79	96	96	70	111	146	126	149	120	97	57	55	41	60	41	44
EE	3	2	2	1	0	0	1	1	0	1	0	1	0	0	0	1	0	0	1	1	2	0	1	1	20	22	23	16	23	14	57	59	65	59	47	59	7	5	4	7	7	3
FI	17	31	36	54	28	22	3	3	6	6	1	4	8	8	8	12	6	6	11	27	27	34	20	17	39	61	52	53	45	33	109	132	115	111	77	102	34	59	47	50	53	39
FR	53	122	232	219	215	200	7	29	53	39	60	51	5	10	24	15	11	16	29	79	157	148	126	123	98	175	338	286	346	313	183	281	389	344	383	388	39	57	118	80	98	88
DE	311	477	356	372	435	367	56	101	50	48	56	56	48	73	46	79	69	52	174	245	164	150	216	192	280	417	414	421	460	395	374	506	456	447	464	448	122	165	119	126	103	102
EL	0	33	17	3	11	11	0	1	1	0	1	0	0	33	13	2	5	2	0	7	4	1	5	8	0	31	34	11	43	19	2	96	87	28	140	56	0	16	19	10	25	10
HU	15	17	29	50	35	33	2	3	4	10	4	4	9	14	18	28	22	18	6	13	8	10	11	12	61	77	95	99	106	85	132	173	197	174	154	186	14	23	28	25	18	23
IS	0	2	2	1	0	0	0	1	1	1	0	0	0	1	0	0	0	0	2	1	0	0	0	0	3	6	0	2	6	6	11	7	6	9	3	5	2	4	2	1	2	1
IE	11	11	24	20	21	14	5	6	1	2	1	1	9	13	19	15	16	8	2	3	4	8	3	4	20	23	19	27	18	20	50	54	44	49	47	43	16	29	19	27	12	13

	Trial type: Human pharmacology (Phase I)						Trial type: First administration to humans						Trial type: Bioequivalence study						Trial type: Other						Trial type: Therapeutic exploratory (Phase II)						Trial type: Therapeutic confirmatory (Phase III)						Trial type: Therapeutic use (Phase IV					
YEAR:	**05**	**06**	**07**	**08**	**09**	**10**	**05**	**06**	**07**	**08**	**09**	**10**	**05**	**06**	**07**	**08**	**09**	**10**	**05**	**06**	**07**	**08**	**09**	**10**	**05**	**06**	**07**	**08**	**09**	**10**	**05**	**06**	**07**	**08**	**09**	**10**	**05**	**06**	**07**	**08**	**09**	**10**
IT	8	12	22	74	83	59	0	0	0	19	22	19	6	13	18	11	8	6	1	0	6	28	19	24	145	208	529	326	369	245	213	280	603	431	371	289	35	58	152	111	161	94
LV	3	3	2	3	2	2	1	0	1	2	2	0	2	0	0	0	0	1	0	2	5	1	0	2	15	20	32	27	28	18	42	51	56	58	45	57	7	2	4	9	1	2
LT	0	3	0	1	1	0	0	0	0	1	1	0	0	1	0	0	0	0	1	1	1	0	0	0	22	28	42	30	23	17	60	75	79	75	51	77	9	8	4	7	2	2
LU				0		0				0		0				0		0				0		0				0		1				0		7				1		0
MT	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	2	0	0	1	3	3	3	4	3	0	0	2	0	0	1
NL		80	146	156	105	15		21	45	51	41	4		5	7	7	5	0		57	101	95	59	9		102	162	162	99	10		126	175	214	140	31		62	98	105	64	6
NO	5	8	9	8	6	10	2	2	3	5	1	0	0	2	0	1	0	0	9	8	7	2	5	11	38	42	51	47	46	34	94	82	81	87	54	56	41	38	40	30	26	20
PL			31	42	38	39			5	8	4	9			16	20	16	22			17	17	15	13			122	156	198	136			203	259	276	230			20	29	33	20
PO	1	3	8	4	6	2	0	0	0	0	1	0	0	0	3	0	0	1	1	3	7	4	7	1	12	18	31	28	28	18	32	120	74	101	73	77	6	20	25	15	11	10
RO				0	5	9				0	2	2				0	0	2				0	5	7				9	38	82				9	77	166				2	5	14
SL	7	5	1	15	9	11	1	0	0	1	0	1	2	2	1	4	5	4	2	4	1	9	5	8	24	23	15	63	35	37	53	91	39	160	73	113	5	8	4	13	7	10
SI	0	1	1	0	1	1	0	1	1	0	1	0	4	2	0	0	0	0	0	0	1	0	1	0	9	5	4	7	7	9	19	19	20	15	12	11	2	8	6	4	8	6
ES	87	76	82	101	110	159	9	10	15	18	22	36	40	44	33	35	42	55	42	24	31	52	47	63	138	150	194	204	248	269	241	262	261	275	265	396	104	100	90	124	100	142
SE	77	91	98	81	72	57	20	22	31	26	18	10	8	10	2	6	4	2	40	61	52	51	49	50	89	116	117	109	111	74	154	162	171	166	144	139	69	52	58	53	56	39
UK	625	333	345	317	282	392	154	78	100	83	76	93	57	34	35	26	21	31	346	170	168	183	134	201	387	266	294	275	298	344	429	248	280	307	253	386	341	198	202	189	150	205
Total	**1428**	**1552**	**1680**	**1808**	**1716**	**1687**	**306**	**346**	**371**	**403**	**386**	**366**	**237**	**314**	**296**	**315**	**277**	**286**	**787**	**816**	**878**	**923**	**847**	**883**	**1794**	**2226**	**3040**	**2912**	**3123**	**2631**	**2938**	**3579**	**4119**	**4256**	**3882**	**4100**	**1048**	**1097**	**1250**	**1232**	**1098**	**1029**

5. Number of subjects planned

Table 6: Number of subjects planned per year per clinical trial

MS concerned	2007	2008	2009	2010
1	134,954	87,73	98,056	130,780
2	51,726	33,422	31,323	33,412
3	45,043	34,310	29,374	33,962
4	61,973	19,839	23,871	25,561
5	18,207	21,573	19,94	26,726
6	25,724	22,12	20,129	20,202
7	24,254	15,2300	12,308	15,638
8	16,705	16,346	11,948	11,992
9	12,98	38,838	12,308	28,467
10	18,974	8,343	11,455	15,909
11	13,525	11,000	10,519	4,280
12	11,928	11,585	8,118	3,139
13	12,401	11,552	16,849	3,985
14	13,023	4,526	7,818	10,383
15	21,970	6,949	11,083	2,435
16	16,231	13,956	2,200	5,744
17	1,000	4,193	4,824	3,200
18	7,843	11,173	1,307	7,775
19	850	9,062	8,300	3,715
20	10,665	13,229	8,331	5,143
21	5,900	-	1,815	6,340
22	4,395	7,507	-	-
23	-	3,320	-	-
24	4,500	2,817	8,000	743
25	-	-	-	-
26	-	-	-	-
27	--	-	-	-

Table 7: Number of planned subjects in clinical trials in the EU[40]

Year	2007	2008	2009	2010
	544287	410568	367036	408294

Table 8: Total number of planned subjects in clinical trials with at least one site in the EU

Year	2007	2008	2009	2010
	1043642	781695	677723	881546

6. Number of substantial amendments

1.1. Submissions to NCAs

As a rough estimate, every year each clinical trial is amended, on average, twice, insofar as submission to the NCA is concerned. This means that each year approximately 24000 SAs are made to clinical trials in the EU as far as this is of relevance for NCAs.

This is confirmed by a survey of the Commission amongst Member States (Table 9).

Table 9: Number of substantial amendments submitted to NCAs (2010)[41]

AT	945[42]
BE	1610
BG	489
CY	
CZ	1880 including IPS/ICF
DE (BfArM)	4256
DE (PEI)	914
DK	609 (Jan-Nov)
EE	180
EL	362
ES	5290 SA received, out of which we estimate 2973 were for assessment
FI	358
FR	3166 : 1609 for authorisation + 1557 for information
HU	1604
IE	399
IT	165[43]

40 The total per year is not absolutely identical with the figures in table 6. This can be explained by the fact that data in EudraCT is self-declared by the sponsors and as such not always fully stable.

41 Commission survey amongst NCAs. Substantial amendments (SAs) submitted: the SAs received by the NCA. This excludes by definition (see COM guideline CT-1) SAs submitted for assessment by Ethics Committees, and 'SAs for information only'

42 AT: Classification of the amendment is the remit of the sponsor. This number therefore includes all submission classified by the sponsor as "substantial".

43 According to the Italian legislation, the NCA is responsible for the authorization of phase I (ISS) and Advanced Therapy Investigational Medicinal Products clinical trials (AIFA) substantial amendments. When the NCA is not involved, the coordinating Ethics Committee is responsible for the assessment of the amendments at a national level. When considering all substantial amendments assessed by the NCA or the coordinating EC, the number would be 2,086.

LT	254
LU	
LV	190
MT	14
NL	1401
PL	1100
PT	260
RO	1367
SE	892
SI	66
SK	
UK	4563
IS	18

This estimate is further supported by ICREL: every year, approximately 1 000 SAs are *submitted,* on average, per Member State,[44] i.e. approximately 27 000 SAs per year.[45]

1.2. Submissions to ECs

There are no precise figures for SAs submitted to ECs per Member State. It can be assumed that the number is higher than for NCAs, because most Member States consider adding further investigators or trial centres as a SA. Both investigators and trial centres change frequently. Therefore, it is realistic to assume that the number of SAs submitted to ECs is twice the number submitted to NCAs, i.e. 2 000 SAs per Member State, giving a total of 54 000 SAs.

1.3. Submissions per year (total)

Based on the above it can be assumed that each year 78 000 SAs are submitted to the ECs and NCAs in the EU.

7. Number of SUSARs and SUSAR reports

Table 10: Number of SUSARs and SUSAR reports — Data from Eudravigilance – Clinical Trials Module (EVCTM)

	2009	***2010***
SUSARs		*35 409*
SUSAR reports	*94 600*	*99 583*

44 ICREL, p. 74.

45 Getz, Zuckerman, Cropp, Hinle, Krauss, Kaitin, 'Measuring the incidence, causes and repercussions of protocol amendments', Drug Information Journal, Vol. 45, p. 265 (2.3 amendments per protocol amended).

Table 11: Number of SUSARs and SUSAR reports — Data from Member States (2009/2010)[46]

MS	Number of (unique) SUSARs (2009)	Number of SUSAR reports (2009)	Number of (unique) SUSARs (2010)	Number of SUSAR reports (2010)
AT	N/A[47]	178[48]	N/A	38[2]/657[49]
BE[50]	980 (initial reports)	6334 (initial reports and follow-up)	785 (initial reports)	3293 (initial reports and follow-up)
BG	28 (initial reports)	191 (initial reports and follow-up)	36 (initial reports)	160 (initial reports and follow-up)
CY				
CZ	142 SUSAR reports, right No 49 SUSAR(only from CZ)		129	
DE (BfArM)	23763 (3594 occurred in MS, 20169 outside MS); numbers of initial report without follow up. Note that it is not possible to count the number of SUSARs correctly by taking this number.	60350 (9267 occurred in MS, 51083 outside MS); numbers of follow up reports without the initial report. . Note that it is not possible to count the number of SUSARs correctly by taking this number.	23351 (3923 occurred in MS, 19428 outside MS); numbers of initial report without follow up. Note that it is not possible to count the number of SUSARs correctly by taking this number.	64114 (9855 occurred in MS, 54259 outside MS); numbers of follow up reports without the initial report. . Note that it is not possible to count the number of SUSARs correctly by taking this number.
DE (PEI)	1137	2527(initial reports and follow-up)	1253	2684 (initial reports and follow-up)
DK	133 national SUSARs	291 incl. follow ups (National). 2848 national and EU SUSARs		200 (Jan-Nov) national SUSARs
EE	19		18	
EL	306			
ES	NA	NA	NA	NA
FI		333		290
FR		48 562 reports (initial + follow up/ local + outside)		48742 (initial + follow.up; local + outside)
HU	238	About 3-5 times as much as the unique SUSARs (it's not possible to generate this data from our database)	242	About 3-5 times as much as the unique SUSARs (it's not possible to generate this data from our database)
IE	44	N/A	63	N/A
IT[51]	764	1632	706	1850
LT	NA	301 (national SUSARs reports)	NA	385 (national SUSARs reports)
LU				
LV		193 (SUSAR reports)		100 (national SUSAR reports)

46 Commission survey amongst NCAs. SUSAR: A given suspected unexpected serious adverse reaction. SUSAR reports: the reports received by the NCA. One SUSAR may trigger many reports (for example, follow-up reports or double reporting from different reporting stakeholders).

47 AT: This is an estimation of the total number of received reports. It is not possible to extract the number of unique reports from the Austrian database.

48 AT: National reporting.

49 AT: Direct reporting to Eudravigilance.

50 Data generated from the EudraVigilance Datawarehouse as Belgium has no national database.

51 Data refers to national SUSARs and are generated from the EudraVigilance Datawarehouse as Italy has no national database.

MT	0	0	3 (SUSAR reports)	3 (SUSAR reports)
NL		1607		1268
PL		17183		
PT	84 (national SUSAR)	250 (national SUSAR reports)	70 (national SUSAR)	250 (national SUSAR reports)
RO	256	328	79	191
SE	NA	231	NA	238
SI	16 national SUSARs	N/A	17 national SUSARs	N/A
SK				
UK	16 919 (1624 UK + 15295 foreign)	33292 (2938 UK + 30354 foreign)	19962 (1777 UK and 18185 foreign)	49106 (4053 UK + 45053)
IS	2	2	2	2

The system for SUSAR reporting in the EU is highly diverse. It is therefore not surprising that the figures above diverge so widely, particularly when they are compared with the number of clinical trials performed in each Member State (see Table 5).

Based on these data, however, it can be assumed that each year approximately 35 000 SUSARs occur in the EU. This leads to approximately 200 000 SUSAR reports at national level (NCAs and ECs) and another 100 000 at EU level (phase IV centrally authorised medicines). The latter are not always reported by the sponsor but, depending on the Member State, might be reported by the NCA. It can be assumed that the sponsors submit approximately 50 % of these reports, i.e. 50 000 reports.

It can therefore be concluded that, every year, sponsors submit approximately 250 000 SUSAR reports to different bodies in the EU (Agency, EC, NCA).

8. Number of annual safety reports ('ASR')

The number of ASR *submissions* equals the number of ongoing clinical trials in each Member State concerned.

The number of ASRs *actually drafted* is lower. This is for the following two reasons:

(a) The Sponsor may submit an identical ASR for several clinical trials performed by that sponsor with the same IMP[52] (see table 12);

Table 12: Number of ASRs (2009/2010)[53]

MS	Number of ASRs (2009)	Number of ASRs (2010)
AT[54]	713	757
BE[55]	830	1 031
BG	243 (containing all CTs with the IMP)	221 (containing all CTs with the IMP)
CY		
CZ	N/A	not followed for this year, for next-yes
DE (BfArM)	1287 This data are ASR submissions. It cannot be specified if these ASR cover one or more than one CT or /and one ore more IMP. With these data it is neither possible to calculate ASR numbers of IMPs (now DSUR) nor ASR number of CTs.	1850 This data are ASR submissions. It cannot be specified if these ASR cover one or more than one CT or /and one ore more IMP. With these data it is neither possible to calculate ASR numbers of IMPs (now DSUR) nor ASR number of CTs.
DE (PEI)	247(containing all CT with the IMP)	340 (containing all CT with the IMP)
DK	494	399 (Jan-Nov)
EE	N/A	N/A
EL	221	
ES	Estimated 1 440, not checked if they are or not unique	1288 ASR received in 2011, not checked if they are unique
FI	457	425

52 According to implementing guidance of the Commissoin, the ASR is based on the IMP.

53 Survey of the Commission amongst NCAs. Annual Safety Reports (ASRs): These are the number of 'unique reports'. The number of 'received reports' may be higher: In practice a sponsor may submit the identical 'unique report' to the same NCA several times.

54 AT: This is an estimation of the total number of received reports. It is not possible to extract the number of unique reports from the Austrian database.

55 This is an estimation of the total number of reports. It is not possible to extract the number of unique reports from the Belgian database.

FR	1 070	1 095
HU	N/A	1074
IE	144	158
IT[56]	1202	1111
LT[57]	200	200
LU		
LV	80	114
MT	N/A	8
NL	441	432
PL	477	527
PT	160	179
RO	426 'received reports'	567 'received reports'
SE	721	699
SI	72	76
SK		
UK	1 568	1 756
IS	7	12

(b) Moreover, the figure of total ASR actually drafted as contained in table 12 has to be reduced further because ASRs submitted to different Member States may be identical.[58]

Therefore, to establish the number of ASRs drafted one has to refer to the number of IMPs involved in clinical trials per sponsor.

There is no reliable hard data available on the number of IMPs involved in clinical trials performed at a given point in time in the EU per sponsor. However, it can be assumed from what is mentioned above that the 11 000 ASR versions received by Member States involve approx. 70% of IMPs per sponsor (a sponsor may conduct several clinical trials with the same IMP). This means that there are at a given moment approximately 7 700 IMPs on a per-sponsor basis. This means that each year approximately 7 700 ASRs are drafted by sponsors conducting clinical trials in the EU.

9. Costs of clinical trials

The costs of clinical trials performed in Europe are as follows:

As regards industry-driven research, in 2008 the pharmaceutical industry invested about 26 000 m EUR in research and development,[59] of which 68 % were allocated to clinical trials, i.e. 15 600 m EUR (a).

No figures are available for trials other than industry-driven clinical trials. On the basis of industry driven research investment allocated to clinical trials and taking into account that forty per cent (see Table 1) of all clinical trials are performed by 'non-commercial sponsors' it could be argued that the investment by 'non-commercial sponsors' is:

$$4/6*a = 10.4\,\text{m EUR} = b.$$

56 This is an estimation of the total number of reports.

57 This is an estimation of the total number of reports.

58 Practically all Member State authorities accept the ASR submitted in the English language.

59 'The pharmaceutical industry in figures' (2010), European Federation of Pharmaceutical Industries and Associations.

It has to be borne in mind, though, that clinical trials performed by 'non-commercial sponsors' tend to be less costly. For example, the IMPs used are often authorised and thus do not have specific distribution channels and profit from simplified labelling. Therefore, it is appropriate to deduct 30 % (c) of the costs compared with industry-driven research.

The total costs for clinical trials in Europe per year are therefore:

$$a+b*0.7 = 22\,880 \text{ m EUR.}$$

These costs are mainly generated by the activities listed below. While the costs depend very much on a case-by-case basis[60], an attempt has been made, in meeting with stakeholders,[61] to rank them in importance in terms of costs:

- Quality assurance during conduct of trial: Communicating with clinical trial centres, including monitoring and surveillance (staff costs and support services, such as translation, travel, accommodation, couriers, etc.);
- Remunerating sites and investigators (incl. possible trainings);
- Designing and drawing up the protocol;
- Preparing (including manufacturing and blinding) or purchasing the IMPs[62];
- Distributing the IMPs to the clinical trial centres;
- Analysing data (incl. Data Safety Monitoring Board);
- Administrative costs;
- Insurance;
- Fees.

10. Share of SMEs, including micro-enterprises

Costs for the conduct of clinical trials are ultimately born by the sponsor. Where costs created by regulation (administrative costs or other compliance costs) fall on the investigator (or the respective clinical trial site), they are usually passed on to the sponsor by way of contractual arrangements (see above, 'remuneration of sites and investigators').

In 2010, the share of clinical trials was as follows:

- 1 620 clinical trials were sponsored by 'academic sponsors' (a);
- 2 543 clinical trials were sponsored by 'commercial sponsors', i.e. pharmaceutical companies (b).

60 For example, the purchase of the comparator can be a very important cost factor depending on the purchased medicinal product.

61 See point **Error! Reference source not found.** of the impact assessment report.

62 Costs are very valuable, from low to very high, and depend *inter alia* on therapeutic area.

Amongst academic sponsors, it can be assumed that practically none falls within the definition of a SME: According to the EU definition in Commission Recommendation 2003/361/EC[63] an enterprise is considered to be any entity engaged in an economic activity. Moreover, Article 4(3) of the Annex to that Recommendation provides that an enterprise cannot be considered an SME if 25% or more of the capital or voting rights are directly or indirectly controlled, jointly or individually, by one or more public bodies.

Amongst pharmaceutical companies, it is assumed that approximately 40% fall within the SME definition of the EU.[64] However, a large part of these pharmaceutical companies are active in the area of generic and/or over-the-counter medicines. In these sectors clinical trials activity is rather limited. In particular, pharmaceutical companies for generic medicines limit their activity largely to bioequivalence studies and pharmacokinetic studies. Therefore, it can be assumed that the by far larger part (approximately 85%) of the 2 543 clinical trials of 'commercial studies' are conducted by the 60% of pharmaceutical companies not falling within the EU-definition of an SME. The share of pharmaceutical SMEs sponsoring clinical trials is thus approximately 15%.

The share of SMEs who have to bear the costs for clinical trials is thus as follows:

$$(b*0.15)/(a+b) = 0.09 = 9\%$$

Micro-enterprises are the smallest category of SME, with less than ten employees and a turnover or balance sheet total equal to or less than 2m EUR.[65]

In view of the complexities of the regulatory and business environment in the pharmaceutical sector, in particular in the area of clinical research, it can be assumed that practically no micro-enterprise is active as sponsor in the area of clinical trials.

63 OJ L 124, 20.5.2003, p. 36.

64 See Commission impact assessment report for the proposal of Directive 2011/62/EU (SEC(2008)2674, 10 December 2008), p. 74.

65 Article 2(3) of the Annex to Commissoin Recommendation 2003/361/EC.

11. Staff figures in national competent authorities

Table 13: Number of staff in NCAs[66]

	Clinical trial assessment						Assessing of safety reports		
MS	**Quality assessors**	**Non clinical assessors**	**Clinical assessors**	**External experts**	**Validation assessors**	**Other assessors (details + number)**	**Number of SUSARs assessors**	**Number of ASR assessors**	**Other (detailed + number)**
AT	1.5	1	2	none	1.75		0.25	0.5	
BE	1.5	1.5	0.5	When appropriate in light of expertise	3		0	0	0
BG				2 part time clinical assessors	1		0*	0*	
CY									
CZ	2 full time; 3x0.75 part time; 2x0.2	3x0.2	3x0.75; 2 full time	Flexible; according to our demand	1	Medical device according to state, other assessors are independent of SUKL(Ministry of Envir.- GMO, SÚJB-state office for nuclear safety –radiopharma.IMP)	0 Assessment by clinical assessors according to their indication	0	
DE (BfArM)									
DE (PEI)	Figures of the past were an estimation that is not considered reliable enough to be used or published. In order to provide reliable figures an in depth analysis of each Clinical Trial Application and Approval would be required.								
DK	Not in clinical trial department, but borrows from licensing department (risk based)	1	See external experts	5 part time clinical assessors (10-15 h/week) – 1,5 FTE	1	2,5 pharmacists 1,5 administrative assistants	Part-time allocation so SUSARs app. 10 h/week (incl. EVCTM) ~ 0.25	Part time allocation of clinical assessors ~ 0.5	0.5 for administrative handling
EE	Assessor from licensing department	0	1	As occasion requires.	Responsibility of clinical assessor and partly job of secretary		0 (clinical assessor's responsibility)	0 (clinical assessor's responsibility)	
EL	0	0	0	As occasion requires	2		0	0	0
ES Data expressed in FET	1.25 for Chemical IMP 3 for biological and advanced therapy IMP	1	4	1	3.5 (3 administrative supported by 1 pharmacist)	2.5 pharmacist and 2 administrative in charge of database quality control and administrative procedures of the applications	1* *Dedicated to safety issues of CT	1* *Dedicated to safety issues of CT	
FI	From other departments, when needed.	From other departments, when needed.	From other departments, when needed.	On demand.	0	FIMEA clinical trials department: 1.5 permanent assessors for all clinical trial related tasks.	See column 'other assessors'	See column 'other assessors'	
FR (2011)	From other departments, when needed.	2,3	6.8	Yes on demand	4,7	0.8 reg. affairs	1.6	1	0
HU	5	1	4	7 clinical assessors are available per demand	0.5		0.5	0	0
IE	0.9 FTE for biological products and	0.5	1 FTE = (7 assessors are available per demand from the authorization	on demand- External Experts participate in a monthly Clinical Trials	0	1 scientific officer (part-time) responsible for EudraCT.	0.5	Variable – Done by CTA assessors	

66 Survey of the Commission amongst NCAs. If assessors are used which are actually attributed to other departments (for example, marketing authorization department), the 'share' of resources used for the purpose of assessing clinical trials should be indicated. Management staff (Head of unit etc.) should not be included.

	1FTE for chemical products		and registration department)	Subcommittee where the trials are reviewed and are available on demand					
IT	0.5	0.5	0.5	Yes, on demand	2		0.33	0.33	0.33
LT	0,125	0,25	1,25	On demand	1	-	0	0	
LU									
LV	0,25	0,25	1,25	Flexible;-quality and clinical experts are available on necessity	0,25		0 (done by CTA assessor)	0 (done by CTA assessor)	
MT	6 QAs shared with other procedures such as DCPs/MRPs	1 shared with other procedures such as DCPs/MRPs	3 shared with other procedures such as DCPs/MRPs	On demand	6 pharmacists shared with other procedures		1 pharmacist shared with for all ICSR revievwed	1 pharmacist shared with for all ICSR revievwed	
NL							0	0	/
PL	2	0	0	Yes: 2 non clinical and 20 clinical	8		0*	0*	
PT	0,5 (5 assessors shared with authoriz./ reg. department)	0,5 (2 assessors shared with authoriz./ reg. department)	See external experts	1 (6 clinical + 4 quality assessors available on demand)	2,5		0,1 (done by CTA assessor)	0,1 (done by CTA assessor)	0,5 data entry, administrative handling and scientific review
RO	-2 part time for Chemical IMP -for biological IMP from other department when needed	0	1 clinical assessor full time, 3 part time	0	0 dedicated staff, job done by clinical assesorrs	0	0 (only administrative handling)	0 dedicated staff, job done by clinical assesorrs	0
SE	2	2	4	0.7	0.5	-	0.20	1.0	Total number of SUSAR reports per year increased 2011 (prel number as of mid-Dec = 281)
SI	0	0	0.5	4	1		0	0.1	
SK									
UK	4	2.5	6	Expert Advisory panel when required.	0	2 scientific assessors (safety); 1 scientific assessor (amendments)	1.25	1.25	2 Scientific assessors (safety)
IS	Assessors from licencing department as needed	Access to 5 assessors as needed	Access to 5 clinical assessors as needed	Access to statistician and toxicologist as needed	3 administrators as needed	N/A	Done by clinical assessors	Done by clinical assessors	Quality/other assessors when necessary

12. Number of Ethics Committees

Table 14: Number of Ethics Committees in EU Member States[67]

	Number of Ethics Committees	Number of Ethics Committees (including local ethics committees)
Austria	27	
Belgium	35	215
Bulgaria	103	
Czech	9	>100
Cyprus	1	
Denmark	8	
Estonia	2	
Finland	25	
France	40	
Germany	53	
Greece	1	
Hungary	1	
Ireland	13	40
Italy	264	>900
Latvia	5	
Lithuania	2	
Luxembourg	1	
Malta	1	
Netherlands	31	
Poland	55	
Portugal	1	
Romania	1	
Slovakia	9	89
Slovenia	1	
Spain	136	
Sweden	8	
UK	126	

13. Cost per man-hour

One man-hour for work on regulatory affairs relating to clinical trials costs approximately 60 EUR.[68] This number exceeds the average EU tariff used in particular for calculation of administrative costs by the Commission. This can be explained by the relatively high salaries in the sector of pharmaceutical research and regulatory affairs.

The figure has been double-checked and confirmed with stakeholders at various occasions, including in the 2011 public consultation.

14. Duration of a clinical trial

In terms of clinical trial regulation, the duration of a clinical trial starts with the first authorisation of a clinical trial in a Member State in the EU, and ends with the 'end of

67 European Forum for Good Clinical Practice Ethics Working Party (2007) Subgroup on Ethics Committees reviewing investigatoinal medicinal products with the European Union: the procedure for the ethical review of protocols for clinical research projects in the European Union (Int J Pharm Med 21:1-113 update 2008)

68 Submission by EUCROF in the 2011 public consultation.

the trial'. The end of the trial is defined by the sponsor in the protocol. Typically, it is the last visit of the last subject.

The duration of clinical trials vary greatly. They last from a few days or weeks to several years or even decades. The duration of a clinical trial depends inter alia on the type of clinical trial (phase I-IV), the subject population, and the endpoint.

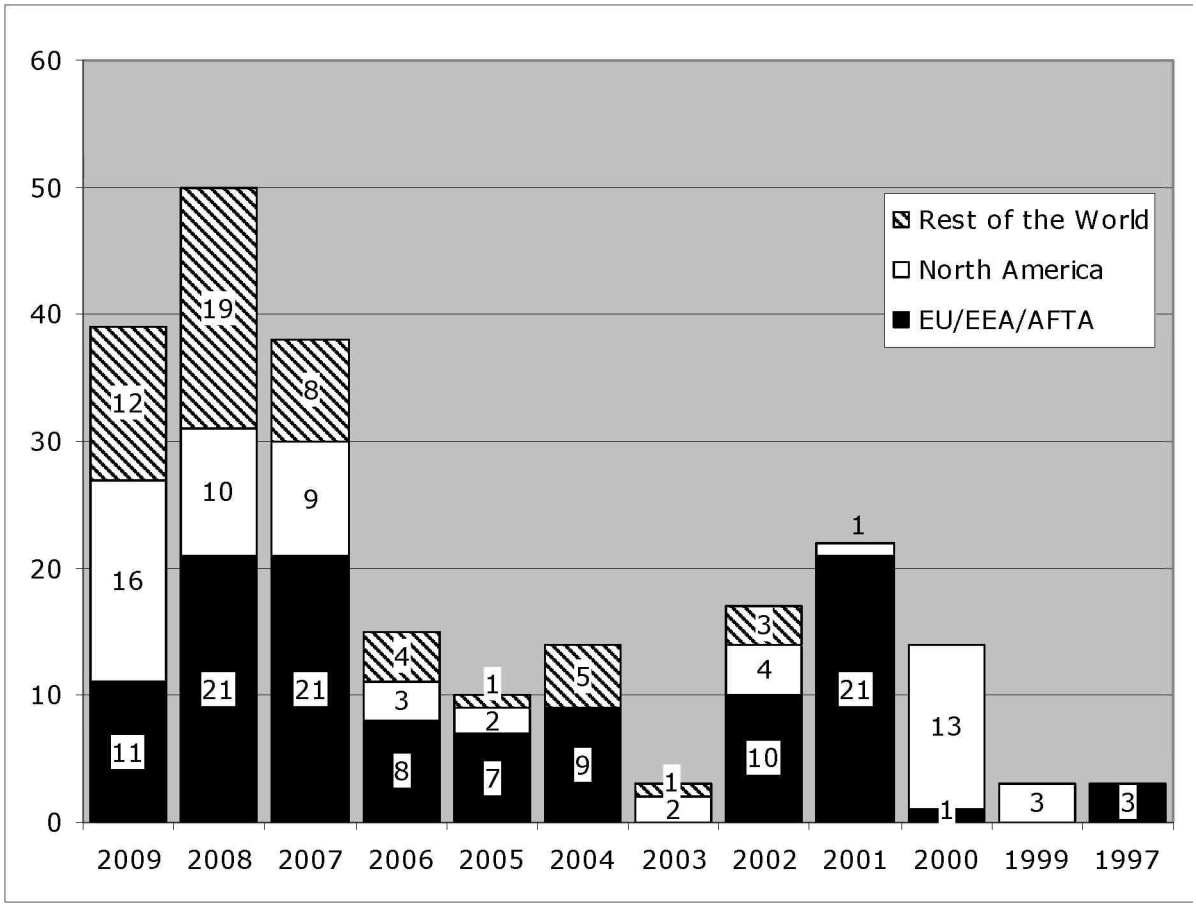
Typically, today, clinical trials tend to last longer than in the past in view of the complexity of the design, the higher recruitment targets, and the choice of the endpoints.

While there is no hard data available, in view of the above considerations, it can be assumed that the average duration of a clinical trial in the EU is 3 years.

Table 14: Number of patients in pivotal trials submitted in MAAs to the EMA per region and year

No of patients	2005		2006		2007		2008		2009		Total	
	Σ	%	Σ	%	Σ	%	Σ	%	Σ	%	Σ	%
EU/EEA/EFTA	**32 090**	**37.0**	**49 960**	**44.2**	**55 667**	**44.1**	**42 024**	**28.6**	**51 628**	**42.1**	**231 369**	**38.8**
comprising:												
EU-15/EEA	27 822	32.1	30 714	27.2	42 894	34.0	27 561	18.7	33 711	27.5	162 702	27.3
EU-10	3 412	3.9	16 601	14.7	11 016	8.7	11 706	8.0	14 768	12.0	57 503	9.7
EU-2	656	0.8	2 146	1.9	1 251	1.0	2 447	1.7	2 628	2.1	9 128	1.5
Switzerland	200	0.2	499	0.4	506	0.4	310	0.2	521	0.4	2 036	0.3
North America	**37 117**	**42.8**	**33 389**	**29.6**	**41 810**	**33.2**	**55 165**	**37.5**	**42 269**	**34.5**	**209 750**	**35.2**
comprising:												
Canada	3 477	4.0	3 919	3.5	6 231	4.9	4 454	3.0	9 581	7.8	27 662	4.6
USA	33 640	38.8	29 470	26.1	35 579	28.2	50 711	34.5	32 688	26.7	182 088	30.6
Rest of world	**17 585**	**20.3**	**29 637**	**26.2**	**28 628**	**22.7**	**49 948**	**33.9**	**28 663**	**23.4**	**154 461**	**25.9**
comprising:												
Africa	523	0.6	1 938	1.7	2 061	1.6	9 962	6.8	3 431	2.8	17 915	3.0
Middle East/ Asia/Pacific	1 694	2.0	9 925	8.8	7 801	6.2	17 458	11.9	9 627	7.9	46 505	7.8
Australia/ New Zealand	1 560	1.8	1 892	1.7	2 663	2.1	1 219	0.8	1 344	1.1	8 678	1.5
CIS	664	0.8	6 939	6.1	2 731	2.2	6 677	4.5	5 653	4.6	22 664	3.8
Eastern Europe (non-EU)	69	0.1	862	0.8	1 202	1.0	1 370	0.9	539	0.4	4 042	0.7
Central/ South America	13 075	15.1	8 081	7.2	12 170	9.7	13 262	9.0	8 069	6.6	54 657	9.2
Total	***86 792***	***100***	***112 986***	***100***	***126 105***	***100***	***147 137***	***100***	***122 560***	***100***	***595 580***	***100***

Table 15: Inspections by the EMA in the EU and in non-EU countries



ANNEX 3: OBJECTIVE NO 1 — A MODERN REGULATORY FRAMEWORK FOR SUBMISSION, ASSESSMENT AND REGULATORY FOLLOW-UP OF APPLICATIONS FOR CLINICAL TRIALS

1. Policy option No 1/1 (baseline)

1.4. Administrative costs per year

Overview

	Number of actions	Duration in man-hours	Cost per man-hour for regulatory affairs	Total (in EUR)	Comments
Initial application					
NCA	9763	40		23431200	
EC	97630	32		187449600	
Follow-up information					
NCA	7810	16		7497600	
EC	7810	16		7497600	
Substantial amendments					
NCA	27000	10		16200000	
EC	54000	10	60 EUR	32400000	
SUSAR reporting					
NCA	250000	1.5		22500000	
EC	35409	1.5		3186810	
ASR					
NCA	29289	1.5		2636010	
EC	29289	1.5		2636010	
End-of-trial reporting					
NCA	9763	0.5		292890	
EC	9763	0.5		292890	
TOTAL				**306020610**	

Explanations

- General remark: All these administrative costs are 'recurring administrative costs' in the context of conducting clinical trials in the EU.

- Initial application:

  - Number of dossiers handled (NCA): EudraCT delivers very precise figures (see Annex 2, point 2). This figure is based on 2010.

  - Number of actions (EC): In practically every Member State submission to the EC is separate from submission to the NCA. Moreover, despite the fact that a 'single opinion' is given (see Annex 1), in many Member States submissions have to be sent to a multitude of ECs (for the number of ECs, see Annex 2, point 12). This figure is based on an estimate of submission, on average, to 10 ECs (a) for each of the 9763 applications for clinical trials (b) in the Member States: a*b = 97630.

- Duration per dossier handled: 5 man-days, i.e. 40 man-hours per application, for the NCA (exclusive preparation of study documents, the protocol, IMP dossier, investigator's brochure, etc.) and 4 man-days, i.e. 32 man-hours per application, for the EC. This figure is based on data submitted in the two public consultations[69] and collated for the 'EU project on baseline and reduction of administrative costs — Measurement data and analysis for the pharmaceuticals legislation priority area'. This figure takes into account that:

  - Submission to additional Member States is less costly than the initial submission;[70]

  - Dossiers have diverging degrees of complexity, depending on the type of clinical trial; and

  - The documentation to be submitted to ECs is usually lighter than the documentation to be submitted to the NCA (less information related to the IMP).[71]

- **Follow-up information**

  - Number of actions (NCA): According to estimates by stakeholders, in approximately 80 % (a) of all applications to conduct a clinical trial an NCA requests additional information or raises grounds for non-acceptance: a*9 763 = 7 810.

  - Number of actions (EC): The same holds true for follow-up information requested by ECs, i.e. 80 % (a) of all applications. However, in most Member States such requests are channelled, as the 'single opinion', via an EC. Therefore, the number of applications equals the number of NCAs, i.e. 9 763 (b). The number of dossiers handled is therefore: a*b = 7 810.

  - Duration per action: Collecting and submitting this additional information takes, on average, approximately 2 man-days, i.e. 16 man-hours.[72]

- **Substantial amendments (SAs)**

  - Number of actions (NCA and EC): See Annex 2, point 6.

  - Duration per action: According to estimates by stakeholders, preparation and submission of an SA takes, on average, approximately 10 man-hours.[73]

---

69 According to a submission by Roche Pharmaceuticals in the 2011 public consultation, 101 hours for a clinical trial in one Member State and 159 hours for a clinical trial in three Member States.

70 Submission by the EUCROF in the 2011 public consultation.

71 Submission by EUCROF in the 2011 public consultation.

72 According to a submission by Roche Pharmaceuticals in the 2011 public consultation, 27 hours for a clinical trial in one Member State and 49 hours for a clinical trial in three Member States.

- **SUSAR reporting**

    - Number of actions (EC): Unlike NCAs (see Annex 2), the figures for SUSARs submitted to ECs are less certain. Many Member States have transposed the Clinical Trials Directive in such a way as to reduce the number of SUSARs reported to ECs. It can be assumed that an adverse reaction is, on average, reported only once to an EC, usually to the EC responsible in the Member State where the adverse reaction occurred. For this figure, see Annex 2.

    - Duration per action: The time needed to submit the information related to SUSARs is approximately 1.5 man-hours.

- **Annual safety report**

    - Number of actions (EC and NCA): The duration of a clinical trial is, on average, approximately 3 years (a). The 9 763 (b) applications mean that a*b = 29 289 ASRs have to be submitted. This holds true for NCAs and ECs. This number is independent of the fact that the number of actual ASRs is lower than the number of *submitted* ASRs (see Annex 2). As the ASR builds on the IMP, fewer ASRs are drafted than submitted (sponsors submit copies of an identical ASR).

    - Duration per action: The time needed to submit the information related to ASRs is approximately 1.5 man-hours.

- **End-of-trial declaration**

    - Number of actions (EC and NCA): The duration of a clinical trial is, on average, approximately 3 years. This means that 3 x 9 763 clinical trials ('in terms of applications) are ongoing at any given time. Of these, one third finish each year.

    - Duration per action: The time needed to submit the information related to ASRs is approximately 0.5 man-hours.

1.5. Administrative burden

These administrative costs are to large extent administrative burdens. Most of these obligations to collect, process and report would not be performed if they were not provided for in the Clinical Trials Directive:

- Initial application: While some of the information would be gathered and processed, this information would not undergo a submission procedure, and certainly not a multiple submission procedure as provided for in the Clinical Trials Directive.

---

[73] According to a submission by Roche Pharmaceuticals in the 2011 public consultation, 16 hours for a clinical trial in one Member State and 38 hours for a clinical trial in three Member States.

- Follow-up information: The administrative costs related to follow-up information would not be incurred if there was not the legal/regulatory requirement to provide such information.

- Substantial amendments: The same applies as for the initial application.

- SUSAR reporting: Sponsors would collect and process this information. However, unless this is provided in the legislation, they would not submit it to supervising authorities.

- Annual safety reporting: This information would not be collected, processed and submitted if this was not provided for by the legislation.

- End of trial reporting: This information would not be collected, processed and submitted if it was not provided for by the legislation.

In summary, and in view of the above explanations, one can conclude the following:

Overview:

Action	Administrative costs (in EUR)	Administrative burdens (as share of administrative costs)	Administrative burdens (in EUR)
Initial application	210 880 800	80%	168 704 640
Follow-up information	14 995 200	100%	14 995 200
Substantial amendments	48 600 000	80%	38 880 000
SUSAR reporting	25 686 810	80%	20 549 448
ASR	5 272 020	100%	5 272 020
End-of-trial reporting	585 780	100%	585 780
	306 020 610 = (a)		248 987 088 = (b)

It can be concluded that the share of administrative burden of all costs is as follows:

$$b/a = 0.814 = 81\%$$

1.6. Other compliance costs

Apart from administrative costs, the Clinical Trials Directive also creates other compliance costs. These include:

- Preparing (including manufacturing and blinding) or purchasing the IMPs;

- Communicating with clinical trial centres, including monitoring and surveillance;[74]

- Analysing data;

[74] To the extent that this communication is a legal obligation.

- Insurance;
- Fees.

On the basis of publicly-available information[75] the Commission has held, from 2008 until 2011, discussions on the costs of clinical trials.[76]

While it is relativey straightforward to establish the total costs of clinical trials for sponsors (see Annex 2, point 9), and to establish the administrative costs and administrative burdens (see point 1.2 of this Annex), it is a challenge for sponsors to establish precisely which non-administrative costs are the results of a regulatory obligation (i.e. fall under the definition of 'other compliance costs') and which costs incur for other reasons, such as as standard or good practices of the organisation.

Despite these difficulties, in the abovementioned discussions it became clear that only a relatively minor part of non-administrative costs is actually a result of regulation. In particular, the costs for quality assurance during the conduct of the clinical trial (see Annex 2, point 9), which create in most cases the bulk of the costs for a clinical trial, are not directly caused by regulation. Rather, these costs follow from the inherent need to produce reliable and robust results, in order for the sponsor to have reasonable certainty that the data is not rejected or put otherwise in question.

A similar reasoning applies to the costs incurred for the designing and drawing up of the protocol: While it is a regulatory requirement to have a protocol for each clinical trial, the costs for designing the trial are not a direct consequence of regulation, but rather caused by the sponsor's interest to have a sound, reliable protocol which is going to address the question addressed in the clinical trial.

On the basis of these discussions a careful estimation allows for assuming that approximately 10 % of the costs for clinical trials in the EU fall under the definition of 'other compliance costs'. These totals thus approximately 22 000 m EUR (see Annex 2). Other compliance costs are therefore 2 200 m EUR per year.

2. Policy option No 1/2 — Central submission with separate assessment

1.7. Administrative costs per year

The impact on administrative costs for initial submission would be as follows:

Overview

	Number of actions	Duration in man-hours	Cost per man-hour for regulatory affairs	Total (in EUR)	Comments
Initial application	4 400	40	60 EUR	10 560 000	
Follow-up information					
NCA	7 810	16		7 497 600	
EC	7 810	16		7 497 600	

75 Publications on the share of the costs of these specific aspects of clinical trials are limited. One public source is the report 'Clinical Trials in Poland' PriceWaterhouseCoopers, November 2010, p. 3 (http://www.pwc.com/gx/en/pharma-life-sciences/publications/clinical-trials-in-poland-2010.jhtml).

76 See Annex 2.

Substantial amendments	24 000	10		14 400 000	
SUSAR reporting	52 500	1.5		4 725 000	
ASR	7 700	1.5		693 000	
End-of-trial reporting	4 400	0.5		132 000	
TOTAL				**45 505 200**	

Explanations

- Initial application: In this policy option, there would be one application per clinical trial.

- Follow-up information: In this policy option, the follow-up information would be dealt with as in the baseline option.

- Substantial amendments: On average, a clinical trial is amended approximately twice (a) per year. This includes SAs regarding trial sites, which are typically assessed by ECs. At any given time, there are approximately 12 000 clinical trials ongoing in the EU (b). The number of SAs submitted in this policy option would therefore be: a*b = 24 000.

- SUSAR reporting: As indicated in Annex 2, approximately 35 000 SUSARs (a) occur in the EU every year. In this policy option, each SUSAR would be reported only once. However, in view of possible follow-up reports, the number should be increased by 50 % (b): a+(a*b) = 52 500.

- Annual safety reporting: The report would be submitted only once per sponsor per IMP. Approximately 7 700 ASRs are drawn up each year (see Annex 2)

- End-of-trial reporting: On average, one third of all clinical trials in progress (4 400 in 2010) finish in any given year. A clinical trial lasts, on average, 3 years.

1.8. Implementation costs

Regarding the implementation costs for the Agency/Commission, reference is made to Annex 6.

3. Policy option No 1/3 — Central submission with joint assessment

1.9. Administrative costs per year

Overview

	Number of actions	Duration in man-hours	Cost per man-hour for regulatory affairs	Total (in EUR)	Comments
Initial application	4 400	40	60 EUR	10 560 000	
Follow-up information	3 960	16		3 801 600	
Substantial amendments	24 000	10		14 400 000	
SUSAR reporting	52 500	1.5		4 725 000	
ASR	7 700	1.5		693 000	

End-of-trial reporting	4 149	0.5		132 000	
TOTAL				**34 300 600**	

Explanations

The impact on administrative costs is identical to policy option No 1/2, with the exception of the follow-up information. It is assumed that this information is requested for 90 % (a) of all 4 400 clinical trials (b). This is in line with the baseline, where it is assumed that 80 % of all *applications* are followed up with questions: a*b = 3 960.

1.10. Other compliance costs

The other compliance costs generated by the Clinical Trials Directive are mainly linked to:

- Preparing (including manufacturing and relabelling) or purchasing the IMPs;
- Communicating with clinical trial centres, including monitoring and surveillance;
- Analysing data;
- Insurance;
- Fees.

The joint assessment proposed under this policy option would allow a common approach to the issues related to the preparation (incl. blinding.) of the IMP, monitoring and surveillance.

Currently approaches diverge between Member States, which adds to the costs for compliance with the Clinical Trials Directive.

In this context, tt is not possible to assess the costs/savings with the same degree of precision as for administrative costs. However, this matter was discussed with stakeholder experts during the various meetings and workshops between 2008 and 2011 (see point **Error! Reference source not found.**). On the basis of these discussions one can reasonably expect that the savings in other compliance costs under this policy option add up to 20 % of the other compliance costs in the baseline option, i.e. 0.2*2 200 m EUR = 440 m EUR. This estimation is based on

- A single product file, thus not requiring adaptation of the product charateristics to different Member States; and
- A single set of rules for analysing data and communicating between the clinical trial centres and the sponsors, thus not requiring varying standard operating procedures, with corresponding training and staff needs.

1.11. Implementation costs

Implementation costs at EU level:

This is set out in detail in Annex 7.

Implementation costs for national administrations

Costs for national administrations would go down insofar as joint assessment/mutual recognition would not necessarily require indepth assessment of the dossier by every Member State concerned.

4. Policy option No 1/4 - Central submission with central assessment

1.12. Administrative costs per year

The savings in terms of the submission procedure and follow-up would be similar to those generated by policy option No 1/3. However, additional costs would be generated by the 'dual approval', due to national follow-up questions.

	Number of actions	Duration in man-hours	Cost per man-hour for regulatory affairs	Total (in EUR)	Comments
Initial application	4 400	40		10 560 000	
Follow-up information					
EMA level	3 960	16		3 801 600	
National level	7 810	16		7 497 600	
Substantial amendments	24 000	10	60 EUR	14 400 000	
SUSAR reporting	52 500	1.5		4 725 000	
ASR	7 700	1.5		693 000	
End-of-trial reporting	4 149	0.5		132 000	
TOTAL				**41 798 200**	

Explanations — follow-up information

At EMA level, it is assumed that this information is requested for 90 % (a) of all 4 400 clinical trials (b). This is in line with the baseline, where it is assumed that 80 % of all *applications* are followed up with questions: a*b = 3 960.

At national level, the same reasoning as for policy option No 1/1 applies:

Number of actions (EC): The same holds true for follow-up information requested by ECs, i.e. 80 % (a) of all applications. However, in most Member States such requests are channelled, as the 'single opinion', via an EC. Therefore, the number of applications equals the number of NCAs, i.e. 9 763 (b). The number of cases handled is therefore: a*b = 7 810.

1.13. Implementation costs

In terms of resources of the Agency, the impact would be as follows:

A central assessment would apply to all clinical trials planned in the EU, whether mono-national or multinational. This scope is necessary to ensure that the main benefit of this policy option materialises, i.e. easier roll-out of a clinical trial in an additional Member State.

The assessment would not be carried out by Agency staff, but by rapporteurs from Member States. However, Agency staff would coordinate this process. This compares with the centralised marketing authorisation. Every year approximately 100 applications (a) are submitted to the Agency. Every year, approx. 850 major changes (Line extension or major variation Type II) (b) to the marketing authorisation application dossier are submitted subsequently to the granting of the marketing authorisatoin of the Commission. The Agency has approx. 50 FTEs (c) to coordinate the initial authorisation process, and 65 FTEs (d) for subsequent changes to the variations.

On the basis of these figures, and considering the number of initial applications (approx. 4 400) (e) and follow-up changes (SAs, approx. 24 000) (f) to clinical trials, the staff need wold be as follows:

Initial application: c*e/a = 2 200 FTEs (g)

Subsequent changes: f*d/b = 1 835 FTEs (h)

Total: g + h = 4 035 FTEs

ANNEX 4: OBJECTIVE NO 2 — REGULATORY REQUIREMENTS ADAPTED TO PRACTICAL CONSIDERATIONS AND NEEDS

1. Policy option No 2/1 — calculation of baseline

Obligatory insurance

Administrative costs

Collecting information regarding the current rules, putting papers and documents together, filling in forms, sending them, etc. in order to comply with national insurance/indemnity requirements takes, on average, approximately 4 man-hours per application to conduct a clinical trial (a).[77] One man-hour costs 60 EUR (b).

In view of the 7963 applications per year (2010) (c), the administrative costs for insurance/indemnity requirements are:

a*b*c = 1 911 120 EUR.

Other compliance costs

Example: Costs per patient per year for insurance in different Member States (in EUR):[78]

Belgium	14.50
France	75.00
Germany	75.00
Italy	50.00
The Netherlands	23.00

On the basis of these figures, along with other figures submitted in the 2011 public consultation,[79] it can be assumed that the average costs of insurance per participant in a clinical trial are 50 EUR per year (a).

As a clinical trial lasts, on average, approximately 3 years, in view of the number of subjects planned for recruitment (see Annex 2), it can be deduced that at any given time approximately 1 500 000 patients are enrolled in clinical trials (b).

Consequently, the other compliance costs per year are:

a*b = 75 m EUR.

77 Submission by EUCROF in the 2011 public consultation.

78 Source: Submission by stakeholder.

79 See submission by the EORTC in the 2011 public consultation: depending on the Member State, costs range from 32 EUR to 250 EUR per person per year.

Number of claims/level of damages

There are very limited figures on the number of damages claims. In any case, damages claims are extremely rare.

– Data from one insurance company in the Netherlands show that over a period of nine years 14 claims were granted. The total amount of compensation for these cases was 43 000 EUR. The administrative costs for the insurance company totalled approximately 38 000 EUR. The total costs for the policy are approximately 235 000 EUR.[80]

  In the Netherlands, every year between 350 and 650 clinical trials are applied for (2006: 445; 2007: 638; 2008: 642; 2009: 358). According to EudraCT, since the Clinical Trials Directive came into force, enrolment of 232 661 participants in clinical trials has been planned.

– The German 'KKS Netzwerk — Koordinierungszentren für klinische Studien' reported, over a period of 10 years (1997-2007) involving more than 20 000 trial subjects, three liability cases with minor damages.[81]

– The 'Insurance Working Group' of the Permanent Working Party of Research Ethics Committees in Germany reported that every year about 80 to 100 new liability claims are investigated. Between 2005 and 2010, recruitment of 700 000 subjects was planned, i.e. approximately 117 000 per year. In most of the cases where liability was accepted the sum was low, but in a very few an amount of more than 100 000 EUR has been paid in compensation in recent years.[82]

– Between 2005 and 2010, the Finnish Patient Insurance Centre and the Finnish Pharmaceutical Insurance Pool handled 19 claims for compensation, of which four led to compensation payments.[83] According to EudraCT, between 2005 and 2010 enrolment of 299 059 participants in clinical trials was planned in Finland, i.e. 50 000 per year.

– According to the Danish Patient Insurance System (DPIS), over a period of 10 years out of 49 claims for compensation by patients participating in clinical research projects 27 were accepted. This added up to a total of approximately 550 000 EUR.[84] According to EudraCT, from the entry into force of the Clinical Trials Directive until 2010 enrolment of approximately 120 000 participants in clinical trials was planned in Denmark, i.e. approximately 20 000 per year.

– The European Organisation for Research and Treatment of Cancer (EORTC) reported that, in the five years up to 2011, ten damages claims from two countries (only one of which was a Member State) led to indemnity of 60 000 EUR. This

80 Source: Submission following workshop on clinical trials with the European Science Foundation.

81 Source: Submission following workshop on clinical trials with the European Science Foundation.

82 Submission by the Permanent Working Party of Research Ethics Committees in Germany in the 2011 public consultation.

83 Source: *Ad hoc* group on clinical trials.

84 Source: Submission following workshop on clinical trials with the European Science Foundation.

was for a population of approximately 30 000 subjects recruited in 43 clinical trials.[85]

In view of the foregoing, the following assumptions can be made:

Damages claims

The figures from Denmark, Germany and Finland show that between 0.006 % and 0.08 % of subjects (DK: 0.0245 %, DE: 0.08 %, FI: 0.00635 %) claim damages.

For the purposes of this impact assessment, it will be estimated that, as an EU average, 0.05 % of recruited subjects claim damages — be it successfully or not.

Compensation granted

The question of whether, following a claim, compensation is actually paid depends strongly on the civil law systems in the Member States. On the basis of the figures set out above, it can be assumed that approximately 50 % of the claims lead to compensation being granted, i.e. to 0.025 % of all subjects enrolled.

Level of compensation

The figures set out above show that, on average, damages claims range from 3 000 to 6 000 EUR. This assumption is in line with various estimates made in publications[86] and discussions in conferences.[87]

Annual safety report

Administrative costs

The administrative costs for the annual safety report are indicated in Annex 3 (2 x 2 636 010 EUR = 5 272 020 EUR).

Other compliance costs

Apart from the administrative costs, there are the costs of the actual drafting and setting-up of the report. The ASR requires approximately 40 man-days, i.e. 320 man-hours (a). This already factors in the fact that, over the years, the efforts for drafting decrease: in subsequent years, only an update of the report for the previous year is required. One man-hour costs 60 EUR (b).

The report to be submitted is largely identical in format and content. Moreover, practically all Member States accept the report in English, i.e. without any need for a translation.

The report addresses subject safety in the light of the investigational medicinal product. It can be assumed that each year approximately 7 700 ASRs are drafted (see Annex 2, point 8) (c).

---

85 Submission by the EORTC in the 2011 public consultation.

86 Jungk, 'Schadenersatzansprüche von Patienten in klinischen Prüfungen — ein Überblick', DZKF, 7/8-2007, p. 49.

87 See point **Error! Reference source not found.**.

The other compliance costs per year for the annual safety report are therefore:

$$a*b*c = 147.8\,\text{m EUR}.$$

2. Policy option No 2/2 — Enlarging the scope of non-interventional studies

In 2010, a total of 707 Phase IV clinical trials were authorised (a). These involved 1 029 applications (b) and 52 230 patients (c).[88]

If the definition of 'non-interventional study' were enlarged, it can reasonably be assumed that approximately 50 % of these phase IV trials, the associated applications and the patients participating would be freed of the obligations imposed by the Clinical Trials Directive.

Obligatory insurance

Administrative costs

Collecting information regarding the current rules, putting papers and documents together, filling in forms, sending them, etc. in order to comply with the submission requirements for national insurance and indemnity takes approximately 4 man-hours (d). One man-hour costs 60 EUR (e).

On this basis, this means the following savings in administrative costs:

$$b/2*d*e = 123\,480\ \text{EUR}.$$

Other compliance costs

As indicated above, the average cost of insurance per participant is 50 EUR per year (g).

The 707 phase IV trials approved in 2010 involved 52 230 patients (c). As indicated above, participation in a clinical trial lasts, on average, approximately 3 years (i).

The yearly savings in other compliance costs are therefore:

$$c/2*i*g = 3.92\,\text{m EUR}.$$

Annual safety report

Administrative costs

Collecting information regarding the current rules, putting papers and documents together, filling in forms, sending them, etc. in order to comply with the requirements for the annual safety report takes approximately 1.5 man-hours (k). One man-hour costs 60 EUR (l).[89]

On average, each clinical trial is conducted over a period of approximately 3 years (m).

---

88 EudraCT.

89 This is calculated on the basis of a single submission point (cf. policy options No 1/2 to No 1/4).

This means that this policy option would bring about the following savings in administrative costs:

a/2*m*k*l = 95 445 EUR.

Other compliance costs

As shown in Annex 2 (point 8), the approximately 12 000 ongoing clinical trials lead to the drafting of approximately 7 700 ASRs per year.

Of these ongoing clinical trials 3*707 (3 years is the average duration of a clinical trial) are assumed to be phase IV trials, i.e. 2 121 clinical trials. 50% of these phase IV trials are of interest here, i.e. 1 060 clinical trials.

It follows that the amount of ASR which would not have to be drafted is

7 700*1 060/12 000 = 680 = (o)

As indicated above, drafting the report takes approximately 40 man-days, i.e. 320 man-hours (p). This already factors in the fact that, over the years, the efforts for drafting decrease: in subsequent years, only an update of the report for the previous year is required. One man-hour costs 60 EUR (q).

This means that this policy option would yield the following savings:

o*p*q = 13.06 m EUR.

3. Policy option No 2/3 — Excluding 'academic sponsors'

In 2010, some 1 620 clinical trials by 'academic sponsors' were authorised (a).[90] These involved 2 037 applications (b) and 93 242 patients (c).[91]

Obligatory insurance

Administrative costs

As indicated above, collecting information regarding the current rules, putting papers and documents together, filling in forms, sending them, etc. in order to comply with national insurance/indemnity requirements takes, on average, approximately 4 man-hours per application (d).[92] One man-hour costs 60 EUR (e).

In view of the 2 037 applications per year (2010) (b), the savings in administrative costs under this policy option, compared with the baseline, are:

b*d*e= 488 880 EUR.

Other compliance costs

90 EudraCT.

91 EudraCT.

92 Submission by EUCROF in the 2011 public consultation.

As indicated above, the average cost of insurance per participant in a clinical trial is 50 EUR per year (g).

The 1 620 trials approved in 2010 involved 93 242 patients (c). As indicated above, participation in a clinical trial lasts, on average, approximately 3 years (i).

The yearly savings in other compliance costs are therefore:

c*i*g = 13.99 m EUR.

Annual safety report

Administrative costs

Collecting information regarding the current rules, putting papers and documents together, filling in forms, sending them, etc. in order to comply with the requirements for the annual safety report takes approximately 1.5 man-hours (k). One man-hour costs 60 EUR (l).[93]

On average, each clinical trial is conducted over a period of approximately 3 years (m).

This means that this policy option would yield the following savings in administrative costs:

a*k*l*m = 437 400 EUR.

Other compliance costs

As shown in Annex 2, the approximately 12 000 ongoing clinical trials lead to the drafting of approximately 7 700 ASRs per year.

Of these ongoing clinical trials 3*1620 are assumed to be sponsored by 'academic sponsors', i.e. 4 860 clinical trials.

It follows that the amount of ASR which would not have to be drafted is

7 700*4 860/12 000 = 3118 = (o)

As indicated above, drafting the report takes approximately 40 man-days, i.e. 320 man-hours (p). This already factors in the fact that, over the years, the efforts for drafting decrease: in subsequent years, only an update of the report for the previous year is required. One man-hour costs 60 EUR (q).

This means that this policy option would yield the following savings:

o*p*q = 59.9 m EUR.

4. Policy option No 2/4 — Removing regulatory requirements on the basis of the knowledge of the IMP

[93] This is calculated on the basis of a single submission point (cf. policy options No 1/2 to No 1/4).

Phase IV clinical trials are, by definition, clinical trials with authorised medicines. However, not each and every phase IV clinical trial is limited to the authorised indication. Moreover, certain phase I to III clinical trials may be performed with medicines whose active ingredient is already contained in authorised medicines.[94]

For the purposes of this assessment, it is therefore assumed that all Phase IV clinical trials, and only Phase IV clinical trials, involve authorised IMPs in the authorised indication.

In 2010, a total of 707 Phase IV clinical trials were authorised (a). These involved 1 029 applications (b) and 52 230 patients (c).[95]

Obligatory insurance

If the obligatory insurance were waived for clinical trials with authorised IMPs, the following would apply:

Administrative costs

Collecting information regarding the current rules, putting papers and documents together, filling in forms, sending them, etc. in order to comply with the national insurance/indemnity requirements takes approximately 4 man-hours (d). One man-hour costs 60 EUR (e).

On the basis of the foregoing, this means the following annual savings in administrative costs:

b*d*e = 246 960 EUR.

Other compliance costs

As indicated above, the average cost of insurance per participant in a clinical trial is 50 EUR per year (g).

The 707 phase IV trials approved in 2010 involved 52 230 patients (c). As indicated above, participation in a clinical trial lasts, on average, approximately 3 years (i).

The yearly savings in other compliance costs are therefore:

c*i*g = 7.84 m EUR.

Annual safety report

Administrative costs

Collecting information regarding the current rules, putting papers and documents together, filling in forms, sending them, etc. in order to comply with the requirements

[94] For example, bioequivalence studies.

[95] EudraCT.

for the annual safety report takes approximately 1.5 man-hours (k). One man-hour costs 60 EUR (l).[96]

On average, each clinical trial is conducted over a period of approximately 3 years (m).

This means that this policy option would yield the following savings in administrative costs:

a*l*b*k = 190 890 EUR.

Other compliance costs

As shown in Annex 2, the approximately 12 000 ongoing clinical trials lead to the drafting of approximately 7 700 ASRs per year.

Of these ongoing clinical trials 3*707 are assumed to be sponsored by 'academic sponsors', i.e. 2 121 clinical trials.

It follows that the amount of ASR which would not have to be drafted is

7 700*2 121/12 000 = 1360 = (n)

As indicated above, drafting the report takes approximately 40 man-days, i.e. 320 man-hours (o). This already factors in the fact that, over the years, the efforts for drafting decrease: in subsequent years, only an update of the report for the previous year is required. One man-hour costs 60 EUR (p).

This means that this policy option would yield the following savings:

n*o*p = 26.1 m EUR.

5. Policy option No 2/5 —Insurance/Optional 'national indemnification mechanism'

This policy option provides for an optional national indemnification mechanism. The calculation of the costs and risks related to this mechanism is based on the assumption that all sponsors make use of this mechanism: indeed, in view of how difficult it is for sponsors to obtain insurance cover, it is very likely that they will practically all opt in to this mechanism.

Administrative costs

The national indemnification mechanism would make the difficult researching for the national requirement superfluous. Instead, opting in to the mechanism would suffice to prove that the patient is covered for damages. A simple document could prove this. Obtaining and submitting this document would generate administrative costs of 0.5 man-hours (a) per application. One man-hour costs 60 EUR (b).

In view of the 7 924 applications per year (2010) (c), the administrative costs for insurance/indemnity requirements are:

[96] This is calculated on the basis of a single submission point (cf. policy options No 1/2 to No 1/4).

a*b*c = 237 720 EUR.

Implementation costs for the national indemnification mechanism

Running costs to maintain the national indemnification mechanism

Some Nordic Member States have set up a compensation scheme like that proposed in this policy option. Their experience teaches lessons about the costs for running such a scheme — apart from the actual costs to cover damages.

These costs must be assessed on the basis of the *claims*, not of the cases where damages were granted. For example, in Denmark, the Patient's Insurance Association deals with approximately 8 000 claims (d) for damages per year (clinical-trial-related and other). To deal with all incoming claims, the Association has approximately 130 staff (e).

As shown above, approximately 0.05 % of all enrolled subjects claim damages in a given year (f). Each year, 400 000 subjects (g) are enrolled in clinical trials in the EU. A clinical trial is assumed to last, on average, 3 years (h).

The total claims per year in the EU are therefore:

f*g*h = 600 = i.

These figures allow some extrapolation and show that the running costs, in terms of staff, of a national indemnification mechanism in the EU per year are:

e*i/d= 9.75 FTEs.

This means costs of approximately 9.75*70 000 EUR per year, i.e. 682 500 EUR (o).

It is assumed that the costs for this personnel are recouped by Member States via fees.

Costs for covering damages

The national indemnification mechanism, i.e. Member States, would have to bear the costs for damages occurring in clinical trials in the Union.

Every year 400 000 clinical trial subjects can be expected to participate in a trial (2010) (k). Each clinical trial lasts approximately 3 years (l).

As shown above, it can be assumed that 0.025 % of participants justifiably claim damages linked to a clinical trial (f).

On average, damages claims range from 3 000 to 6 000 EUR. For the purposes of this calculation, a value of 4 500 EUR will be assumed (n).

This means that the costs of damages per year are:

k*l*f*n = 135 000 EUR = (p).

It would be left to each Member State to decide whether and how it intends to cover these costs.

Other compliance costs

It is assumed here that implementation costs are borne, by way of fees, by the sponsors. These costs would be, per year:

o+p = 817 500 EUR.

6. Policy option No 2/6 —Combination of policy option No 2/4 and No 2/5

Regarding annual safety report:

As policy option No 2/5 does not have an impact on the obligation to draft and submit an annual safety report, the economic impact in comparison to the baseline is identical as under policy option No 2/4.

Regarding obligatory insurance/indemnification:

Regarding administrative costs, according to policy option No 2/4, 1029 clinical trials applications (a) would not be covered by the obligatory insurance/indemnification: As set out under policy option No 2/5, the administrative costs in a national indemnification mechanism would be 0.5 man-hour (b) per application with a value of 60 EUR per hour (c).

This means that, in terms of administrative costs the additional savings compared to policy option No 2/5 are

a*b*c = 30 870 EUR

The impact of this policy option on other compliance costs compared to the baseline is identical to policy option No 2/5. Wee the impact assessment report for more explanation.

ANNEX 5: OBJECTIVE NO 3 — ADDRESSING THE GLOBAL DIMENSION OF CLINICAL TRIALS WHEN ENSURING COMPLIANCE WITH GCP

1. Policy option No 3/2: Facilitating GCP inspections by increasing transparency (database of all clinical trials)

The costs of this policy option are limited to administrative costs.

It is estimated that approximately 30% (a) of all clinical trials requested in an application for an EU marketing authorisation are conducted exclusively in non-EU countries. Each year, about 100 applications (b) are submitted to the Agency,[97] each of which refers, on average, to approximately 100 clinical trials (c).

In addition, every year approximately 2000 (d) applications for national marketing authorisation are submitted.[98] Each involve, on average, 10 clinical trials (e). Of these, it can be estimated that 20% are performed exclusively in non-EU countries (h).

Publication of this information in an official public register takes approximately 2 man-days, i.e. 16 man-hours (f). One man-hour costs approximately 60 EUR (g).

Consequently, the administrative costs for this policy option are:

$$a*b*c*f*g + d*e*h*g*f = 2.88\,\text{m EUR} + 3.84\,\text{m EUR} = 6.72\,\text{m EUR}.$$

2. Policy option No 3/3: Inspections of the third countries' regulatory systems for clinical trials

Currently there are no inspection capacities at EU level foreseen. However, a somewhat comparable capacity exists at EU level for system inspections (audits) in the food and veterinary sector: the Food and Veterinary Office of the European Commission ('FVO'). In 2010 the FVO performed 248 audits, of which 105 were in non-EU countries. The inspections in non-EU countries cost approximately 800 000 EUR. The other compliance costs, including costs for staff, must be added to this: In terms of staff, the 248 FVO audits in 2010 were performed by 85 auditors, backed up by an additional 52 support staff.

On the basis of these figures one can extrapolate that, for approximately 8 system inspections per year, the following resources would be required:

- Staff: 3 FTE (inspectors), plus 2 FTE (support staff);
- Costs for conducting inspections: approximately 76 000 EUR.

[97] See also the Final Report of the European Medicines Agency (2010), p. 174 (http://ec.europa.eu/health/files/pharmacos/news/emea_final_report_vfrev2.pdf).

[98] Idem, p. 53.

To finance this policy option, the following approaches shall be discussed here:

- Financing through fees is not conceivable, as system inspections would require fees to be paid by the government of a third country.

- Subsidies through the EU budget (structural) is difficult to envisage in view of the political commitment of the Commission to reduce staffing level at EU institutions.

- Cross-subsidies from fees for assessment of the marketing authorisation application. This financing strategy would only be possible if the system inspection was located with the Agency. In technical terms, the legislative framework for fees would have to be amended. In political terms, this approach would lead to an unfair distribution of burden for those actors who pursue (obligatorily or voluntarily) the centralised marketing authorisatoin procedure. Moreover, it would not correspond to the principle of "fee for service".

- Re-allocation of existing resources within the Commission or the Agency: Within the Commission, a re-allocation of resources on the scale set out here is enviseagable.

3. Policy option No 3/4: GCP inspections of non-EU countries' clinical trial sites by the Agency

As for policy option No 3/3, currently there are no inspection capacities dedicated to GCP inspections by the Agency or the Commission.

Data from Member States show that a team of 6 GCP-inspectors (plus support staff) can perform approximately 55 inspections per year, including 12 inspections in third countries.[99] GCP inspections in non-EU countries require typically more preparatory time, as well as more travel time, than domestic inspections. Therefore, it is assumed that one inspector-FTE can conduct 6 GCP inspections in non-EU countries per year.[100]

The number of sites included in pivotal clinical trials submitted to the Agency in the context of marketing authorisations is approximately 8 000 per year.

As set out in the impact assessment report, it is assumed, that only 10% of these sites are inspected. An extrapolation of the figures above shows that this approach would require approx. 1 300 FTE in inspectors, plus support staff.

In view of the present difficulties to obtain additional resources at EU level, it is difficult to conceive an increase in the range set out in this policy option.

---

99 The efficiency of inspections of national clinical trial sites is higher than system-inspections in third countries.

100 This figure takes account of the fact that GCP inspections are usually conducted in a team.

ANNEX 6: COSTS AND FINANCING STRATEGIES FOR THE SINGLE SUBMISSION POINT

This annex presents the details of the costs for the single submission point (1) and possible ways to finance it (2).

1. Costs for a single submission point

   During the impact assessment process, the Agency has been consulted on the costs of a single submission point. Equally, Commission inhouse expertise has been sought.

   As a result two different approaches could be pursued:

- 'Extensive IT solution':

  The Agency would pursue an 'extensive IT solution' including user validation functionalities, an IT helpdesk, a business support helpdesk, and operational support.

  The one-off costs for an 'extensive IT solution' would be 6.3m EUR (a) (including 0.6m EUR (b) for updating the pharmacovigilance system for SUSAR reporting).

  Running costs would be 20% (c) of the one-off costs per year. Thus running costs (excl. staff) would thus be

  $$a*c = 1.26\text{m EUR}$$

  To this adds, in terms of human resources, 11 Administrator posts (g) and 8 Assistant posts (d). These FTEs do not include the FTEs referred to in policy option No 1/3. According to previous calculations of the Agency, costs per FTE are 153 226 EUR (AD, e) and 81 617 EUR (AST, f). To this adds an overhead of 48.5%.

  The running annual costs (incl. staff) of the 'extensive IT solution' would be thus

  $$a*c + g*e*1.485 + d*f*1.485 = 4.73\text{m EUR}$$

- 'Limited IT solution':

  The Commission would pursue a 'limited IT solution' which would include less support activities, such as Helpdesks for IT. Moreover, it would build on existing IT functionalities within the Commission.

  Only the update of the pharmacovigilance system would remain with the Agency, as the Agency has already a pharmacovigilance IT system in place.[101]

  In this case, one-off costs would be 1.02m EUR, plus 0.6m EUR for pharmacovigilance, i.e. 1.62m EUR.

[101] Transferring this system to the Commission, as regards clinical trials, would create considerable inefficiencies.

Running costs would be 0.22m EUR per year, plus 20% of 0.6m EUR for pharmacovigilance, i.e. 0.34m EUR per year. These costs include staff requirements for the programming.

In this 'limited IT solution', an additional 0.25 FTEs would be required to support the programming activity in terms of regulatory expertise.

2. Financing strategies

When looking at strategies as to financing these costs, there are three viable possibilites which shall be presented below. Of these three possibilities, two are only workable if the political decision was taken to allocate the single submission point within the Agency.

a. Cross-subsidy from fees for marketing authorisation activities of the Agency (only possible if single submission point is allocated with the Agency)

This approach would impose the costs for the single submission point on the pharmaceutical companies whose products have to be assessed by the EMA (rather than national agencies) prior to marketing authorisation by the Commission.

The EMA conducts approximately 100 assessments in connection with marketing authorisations per year. The fee for such assessments is currently approximately 260 000 EUR.

In view of the costs (see point 1; it is assumed that the one-off costs occur in the first three years), the authorisation fee would have to increase by 79 000 EUR, i.e. by approximately 30%. After the first three years, the fee would rise by 58 600 EUR per marketing authorisation application, i.e. by approximately 25%.

This approach would mean that a relatively small number of companies would bear the burden for a tool which is of benefit not only to them, but also to their competitors and academic researchers. Moreover, it would not correspond to the principle of "fee for service".

In technical terms, amendment of the ‘Fees Regulation’ (Regulation (EC) No 297/95) would be required.

b. Separate fee for all applicants for approval of a clinical trial (‘28th fee’ - only possible if single submission point is allocated with the Agency)

This approach would entail a separate fee in addition to the national fees (potentially 27 national fees, plus the EU fee).

In view of the 4 400 clinical trials per year, if the fee was only imposed at the moment of the application for authorisation of a clinical trial that fee would have to be, in the first three years, 1 800 EUR. After the first three years, the fee would have to be 1 330 EUR.

The critical point would be the collection of fees which, in itself, requires an important amount of resources. These resources are largely independent of the sum collected by way of fees.

c. Support from the EU budget (possible no matter if single submission point is allocated with the Agency or with the Commission)

This approach would entail a subsidy from the EU budget to set up and maintain the single submission point.

Regarding the EU budget, the Commission has proposed the EU 'public health program' on 9 November 2011.[102],[103] If the program is adopted as proposed by the Commission, it could potentially provide the financial means to finance the 'limited IT solution'. However, the financial means available through this program would not allow for financing the 'extensive IT solution'.

[102] COM(2011) 709.

[103] Another possibility for financing the single submission portal that could be explored is via the EU program 'interoperability solutions for European public administrations' ('ISA' - Decision No 922/2009/EC).

ANNEX 7: POLICY OPTION 1/3: SUPPORT STRUCTURE AT EU LEVEL - IMPLEMENTATION COSTS

1. Costs at EU level

Apart from the costs for the single submission portal (see Annex 6), the implementation costs would be linked to technical support and the role of a 'facilitator' of the joint assessment.

As with the single submission portal (see Annex 6) the Agency has been consulted on the costs of implementation at EU level. Also in this case there are two possible approaches:

'Extensive support structure': according to estimations of the Agency, its resource requirements would be 7 FTEs (3 administrators (a) and 4 assistants (b)). According to previous calculations of the Agency costs per FTE are 153 226 EUR for administrators (c) and 81 617 EUR per assitstant (d). To this adds an overhead of 48.5%.

The running annual staff costs of the large-scale solution of the Agency would be thus:

$$a*c*1\,485 + b*d*1\,485 = 1.17\,\text{m EUR}$$

'Limited support structure': the Commission would pursue a limited support structure. Such structure would require, in addition to the existing available resources of 0.25 FTE (see above) an additional resource of 1.50 FTEs (all administrators, including overhead).

Additional costs for travel expenses: It is assumed that one meeting every two months is necessary to deal with all structural and cross-cutting issues. One delegate per Member State would be reimbursed.[104]

If the support structure is provided by the Agency meetings would take place in London. The Agency would calculate 1 300 EUR per delegate per meeting (i.e. 6*27*1 300 EUR = 210 600 EUR per year).

If the support structure is provided by the Commission, the meetings would take place in Brussles. The Commission would calculate, in accordance with the applicable rules for the Commission, costs of 630 EUR per delegate per meeting (i.e. 6*27*630 EUR = 102 060 EUR).

2. Financing strategies

In view of the political commitment of the Commission to reduce staffing level at EU institutions,[105] an increase in staff can be pursued only as follows:

[104] If, in a given Member States more than one national body is involved (for example, NCA and EC), that Member State has to find internal arrangements to ensure appropriate representation of views.

- Fees or cross-subsidies as set out in Annex 6 (2), points (a) and (b). These two financing strategies would only be possible if the support structure was located with the Agency.

- Re-allocation of existing human resources within the Commission or the Agency.

[105] See Commission Communication 'A budget for Europe 2020', COM(2011)500, 29.6.2011, point 6.1.5. ('5% reduction in the staffing levels of each institution/service, agency and other body').

ANNEX 8: INVOLVEMENT OF COMMISSION OR AGENCY – KEY POINTS FOR CONSIDERATION

The impact assessment addresses additional tasks for EU-bodies in three contexts:

- Setting-up and maintaining a single submission point; and
- Technical support and 'facilitator' of the joint assessment, as referred to in point **Error! Reference source not found.** of the report;
- 'Systems inspections', as referred to in point **Error! Reference source not found.** of the report.

In all three contexts the impact assessment leaves open whether these tasks should be performed by the Agency or the Commission. This decision is left to political decision-making on the basis of the aid and information provided in this impact assessment.[106]

In this respect the following arguments and counter-arguments in favour and against both the Agency and the Commission should be born in mind:

1. Setting up and maintaining the single submission point

- Costs and financing: The estimated costs are in a large range depending on the IT solution chosen (see Annex 6). It is not clear whether the Agency would be in a position to pursue a 'limited IT solution' in view of the costs estimated by EMA.

  Allocation of the single submission point with the Agency gives a broader range of means to finance this IT solution, such as fees (see Annex 6). On the other hand, as set out in Annex 6, it is not certain whether financing tools other than the EU budget are viable.

- Experience: The Agency is already today in charge of programming and maintaining EudraCT. EudraCT contains information on all clinical trials for which a request for authorisation has been submitted. Some information contained in EudraCT has been made public through the ClinicalTrialsRegister.eu.

  EudraCT could be used as a starting point for the single submission point.

  On the other hand, it is far from certain if the IT framework for EudraCT can support the functionalities required for a single submission point. In this respect the Agency has highlighted that a strategy of a completely new system may be more cost efficient in the longer term.

  Moreover, the Commission, and in particular the lead-service DG SANCO, has experience with similar systems of submission points in in other policy areas.

- Synergies with medical devices legislation: The revision of the medical devices legislation is ongoing. Currently, it is being considered to introduce, as regards

[106] See point 1 of the European Commission impact assessment guidelines ('Impact assessment is an aid to political decision-making, not a substutitue for it').

clinical experiments with medical devices (so-called 'clinical investigations'), a single submission point, too. While a final decision as to where this point is allocated is still to be made (the impact assessment on the recast of the medical devices Directive has left this open)[107], it would be preferable that both submission points are allocated with the same body (Commission or Agency). This would create (cost-saving) synergies. It would also facilitate a coherent message to stakeholders.

2. Technical support and 'facilitator' of the joint assessment

   Both the Commission and the Agency have experience in this type of activity. In particular, the existing fora (see point **Error! Reference source not found.**) can be considered as equivalent to the technical support and 'facilitator' provided in this policy option.

   In terms of costs, the difference would be limited to higher travel expenses costs if the support function would be allocated with the Agency (see Annex 7).

3. 'System inspections'

   While the Agency has strong experience in the coordination of GCP inspections, the Commission has experience with the conduct of 'system-inspections' in non-EU countries - albeit in a different area (food and veterinary sector).

   In terms of costs, the Commission would be in a position to re-allocate to this task some resources currently located in the Commission.[108]

[107] Commission Staff Working Paper: Impact assessment – Revision of the regulatory framework for medical devices (not yet published), point 5.8.4. (*Comparison of policy options 7A-7D).*

[108] For details, see Annex 5.