

Investigator-Initiated Trials on Medical Devices  
- Legal Basis and Regulatory Aspects -

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## List of Abbreviations

AMG	Medicinal Products Act (Arzneimittelgesetz)
BfArM	Federal Institute for Drugs and Medical Devices ( <i>Bundesinstitut für Arzneimittel und Medizinprodukte</i> )
BMBF	Federal Ministry of Education and Research ( <i>Bundesministerium für Bildung und Forschung</i> )
BMG	Federal Ministry of Health ( <i>Bundesministerium für Gesundheit</i> )
CA	Competent Authority
CRO	Contract Research Organization
DIMDI	German Institute of Medical Documentation and Information ( <i>Deutsches Institut für Medizinische Dokumentation und Information</i> )
DIMDIV	Ordinance on the Database-assisted Information System of Medical Devices of the German Institute for Medical Documentation and Information ( <i>Verordnung über das datenbankgestützte Informationssystem über Medizinprodukte des Deutschen Instituts für Medizinische Dokumentation und Information</i> )
DoH	Declaration of Helsinki
DRKS	German Clinical Trials Register ( <i>Deutsches Register klinischer Studien</i> )
EC	Ethics Committee
EEA	European Economic Area
EU	European Union
EUDAMED	European Databank on Medical Devices
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HTA	Health Technology Assessment
ICH	International Conference on Harmonisation
IIT	Investigator initiated trial
IMP	Investigational Medicinal Product
ISO	International Organization for Standardization
KKS	Coordination Centres for Clinical Trials ( <i>Koordinierungszentren für Klinische Studien</i> )
KKSN	KKS network

KMU	Small and medium-sized enterprise ( <i>Kleine und mittlere Unternehmen</i> )
MBO	Medical Association's Professional Code of Conduct ( <i>(Muster-)Berufsordnung für die in Deutschland tätigen Ärztinnen und Ärzte</i> )
MD	Medical Device
MDD	Medical Device Directive
MDRA	Master of Drug Regulatory Affairs
MPG	Medical Devices Act ( <i>Medizinproduktegesetz</i> )
MPKPV	Ordinance on Clinical Investigations of Medical Devices ( <i>Verordnung über klinische Prüfungen von Medizinprodukten</i> )
MPSV	Ordinance on Medical Devices Vigilance ( <i>Medizinprodukte-Sicherheitsplanverordnung</i> )
MS	Member State
PMCF	Post-Market Clinical Follow-up
SAE	Serious adverse event
SOP	Standard Operating Procedure
TAB	Office of Technology Assessment at the German Bundestag ( <i>Büro für Technikfolgen-Abschätzung beim Deutschen Bundestag</i> )
TMF	Technology, Methods, and Infrastructure for Networked Medical Research ( <i>Technologie- und Methodenplattform für die vernetzte medizinische Forschung e.V.</i> )

## **1. Introduction**

The medical device industry is a fast-growing field. Medical devices essentially contribute to the medical care of the population. The use of medical devices offers many new options, amongst others for the diagnosis, prevention, monitoring, treatment or alleviation of diseases, injuries or handicaps. The nature of medical devices is widespread and diversifies from instruments, apparatus, appliances, implants, software, substances and preparations made of substances as well as other articles. Fundamental regulatory requirements for medical devices were developed and harmonized in the European Union (EU) in the 1990s, because the rules relating safety and performance of medical devices differed between the Member States (MS) as well as within MSs between different kinds of medical devices. Based on the New Approach [18], the core legal framework in the EU was developed and consists of three directives: Directive 90/385/EEC regarding active implantable medical devices, Directive 93/42/EEC regarding medical devices (MDD) [11] and Directive 98/79/EC regarding in vitro diagnostic medical devices (all as amended). These directives are transposed into national law by the MSs. But the framework, including these three main directives and a number of modifying or implementing directives, has been criticized to be too fragmented and difficult to follow. The European Commission committed in its Communication to the European Parliament and Council, COM (2005) 535 [8] to “recast” the directives resulting in simplification of legislation. One important fact is that the current directives will be transformed into regulations thus directly binding law, which don't have to be transposed into national law. Clinical investigations, which are the subject of this master thesis, are not a key element within this simplification commitment. But some respondents to the public consultation on the ‘Recast of Medical Device Directives’ made suggestions that clinical trials of medical devices are currently not defined [19]. The expected date of adoption of the new regulations is the second quarter 2012.

In the following this master thesis refers to the MDD, as active implantable medical devices and in vitro diagnostic medical devices as well as performance evaluation studies thereof are not considered.

Medical devices may only be placed on the market and/or put into service if they fulfil the following requirements: they have to meet the Essential Requirements set out in Annex I of the MDD [11], they must have been the subject of an assessment



of their conformity to demonstrate their compliance with the Essential Requirements and they have to bear the CE-marking. Then medical devices have free access to the markets of all MSs of the EU and of the European Economic Area (EEA).

The applicable Essential Requirements and the conformity assessment procedure depend on the nature of the medical device. Medical devices are classified into four classes according to Annex IX of the MDD [11] taking into account the duration of application and whether the device is invasive and/or active. The four classes (I, IIa, IIb and III) reflect the degree of inherent risks: class I are low risk medical devices and class III are very high risk devices. Depending on the risk class of the medical device different conformity assessment procedures can be applied. Irrespective of the risk class, all conformity assessment procedures require a clinical evaluation in accordance with Annex X of the MDD [11]. Objectives of the clinical evaluation are to assess the characteristics and performances, the evaluation of side-effects and the acceptability of benefit/risk ratio under normal conditions for use of the device and relating to the intended use. The clinical evaluation can be either based upon the critical evaluation of relevant scientific literature or of clinical investigations results or of both combined. The recommendations within the guideline MEDDEV 2.7.1 [39] about clinical evaluation and the Recommendation NB-MED/2.7/Rec. 3 [9] assist manufacturers to assess if a clinical investigation of the respective medical device is necessary to provide sufficient data for performing an exhaustive clinical evaluation. Clinical investigations for the purpose of conformity assessment are carried out by or on behalf of the manufacturer. The reason for their conduction is commercialization: to receive marketability of the respective medical device. The objectives of these commercial clinical trials are to verify the suitability of the medical device for the intended purpose, to determine any undesirable side-effects and to assess the benefit/risk ratio, all under normal conditions of use. These clinical investigations are regulated by national laws, ordinances and regulations.

In most cases the long process to a certified, CE-marked medical device is carried out by the industry. During the development process of innovative medical devices universities and institutes are often involved in the application-oriented research. Clinical investigations of already marketed medical devices may also be initiated and sponsored by universities, institutes or hospitals. These clinical investigations

do not serve the conformity assessment and are called investigator-initiated trials (IITs) or non-commercial clinical trials. They play an important role to answer questions which arise during the practical application of medical devices. The independent, non-commercial clinical research is necessary to control and correct methods of treatment, for example by comparing two or more therapy options, by comparing with the standard therapy or by determining medium-term and long-term safety aspects. The German Medical Association (*Bundesärztekammer*) declared on its German Medical Assembly (*Deutscher Ärztetag*) in 2009 that investigator-initiated clinical studies should be better assisted to be able to examine and answer independently questions regarding patient care [6]. This statement primarily referred to medicinal products, but is assignable to medical devices. Currently those clinical investigations are insufficiently regulated. This fact causes uncertainties and discussions from the regulated, in this case rather unregulated, parties.

The objective of this master thesis is to elaborate the legal basis and regulatory framework for investigator-initiated clinical investigations (investigator-initiated trials, IITs) of medical devices in Germany in comparison to clinical investigations within the scope of the conformity assessment. By means of questionnaires the experiences and positions of two organisations (Coordination Centres for Clinical Trials, ethics committees), who deal with the legal and regulatory provisions during the planning, conduction and after completion of investigator-initiated clinical investigations were analysed. The aim of the master thesis is to present possibilities of improvements concerning the legal and regulatory framework for investigator-initiated clinical investigations with the objective to enhance the quality of those investigations and the safety of patients and subjects, but not to hinder the conduction of investigator-initiated trials.

## **2. Legal and regulatory framework concerning clinical investigations**

### **2.1 A side note to medicinal products**

A glance to medicinal products shows that the International Conference on Harmonisation (ICH) established recommendations for Good Clinical Practice (GCP) which “is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects” [31]. In 2004 the Clinical Trials Directive, Directive 2001/20/EC [14] has come into force, which relates to the implementation of GCP in the conduct of clinical trials on medicinal products for human use. The objectives of this directive were to ensure the protection of human rights and dignity of subjects participating in clinical trials, especially of those who are incapable of giving their consent (e.g., children or persons with dementia), to ensure compliance with GCP for all trials with an Investigational Medicinal Product (IMP) and to ensure Good Manufacturing Practice (GMP) for IMPs, to define Europe-wide harmonized procedures and time frames for Competent Authorities (CA), Ethics Committees (EC), and sponsors [34]. Other essential objectives were to establish EU-wide databases to provide CAs with overview over all planned and ongoing trials via the EudraCT database and to ensure CA’s EU-wide supervision of drug safety via the Clinical Trials Module of the EudraVIGILANCE database [34]. Some of the most important changes coming into effect were the need of trial authorizations by CAs and by ECs (one opinion per MS), the increase of responsibility of the sponsor for the overall trial, extended safety reporting in clinical trials, implementation of procedures for GCP and GMP inspections by CAs and enabling CAs to suspend trials [34]. In the course of the Clinical Trials Directive, in particular article 1(3), article 13(1) and article 15(5) thereof, the Commission adopted the Commission Directive 2005/28/EC [7], called GCP-Directive. This directive lays down provisions to be applied to IMPs for human use as principles for the design, conduct and reporting of clinical trials involving IMPs, as well as requirements for authorization of the manufacturing or importation of IMPs and detailed guidelines on the documentation relating to clinical trials, archiving, qualification of GCP inspectors and for GCP inspection procedures. According to article 1(2) MSs shall take into account the guidance documents, which are published in “The rules governing medicinal products in the European Union”, when applying the principles, detailed guidelines and requirements. Guidelines relating to clinical

trials are published in EudraLex Volume 10 [26]. The GCP-Directive also highlights provisions for non-commercial clinical trials.

In Germany, the rules relating to clinical investigations of medicinal products are laid down in chapter six (sections 40 to 42b) of the Medicinal Products Act (*Arzneimittelgesetz, AMG*) [22] and in the *GCP-Verordnung* [47]. Requirements regarding the format and content of the documentation which has to be submitted as an application for an authorization of a clinical trial are described in detail in the 3. Notification on the clinical trial of medicinal products for human use issued by the Federal Institute for Drugs and Medical Devices (*Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM*) and the Paul-Ehrlich-Institut (PEI) [1]. The legal and regulatory framework for IITs of medicinal products is summarized in another notification issued by the BfArM and the PEI and allows for alleviations concerning the labeling of medicinal products used in IITs as well as concerning the submission of documents and information for the application for authorization of an IIT [2].

Because of the fundamental difference between the legal framework of medicinal products and medical devices and furthermore the difference between their mode of actions, provisions set for medicinal products cannot be easily assigned for medical devices.

## **2.2 Medical devices**

### **2.2.1 Status quo on the European scale**

Basis for all legislation in European MSs is the MDD. This directive was last amended by the Directive 2007/47/EC of the European Parliament and Council of 5 September 2007 [15] with the purpose of improving public health and safety by implying in particular precise and tightened requirements regarding clinical evaluation and clinical investigations. Following main provisions were put straight by amending article 15 and Annex X of the MDD:

- A clinical evaluation must be performed for all medical devices (class I to III).
- In the case of implantable devices and devices of Class III, clinical investigations shall be performed categorically (unless it is justified to rely on existing clinical data).
- The documentation of the clinical evaluation and its outcome shall be documented and included in the technical documentation.

- The clinical evaluation must be updated regularly with data from the post-market surveillance, e.g. from the post-market clinical follow-up.
- All serious adverse events (SAEs) must be recorded and notified to all concerned competent authorities.

Furthermore, the documents and information, which have to be submitted for devices intended for clinical investigations, are listed in section 2.2 of Annex VIII and now contain the clinical investigation plan, the investigator's brochure, the documents used to obtain informed consent and the confirmations of insurance of trial subjects. The latter evidences increased protection of subjects participating in clinical investigations.

Section 2.2 of Annex X states the objectives of clinical investigations: verification of the performance of the device under normal conditions of use in conformity to the relevant Essential Requirements, determination of any undesirable side-effects under normal conditions of use and assessment whether they constitute risks when weighed against the intended use.

Regarding clinical investigations, a very important fact is that clinical investigations must be carried out in accordance with the Helsinki Declaration [51], as last amended by the World Medical Assembly, as stated in section 2.2 of Annex X. The declaration of Helsinki (DoH) entitled "Ethical Principles for Medical Research Involving Human Subjects" was adopted by the 18<sup>th</sup> World Medical Assembly in Helsinki in 1964 and is considered as an ethical standard for physicians.

In order to specify the requirements for clinical investigations and to provide an instrument for the conformance with the Essential Requirements of the MDD regarding clinical investigations, the International Standard Organisation (ISO) developed the international standard ISO 14155:2011 + Cor. 1:2011 'Clinical investigation of medical devices for human subjects – Good clinical practice' [13]. The standard has the status of a harmonized standard and has been published in the Official Journal of the European Communities. According to article 5 of the MDD MSs shall presume compliance with the relevant Essential Requirements in respect of devices which are in conformity with the standard. This standard represents the current scientific and technical knowledge, which has to be applied for performing clinical investigations.

The European Commission issued a series of guidelines, called MEDDEVs, to support manufacturers and notified bodies by providing detailed guidance on performing, assessing and SAE reporting relating to clinical investigations:

- MEDDEV 2.7/2 Guide for Competent Authorities in making an assessment of clinical investigation; notification (2008) [40]
- MEDDEV 2.7/3 Clinical investigations: serious adverse event reporting (2010) [41]
- MEDDEV 2.7/4 Guidelines on Clinical investigations: a guide for manufacturers and notified bodies (2010) [42]

Another source of guidance documents is the European Association of Notified Bodies for Medical devices (Team NB), which is being formed in 2001 as a focal point and the single voice of Notified Bodies. Relating to clinical investigations this association issued the Recommendation-NB-MED-2.7/1 [10].

### **2.2.2 Implementation in Germany**

In Germany the purpose of the Medical Devices Act (*Medizinproduktegesetz*, MPG) “is to regulate the trade in medical devices and, by doing so, to guarantee the safety, suitability and performance of medical devices as well to ensure health and adequate protection of patients, users and other persons” [23]. The MPG transforms the three European directives concerning medical devices (90/385/EEC, 98/79/EC and 93/42/EEC) into German national law. The MPG is rather kept generally and refers to the directives (e.g. section 7 Essential Requirements), which then are legally binding. In addition to the MPG, a bunch of ordinances regulates the development, production, sale, distribution, information and documentation, safety reporting and use of medical devices.

Directive 2007/47/EC had to be implemented into national law which was realized with the 4<sup>th</sup> Amendment of the MPG by the *Gesetz zur Änderung medizinprodukte-rechtlicher Vorschriften* [24], both came into effect simultaneously on 21<sup>st</sup> March 2010. Clinical investigations with medical devices are subject of chapter four (sections 19 to 24) of the MPG. On the basis of the new section 37 subsection 2a MPG the Federal Ministry of Health (*Bundesministerium für Gesundheit*, BMG) passed the *Verordnung über klinische Prüfungen von Medizinprodukten* of 10<sup>th</sup> May 2010 (MPKPV) [49] to regulate all relevant aspects regarding approval procedures by the national CA, the BfArM, and by an Ethics Committee (EC), as

well as exemptions thereof [36]. With the 4<sup>th</sup> Amendment of the MPG, hence the implementation of Directive 2007/47/EC, significant changes were introduced resulting in tightened authorization procedures for clinical investigations targeting improved safety and protection of patients and trial subjects, improved quality of clinical investigations and of resulting clinical data. One of the most important changes was the introduction of a mandatory authorization of clinical investigations by the national CA (BfArM) in section 20 subsection 1 of the MPG. Directive 2007/47/EC did not necessarily impose such a mandatory approval, but article 15(4) of the MDD provided a basis for enabling the MSs to implement an approval by the CA [36]. The German *Bundestag* as legislative organ argued to adapt the provisions for clinical investigations with medical devices to those for medicinal products by means of an authorization in order to prevent unequal quality of assessment [12]. Until 21<sup>st</sup> March 2010 a notification of the clinical investigation at the federal state authority was sufficient.

Additionally a clinical investigation can only be commenced when a favourable opinion from an EC has been obtained. Until 21<sup>st</sup> March 2010 this EC had to be an independent and interdisciplinary EC which was registered at the BfArM. Since 21<sup>st</sup> March 2010, according to section 22 subsection 1 MPG, the EC has to be an independent, interdisciplinary EC established by federal state law which is responsible for the investigator. Furthermore, before the 4<sup>th</sup> MPG Amendment the sponsor of the clinical investigation could circumvent a missing or even negative EC opinion by waiting for 60 days after notification of the federal state authority and then starting the investigation [36]. Before the 4<sup>th</sup> Amendment of the MPG the EC assessed the investigation plan from ethical and legal aspects, checked the legal requirements for the conduction of a clinical investigation which included technical, safety and scientific aspects of the medical device [36]. The 4<sup>th</sup> Amendment led to a task sharing. The CA is responsible to assess the medical device itself and the clinical investigation plan from the technical and scientific point of view (section 22a subsection 2 MPG). The CA evaluates if the medical device is adequate safe and if possible risks are justifiable due to the design of the clinical investigation (section 6 subsection 4 MPKPV). The EC reviews the submitted documents and the investigation plan from an ethical and legal point of view (section 22 subsection 2 MPG). The EC carries out an ethical legal evaluation ensuring the quality of the respective clinical investigation and the

welfare and health of subjects during the conduct of the clinical investigation as well as afterwards (section 5 subsection 4 MPKPV). The new provisions with the 4<sup>th</sup> MPG Amendment introduced new duties and responsibilities of the involved CA. The BfArM obtained a central role in the development of innovative medical devices with sovereign decision-making power in the field of medical device law [36].

The application and authorization procedures at the CA and EC are not discussed in this master thesis. Several comprehensive publications display all aspects of the procedures in detail, e.g., Lehmann E et al. [36].

Furthermore the 4<sup>th</sup> Amendment introduced provisions in chapter 4 of the MPG regarding

- The withdrawal, revocation and suspension of the authorization or of the favourable opinion (section 22 b),
- Modifications in the documentation after granting of the authorization and the favourable opinion (section 22 c) and
- Procedures for the end of trial notification or notification in case of early termination of clinical investigations (section 23 a).

The *Gesetz zur Änderung medizinprodukte-rechtlicher Vorschriften* [24] imposes also modifications of the Medical Devices Safety Plan Ordinance (*Medizinprodukte-Sicherheitsplanverordnung*, MPSV) [48]. Because of the deletion of the second sentence of section 1, the scope of the MPSV includes medical devices which are used in clinical investigations. Section 2 defines the term serious adverse event (SAE) within clinical investigations subjected to authorization, respectively within clinical investigations for which a waiver of authorization was granted. According to section 44 subsection 5 all new provisions of the Medical Devices Safety Plan Ordinance are also applicable to clinical investigations which have been commenced before 21<sup>st</sup> March 2010.

### **2.2.3 Scope of the German legislation concerning clinical investigations**

In section 1 the MPKPV [49] clearly defines its scope: the ordinance applies to clinical investigations according to sections 20 to 24 MPG if their results are intended

1. For the conduct of a conformity assessment procedure (new medical device).



2. For the conduct of a conformity assessment procedure with a certified CE-marked medical device but for a new intended use.
3. To gain and evaluate experiences of the manufacturer relating to the clinical safety and performance of a certified CE-marked medical device provided that additional invasive or other stressful examinations are carried out.

In contrast the scope of the provisions of sections 20 to 24 MPG is not clearly defined. The history of the MPG and its connection with the European directives (e.g. as in section 22a subsection 1) implicate that sections 20 to 24 MPG apply to clinical investigations with the purpose to gain clinical data which shall be used for the clinical evaluation during the conformity assessment of the respective medical device by the manufacturer [36]. Systematic investigations of medical devices involving human subjects which are carried out for other reasons, are not necessarily within the scope of the MPG.

According to section 20 subsection 1 MPG a waiver from the mandatory authorization is possible for low risk medical devices. Details of this provision are given in section 7 MPKPV: sponsors may apply for a waiver of the approval in case of clinical investigations involving

1. Medical devices of class I,
2. Non-invasive devices of class IIa,
3. Certified and CE-marked medical devices if the clinical investigation comprises additional invasive or other stressful examinations, unless the investigation targets another intended use of the device and not the certified intended use.

The procedure for low risk devices ensures equivalent protection of the subjects and/or patients in comparison to investigations which are subject to authorization. The requirement for a favourable opinion from an EC remains unchanged.

Another intended use of the device and not the certified intended use could be a modified or supplemented or expanded or a new intended use of the respective device, or its use with regard to a another target group or another diagnosis or therapy, or its use in combination with other products [35].

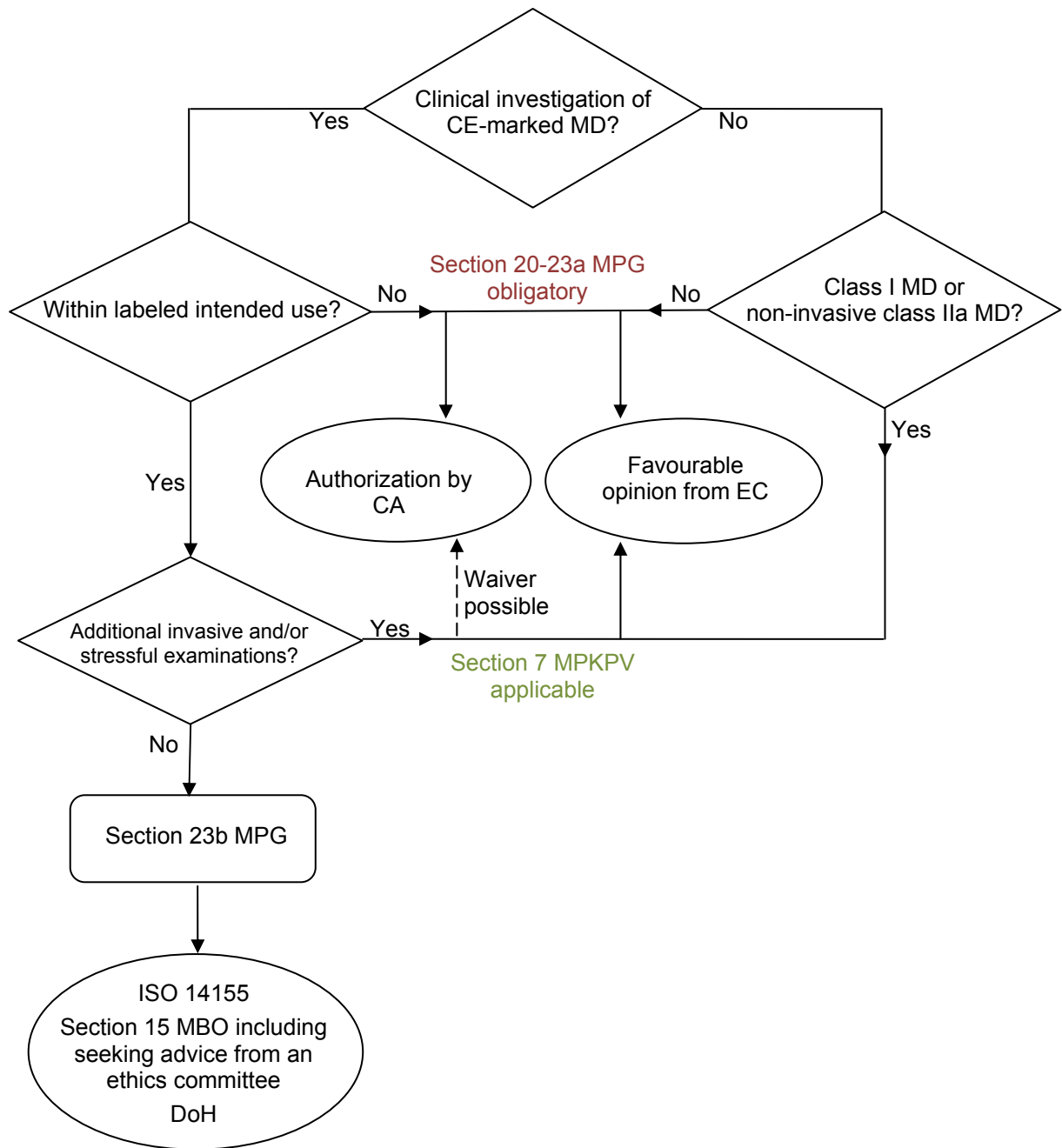
Exemptions from the provisions concerning clinical investigations are stated in section 23b MPG: sections 20 to 23a are not applicable in case of clinical investigations involving certified CE-marked medical devices unless the

investigation targets another and not the certified intended use of the device or additional invasive or other stressful examinations were performed. In this case the sponsor of the clinical investigation does not need an authorization by the CA, a favourable opinion by the EC and an assurance of the human subjects. But the clinical investigation has to be performed in accordance to the standard ISO 14155:2011 and investigators must seek advice on professional ethics and legal regulations from an EC according to section 15 of the Professional Code of Conduct (*(Muster-)Berufsordnung für die in Deutschland tätigen Ärztinnen und Ärzte*, MBO) of the German Medical Association (*Bundesärztekammer*) [44].

Such clinical investigations may be carried out by manufacturers due to the necessity to perform post-market follow-up studies to update the clinical evaluation. According to Annex X section 1.1c MDD manufacturers are obliged to update regularly the clinical evaluation and its documentation. During the pre-market phase the manufacturer may not be able “to detect rare complications or problems that only become apparent after wide-spread or long term use of the device... these residual risks should be investigated and assessed in the post-market phase through systematic Post-Market Clinical Follow-up (PMCF)” [43]. The guidance document MEDDEV 2.12/2 [43] states the definition of a PMCF study as following: “A study carried out following the CE marking of a device and intended to answer specific questions relating to clinical safety or performance (i.e. residual risks) of a device when used in accordance with its approved labeling.”

The following figure illustrates the applicability of the stipulations of the MPG and MPKPV regarding clinical investigations of medical devices.

**Figure 1** Applicability of section 20 (1) MPG, of section 7 MPKPV concerning low risk medical devices and of section 23b MPG



#### **2.2.4 Investigator-initiated trials (IITs)**

In addition to the manufacturer, other natural or legal persons may initiate clinical investigations with medical devices, as defined in chapter 2.2.5, such as universities, hospitals or other medical institutions. Sponsors of such clinical investigations are not the manufacturer but the director of a hospital or a physician for example. These clinical investigations may serve the conformity assessment of medical devices to gain marketability and the sponsors – who are not the manufacturers – are responsible for the initiation, organization and financing of the clinical investigations on human subjects [32]. Then these academic driven trials would be within the scope of the MPG and MPKPV.

However, clinical investigations for the conformity assessment are of commercial interest and are primarily initiated by the industry, particularly the manufacturers of the respective medical device. Clinical investigations with non-commercial sponsors as universities are motivated by medical and scientific needs such as:

- Comparison of different medical devices or therapies,
- Collection of scientific findings concerning diagnosis and therapy of a disease,
- Verification of the efficacy of a medical device under ideal conditions,
- Verification of the effectiveness of a medical device under routine conditions,
- Improvement or further development of treatments or
- For lack of standard therapies [5, 38].

The European Commission describes in the draft guidance on ‘specific modalities’ for non-commercial clinical trials issued in 2006, that “non-commercial sponsors commonly study the ‘effectiveness’ of a medicinal product compared to alternatives, which is of key importance to patients, health professionals and organisations seeking to improve clinical practice” [17]. This draft guideline applies to medicinal products, but general parts are also applicable for medical devices.

Thus the purpose of such investigations is not the conduct of a conformity assessment procedure but a scientific question or a question concerning the public health. These investigations are initiated by investigators or researchers, respectively by their institutions, therefore they are called “investigator-initiated trials” (IITs). Another crucial characteristic of IITs is that these trials are not subject to any commercial interest. The term “non-commercial trial” is used synonymous with “IIT” as definitions are lacking in the European and German legislation. Other

terms as “investigator-initiated study” (IIS) and “investigator-sponsored trial” (IST) are found, but not used frequently.

In the above mentioned draft guidance [17] the criteria for non-commercial clinical trials are specified in detail in section 3.1. as follows:

- The sponsor should be a university, a hospital, a public scientific organization, a non-profit institution, a patient organization or a researcher;
- The ownership of the data of these trials should belong to the sponsor listed in the first bullet point;
- No agreements between the sponsor and third parties allowing them to use the data for regulatory or marketing purposes should be in place; and
- The design, conduct, recording and reporting of the clinical trial should be under the control of the sponsor.
- The studies should not be part of the development programme for a marketing authorization of a medicinal product.

Based on the different objectives of the clinical investigations with medical devices, verification of the suitability for the proposed intended use by a conformity assessment procedure in contrast to scientific investigations out of medical aspects, they differ in the scope of the legal and regulatory framework. Provided that IITs don't serve a conformity assessment, they are not covered by the MPKPV. Currently the BMG argues that IITs are not clinical investigations within the meaning of section 20 MPG because the MPG serves for the purpose to ensure the marketability of medical devices [32]. Thus IITs are not covered by the MPG either. To perform IITs according to the current scientific and technical knowledge, the standard ISO 14155 should be applied, as in addition IITs conform to the definition of a clinical investigation given in number 3.6 of ISO 14155 (see chapter 2.2.5). But it is left to the investigator if he applies to the standard or not [50]. Furthermore the principles of the DoH have to be followed because IITs are medical research involving human subjects. Section 15 MBO and number 15 of the DoH implicate that investigators must seek advice on professional ethics and legal regulations from an ethics committee. All together shows that IITs, even if they are designed as commercial clinical investigations which are covered by the MPG and MPKPV, may be performed without inspection of the technical safety aspects of the medical device itself e.g. by a CA. That means that in the worst case investigators may perform high risk trials with high risk medical devices (class III) and additional invasive and stressful examinations without an

authorization by the BfArM, without the conclusion of an insurance policy with the trial subjects as beneficiaries and below quality standards such as ISO 14155. This demonstrates a considerable gap concerning the protection of the human subjects participating in clinical investigation depending on the purpose of the respective clinical investigation, which cannot be accepted [50].

Basically IITs are subject to the same regulatory framework as investigations according to section 23b MPG, namely the application of the standard ISO 14155, adherence to the principles of the DoH and the obligation to seek for advice on professional ethics and legal regulations from an ethics committee. The difference lies in the reason for the clinical investigation: clinical investigations in line with section 23b MPG are performed due to commercial reasons, e.g. to maintain marketability (in the context of post-market clinical follow-up) as distinguished from IITs which are performed due to scientific or medical reasons.

Considering that the CE-mark is solely effective for the approved intended use, the eligibility to affix the CE-mark lapses once the medical device is used for another and not the approved intended use. This means that an investigator is not allowed to use the medical device in an IIT outside its approved labeling. This provision may be circumvented in case of particular therapies (see chapter 2.2.5). In contrast, the eligibility to affix the CE-mark is not affected if additional invasive and/or other stressful examinations were performed during the clinical investigation.

Publication of clinical data from IITs may also contribute to counteract the publication bias. Industry-driven trials are more likely to show positive results because the investigators are trained on the medical devices which are examined in the clinical investigation. Whereas, in IITs problems can be detected which arise from improper or unskilled use of medical devices under routine conditions.

Specific provisions regarding clinical investigations covered by the law in comparison to investigator-initiated clinical investigations are discussed in chapter 4.

### **2.2.5 Demarcation to other methods of clinical research**

A definition of the term „clinical investigation“ is lacking in the European directives concerning medical devices as well as in the German legislation. The standard

ISO 14155 [13] and the guideline MEDDEV 2.7/4 [42] define the term „clinical investigation” very similar:

ISO 14155 number 3.6: Systematic clinical investigation on one or more human subjects, undertaken to assess the safety or performance of a medical device.

NOTE: The terms “clinical trial” or “clinical study” are synonymous with “clinical investigation”.

MEDDEV 2.7/4: Any systematic investigation or study in or on one or more human subjects, undertaken to assess the safety and/or performance of a medical device.

By means of these definitions following clinical research activities are outlined from clinical investigations, as they were described so far and which are aimed at providing clinical data for the evaluation of the safety and performance of a medical device within the scope of a conformity assessment procedure [32]:

- Acceptance studies regarding the handling, design and functioning of the medical device by users, respectively feasibility studies.  
→ The medical device is not used in or on human subjects and therefore such studies are not clinical investigations. They may be performed during the PMFC with CE marked medical devices. But if medical devices without CE mark or beyond their approved labeling are to be used, sections 20 to 23a MPG are applicable. Furthermore the CE mark is required for medical devices to be placed on the market according to section 6 subsection 1 MPG.
- Collection and evaluation of data from the routine use of CE marked medical devices within their approved labeling, so called medical device registries. A registry is an observational study comparable to *Anwendungsbeobachtungen* of medicinal products. A comprehensive definition of the device registry is found in the guideline MEDDEV 2.12/2 [43]: an organized system that uses observational study methods to collect defined clinical data under normal conditions of use relating to one or more devices to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves predetermined scientific, clinical or policy purpose(s).  
→ Registries are organized systems to collect clinical data and evaluate the device use by dint of this data, but they are not systematic investigations with

specified investigation plans. The results of registry studies may be used for post-market surveillance activities.

- Due to an emergency situation, therapeutic approaches with medical devices outside their approved labeling, so called Off-label use, may be performed.  
→ Therapeutic approaches are not systematic investigations with specified investigation plans. Furthermore this case is in conflict with the *Medizinprodukte-Betreiber-Verordnung* [46] and the responsibility is shifted to the user [35].
- A particular therapy in an individual patient is the use of a therapy which is not yet well-proven to see if it works for the patient. In this case the use of the medical device is not covered with its approved intended use but it is in accordance with the “therapeutic freedom“. Particular therapies are not intended to substitute clinical investigations during the assessment of medical devices e.g. for a new or expanded intended use.  
→ Particular therapies are not systematic investigations with specified investigation plans.
- Health economic studies → Health economic studies do not provide assessment of the safety and/or performance of a medical device.

The above mentioned studies are not provided by law (sections 19 to 23b MPG) and are not within the scope of ISO 14155. In contrary to the above mentioned research methods, IITs clearly are clinical investigations, within the meaning of the definitions given in the standard ISO 14155 and in the guideline MEDDEV 2.7/4, as they are systematic investigations, following defined and specified investigation plans, in or on one or more human subjects, undertaken to assess the safety and/or performance of a medical device.



### **3. Method of analysis**

In the context of this master thesis a survey about the experiences and positions concerning the legal and regulatory framework for IITs was performed. The objective of the survey was to capture the mood about the current situation in Germany, to collect information about the numbers of IITs, the conduction of IITs and to ask for suggestions for improvements.

#### **3.1 Identification of concerned target groups**

The first considerations were to identify target groups who have to deal with the legal and regulatory provisions regarding IITs. Two target groups were identified: Coordination Centres for Clinical Trials (KKS) and ECs affiliated to universities or university hospitals. Both were deemed acceptable as target groups as mentioned below.

##### **3.1.1 Coordination Centers for Clinical Trials**

About 12 years ago Coordination Centers for Clinical Trials (KKS) have been established in line with a new funding program of the Federal Ministry of Education and Research (*Bundesministerium für Bildung und Forschung*, BMBF) to promote and improve the quality of patient-oriented clinical research [37]. Currently there are 18 KKS at universities or university hospitals in Germany, which are united in a network (KKSNet). The members of the KKSNet attend to the consulting, planning and conduction of investigator-initiated as well as industry-driven clinical investigations of both, medicinal products and medical devices [30]. “The KKSNet offers a broad range of scientific services for trial support for clinical investigations”, especially IITs, because “the realization of IITs requires a high level of medical, scientific, and methodical competence as well as specialized expertise” [38]. Additionally, “the KKSNet offers specialized consulting services for IITs within this remit” [38]. As another crucial function, the KKSNet takes an active part in politicking concerning clinical research [4]. Hence assuming that the members of the KKSNet are widely experienced with medical device IITs, they were identified to be one target group of the survey.

##### **3.1.2 Ethics committees**

According to section 15 MBO, physicians performing or engaging in medical research, which is the case for IITs, must seek advice on professional ethics and legal regulations from an EC before starting the project. This advice can be given

by an EC formed by the responsible medical association or by an independent and interdisciplinary EC formed under federal state law. Hence ECs, which are affiliated with universities or university hospitals, appear to be experienced in giving advice in terms of IITs and were identified to be the second target group of the survey. ECs affiliated with state medical associations are rather responsible for clinical investigations within the scope of the MPG and are not included in the survey.

Other possible target groups for the survey would have been contract research organizations (CROs) dealing with IITs and investigators. Due to the complexity to pick out of the quantity of investigators, respectively CROs, representatives who are experienced in IITs, this target groups have not been considered in this thesis.

### **3.2 Questionnaire design**

The experiences and positions of the KKS and the ECs concerning particular provisions and aspects of the legal and regulatory framework were examined via questionnaires. Two questionnaires were developed, one for the KKS (Annex 1) and one for the ECs (Annex 3). The basic composition of both questionnaires is similar. Differences in the questionnaires reflect the different kind of participation in IITs of the two parties: the KKS offer a consulting service with regard to IITs and take over essential duties within the scope of IITs; the ECs give advice on professional ethics and legal regulations within the scope of IITs. In a cover letter (Annex 2 for KKS, Annex 4 for EC) attached to the questionnaire the object of investigation was defined as following:

- Non-commercial clinical investigations (IITs) of medical devices within the meaning of this survey are investigations, in which
- Medical devices (excepting in vitro diagnostic medical devices) are tested on human subjects, whereat
  - The sponsor is not a profit-oriented person or institution.

The questionnaires comprise three parts as illustrated in the following table (table 1). The questions concerning the numbers of clinical investigations and the advices given from the ECs (part one of both questionnaires), as well as the second part of the questionnaire for the KKS which deals the realization of IITs, refer to clinical investigations during the period of 21<sup>st</sup> March 2010 (date when the 4<sup>th</sup> MPG Amendment became effective) until the end of 2011. The questions in the third part were developed on the basis of possible methods of resolution in the

publication of Wachenhausen H (2011) [50]. The respective responses of the KKS and ECs are discussed in detail in chapter 4.

**Table 1** Outline of the questionnaires

Part	KKS	EC
1	Questions about the numbers of clinical investigations in which the KKS took over essential duties, respectively in which the KKS carried out consultations	Questions about the numbers of clinical investigations for which the EC gave advice
2	Questions relating to the realization of IITs	Questions relating to the application and conduct of advice on professional ethics and legal regulations within the scope of medical device clinical investigations which are not subject to authorization
3	Questions regarding the legal and regulatory framework of IITs	Questions regarding the legal and regulatory framework of IITs

### 3.3 Questionnaire distribution, return and evaluation

The addresses of all 18 Members of the KKS were taken from a list (status: 24<sup>th</sup> November 2011) available from the KKS website [30]. The website of the Permanent Working Group of Medical Research Ethics Committees (*Arbeitskreis Medizinischer Ethik-Kommissionen*) [27] provides a list of links to the websites of all 34 ECs affiliated with universities or university hospitals. Using this list, the websites of the ECs were entered to obtain their addresses. Each questionnaire (Annex 1 for the KKS or Annex 3 for the EC) was sent together with a cover letter (Annex 2 for the KKS or Annex 4 for the EC), a confirmation of the university of Bonn and the board of examiners of the postgraduate course of studies “Master of Drug Regulatory Affairs” (MDRA) about the subject of this master thesis (Annex 5) and a stamped addressed envelope. On 20<sup>th</sup> February 2012 the questionnaires were sent to the KKS and on 2<sup>nd</sup> March 2012 to the ECs. The dates for return were on 9<sup>th</sup> March 2012 for the KKS and on 23<sup>rd</sup> March for the ECs as indicated in the cover letters. Actually the last returns arrived in mid of April. The following table (table 2) overviews the number of returns.

**Table 2**      **Numbers of return of questionnaires**

	KKS n = 18 (100%)	EC n = 34 (100%)
answered questionnaire	9 (50%)	8 (24%)
refusal	3 (17%)	6 (18%)
no reply	6 (33%)	20 (59%)

The reasons for refusal were mainly the lack of time to fill in the questionnaire or that no IITs with medical devices were handled during the requested period (21<sup>st</sup> March 2010 to the end of 2011).

Data entry, data evaluation and preparation of graphs were performed with Microsoft Excel 2010. The results of the survey are discussed in chapter 4.

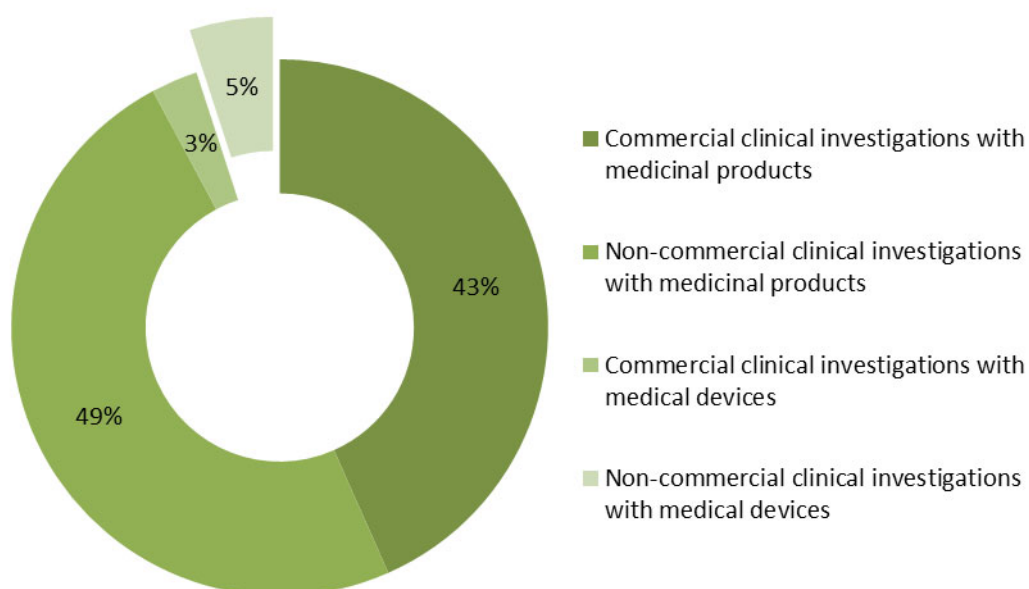
#### 4. Common practice and opinions regarding IITs of two involved parties

The results of the survey, which are illustrated in the following, merely reflect current trends, they assume to be representative but make no claim to be representative for the situation in Germany.

##### 4.1 Proportion of IITs with medical devices in the field of medical research

To get an impression of the proportion of medical device IITs among other clinical investigations, the KKS were asked about numbers of clinical investigations with medicinal products and medical devices within the period from 21<sup>st</sup> March 2010 to the end of 2011, and about details relating to medical device IITs. Figure 2 gives an overview about the percentage of commercial and non-commercial clinical investigations of medicinal products and medical devices. A total of 498 (100%) clinical investigations were stated, in which a KKS took over essential duties, and 5% thereof were IITs with medical devices. All in all about 8% of the clinical investigations were with medical devices.

**Figure 2 Clinical investigations essentially supported by a KKS**



In six cases the clinical investigations of medical devices were performed for the purpose of a conformity assessment procedure (and the verification of the

marketability of the respective device), three investigations thereof were with medical devices without CE-mark and the other three trials were with CE-marked medical devices (e.g., for another intended use).

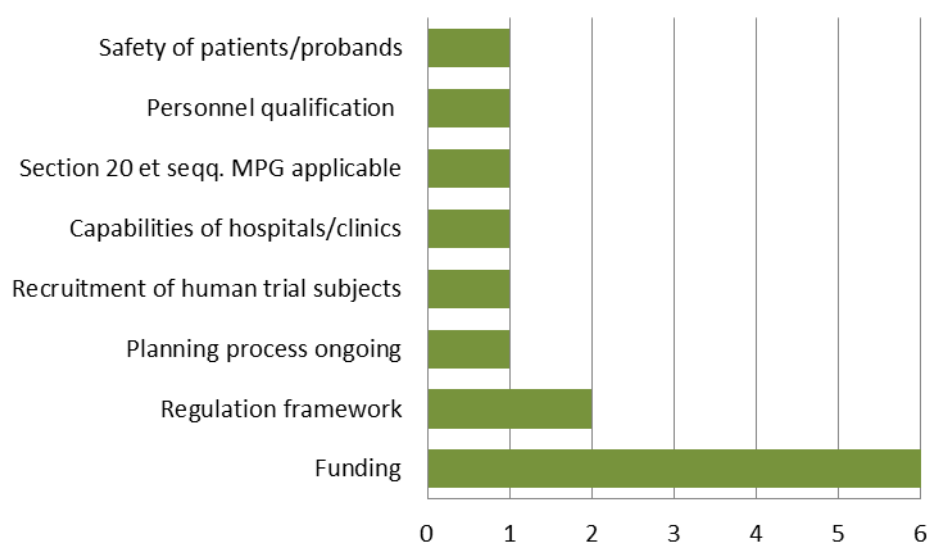
One of the questions was, if there were non-commercial trials with medical devices without a CE-mark. In principle an IIT with a medical device without CE-mark would be possible, if an investigator (or scientist or academic research group) develops a medical device completely independent from any industrial partner. But this is rarely the case because of the high costs which the pre-commercial development of a product implicates. The survey revealed that all IITs in the requested period were performed with CE-marked medical devices.

For two IITs the sponsors obtained an authorization by the BfArM. On inquiry the reason for one of these two authorizations was indicated: the respective IIT was performed with a CE-marked medical device within its labeled use, but the KKS as well as the EC were uncertain, if some of the examinations were additional invasive or other stressful examinations. Therefore an application for an authorization by the BfArM was made. In the end the clinical investigation met the stipulations of section 23b MPG and the clinical trial was exempted from the authorization.

Furthermore the KKS were asked about their consulting activities. All in all the KKS carried out 58 (100%) consultations regarding medical device IITs. For 14% of these consultations scientific advice from the BfArM was requested to decide about the applicability of sections 20 and following of the MPG. About 12% of the consultations finally led to an IIT. The main obstacles why the IITs were not performed after the consultations were shown in figure 3. A total of six KKS gave information (multiple answers were permitted). All of them quoted insufficient financing as obstacle for IITs. A survey of the Office of Technology Assessment at the German Bundestag (*Büro für Technikfolgen-Abschätzung beim Deutschen Bundestag*, TAB) in 2009 [5] pointed out that non-commercial trials (including medicinal products and medical devices) are mainly financed by the industry, followed by public research funding (e.g., by the German Research Foundation, DFG, or the Federal Ministry of Education and Research, BMBF). Further sources of financing are foundations or a mixture of several finance sources. Some of the respondents of the above mentioned survey considered public research funding

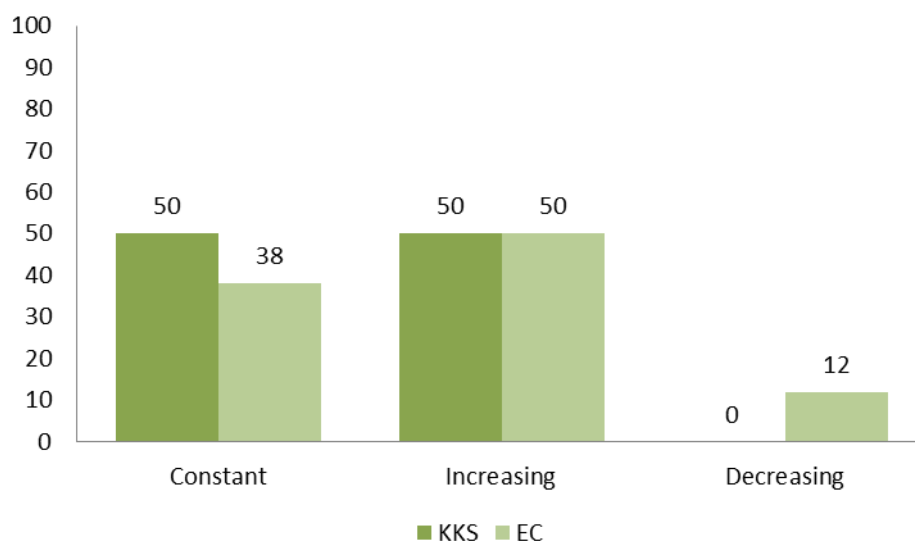
programs to be positive, but not sufficient, and they emphasized that health insurances should contribute to IITs because this patient-oriented clinical research is relevant for the public health care. One suggestion for improvement of the financing problem of IITs could be to implement a research fund for non-commercial trials with contributions from manufacturers, care providers, health insurances as well as tax funds [38]. Two out of six KKS quoted that the regulation framework hinders the conduction of IITs. See figure 3 for other obstacles, each of them quoted from one KKS. The safety of patients and trial subjects is discussed in chapter 4.4. The KKS enhance the personnel qualification by means of education programs in the clinical research field. By providing professional trial support the KKS contribute to the enhancement of the capabilities of clinics and hospitals and to the recruitment for trials.

**Figure 3** Main obstacles retarding the conduction of IITs (n = 6 KKS)



Furthermore the KKS and ECs were asked about the general numbers of clinical investigation of medical devices since the 4<sup>th</sup> MPG Amendment has become effective. 50% of the KKS and the ECs estimated that the numbers increased, 50% of the KKS and 38% of the ECs estimated constant numbers, and one EC (13%) estimated that the numbers decreased (see figure 4).

**Figure 4** Estimation of numbers of clinical investigations since the 4<sup>th</sup> MPG Amendment (% of n = 9 KKS, % of n = 8 EC)

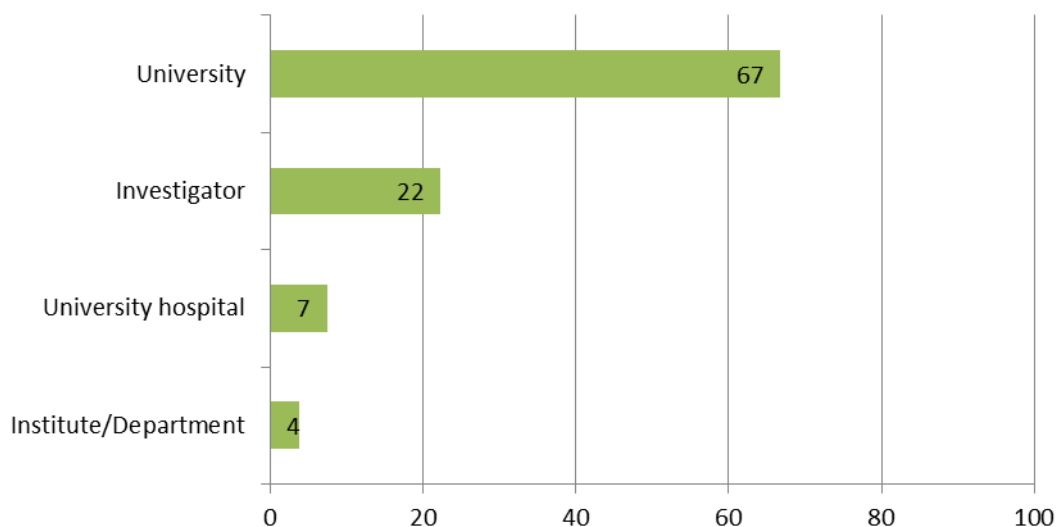


## 4.2 Particular aspects regarding the conduct of IITs with medical device

### 4.2.1 Sponsor

Conventional clinical investigations for the conformity assessment procedure are sponsored by the industry. Non-commercial clinical investigations also need a sponsor. IITs are covered by non-industrial (non-commercial) sponsors. With the 4<sup>th</sup> MPG Amendment a definition of the sponsor was introduced in section 3 number 23 MPG: a sponsor is a natural or legal person who takes responsibility for the initiation, organization and financing of a clinical investigation involving human subjects. The definition given in number 3.40 of the standard ISO 14155 additionally states that the sponsor takes the responsibility and the liability for the initiation or conduction of a clinical investigation. The note appended to this definition specifies the case when an investigator takes over the sponsorship: “When an investigator initiates, implements and takes full responsibility for the clinical investigation, the investigator also assumes the role of the sponsor and is identified as the sponsor-investigator.” The definition makes no difference, if a clinical investigation is commercial or non-commercial. The inquiry of the KKS unfolded that 22% of the IITs were sponsored by investigators, who were then sponsor-investigators. For the other IITs the division onto non-industrial sponsors was as follows: 67 % of the IITs were sponsored by universities, 7% by university hospitals and 4 % by academic institutes or medical departments (see figure 5).



**Figure 5 Sponsors of IITs (% of n = 27 IITs)**

Chapter eight of the standard ISO 14155 refers to the responsibilities of the sponsor:

- Quality assurance and quality control
- Trial planning and conduction
  - Selection of the qualified medical personnel
  - Documentation and preparation of material
  - Trial conduction
  - Monitoring
    - Qualification of monitors
    - Assessment of trial sites
    - Start of trial at trial site
    - Routine visits of monitor
    - End of trial activities
    - Monitoring reports
  - Safety evaluation
  - Termination of a trial
- External transfer of functions and responsibilities
- Communication with inspecting authorities

The list shows that the duties and responsibilities are infeasible for one person, namely the investigator, and that an allocation of duties and responsibilities is indispensable to be able to perform IITs. One KKS stated that five non-commercial trials had industrial sponsors. That means that science-driven trials were

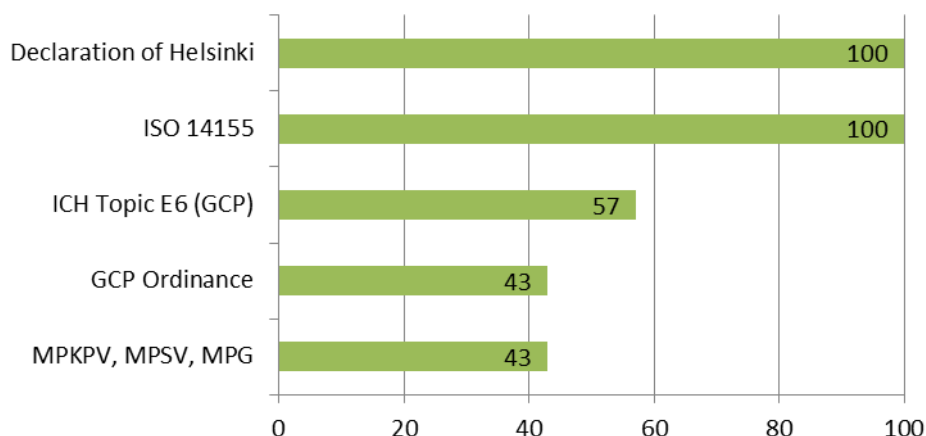
sponsored by the industry, without any commercial interest which is on the one hand unimaginable and on the other hand a commendable method to support IITs.

#### 4.2.2 Quality standards

IITs underlie no legal requirements regarding quality standards. Therefore it is possible and probable to perform clinical investigations for scientific and/or medical reasons applying lower quality standards than those applied to clinical investigations within the scope of a conformity assessment. To estimate the actual situation, the KKS were asked about the quality standards applied for IITs. Seven KKS gave information about this issue: all of them (100%) quoted to adhere to the Declaration of Helsinki and the standard ISO 14155 (see figure 6). This was the expected result. In chapter 2.2.4 was put straight that the principles of the DoH have to be followed as IITs are medical research involving human subjects and the standards ISO 14155 reflects the current scientific and technical knowledge. The scope of the standard ISO 14155:2011 addresses

“Good clinical practice for the design, conduct, recording and reporting of clinical investigations carried out in human subjects to assess the safety or performance of medical devices for regulatory purposes. The principles set forth in ISO 14155:2011 also **apply to all other clinical investigations** and should be followed as far as possible, depending on the nature of the clinical investigation and the requirements of national regulations. ISO 14155:2011 specifies general requirements intended to protect the rights, safety and well-being of human subjects, ensure the scientific conduct of the clinical investigation and the credibility of the results, define the responsibilities of the sponsor and principal investigator, and assist sponsors, investigators, ethics committees, regulatory authorities and other bodies involved in the conformity assessment of medical devices.”

43% of the polled KKS declared, to apply to the provisions of the MPG, the MPKPV and the MPSV although it is not legally required. Additionally some KKS stated to apply to quality standards which were developed for clinical trials with medicinal products: 57% stated to adhere to the Guideline for Good Clinical Practice (ICH Topic E6) and 43% to the German GCP-Ordinance, which transfers the directive 2001/20/EC into German law and is in large part comparable to the ISO 14155. Worth mentioning is the fact that in its introduction the ICH GCP guideline refers to trials that involve the participation of human subject, but this scope is not restricted to medicinal products [31].

**Figure 6** Quality standards applied for IITs (% of n = 7 KKS)

In February 2011 the “Revision of the ‘Clinical Trials Directive’ 2001/20/EC Concept paper submitted for public consultation” [20] has been published by the European Commission. In its comment [33] on the above mentioned concept paper, the KKS indicates that the scope of the Clinical Trials Directive could be extended to encompass clinical trials with medical devices. This would implicate, that the standard ISO 14155, which was updated recently, would need to be adjusted.

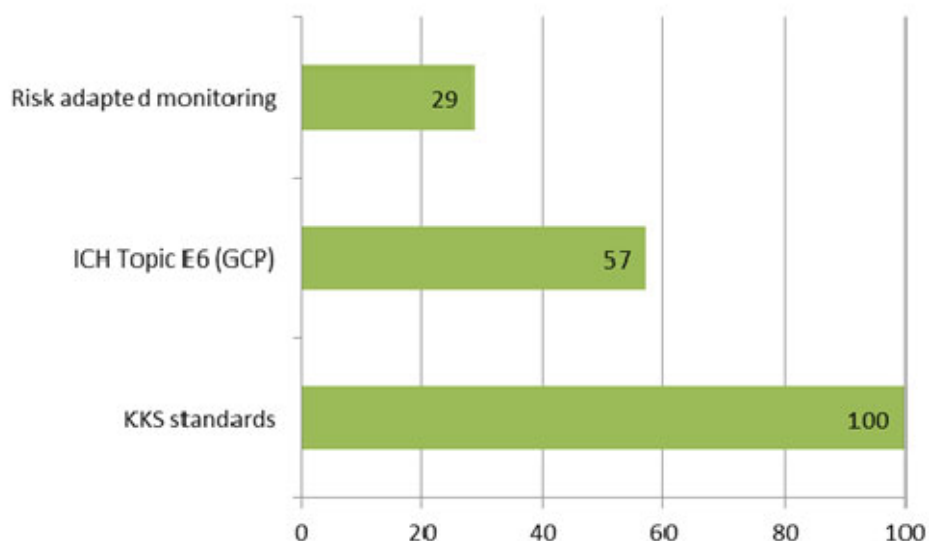
#### 4.2.3 Monitoring

Monitoring is an essential part of quality assurance within clinical trials and contributes to the safeguarding of the safety of patient respectively trial subject and their rights, and to the guarantee of the reliability of trial data and results. For clinical trials on medicinal products the purpose and duties of monitoring are described in the Guideline for Good Clinical Practice (ICH Topic E6). The extent of monitoring activities is not specified in this guideline. The provisions of the standard ISO 14155 concerning monitoring are greatly leant on those of the ICH-GCP. The concern exists, that IITs were performed exerting less or even marginal monitoring activities which may have unknown implication on patient safety and data quality. At least for IITs supported by a KKS this concern seems to be unfounded. All KKS (n = 7, 100%) which answered the respective question in the questionnaire, stated to follow KKS standards for monitoring and 57% adhere to monitoring standards of the ICH-GCP guideline (see figure 7).

The KKS together with the Technology, Methods, and Infrastructure for Networked Medical Research (*Technologie- und Methodenplattform für die*

*vernetzte medizinische Forschung e.V.*, TMF) developed harmonized and standardized standard operating procedures (SOPs, available at: <http://www.tmf-ev.de/Produkte/SOP.aspx>, last accessed on 30.05.2012) for the conduct of clinical trials on medicinal products and medical devices, to support and enable investigators to comply with legal and regulatory obligations especially in IITs. On inquiry the KKS specified, that these SOPs were finalized before the 4<sup>th</sup> MPG Amendment came into force. The SOPs are used for clinical trials according to the AMG and MPG and for trials which underlie neither the AMG nor the MPG. They are used as well for IITs, which may underlie the MPG if CE-marked medical devices are used but not within the certified intended use, respectively if additional invasive or stressful examinations are performed or the IITs may fall into the scope of section 23b MPG. The provided report templates are adapted to medicinal products and the AMG, but in case of trials with medical devices they are adjusted to the peculiarities of medical devices and the MPG. In terms of a monitoring manual applicable monitoring activities for particular studies were defined taking into account the regulatory provisions. In the long term, a modification of the SOPs to incorporate the provisions of the amended MPG seems to be reasonable.

**Figure 7** Monitoring in IITs (% of n = 7 KKS)

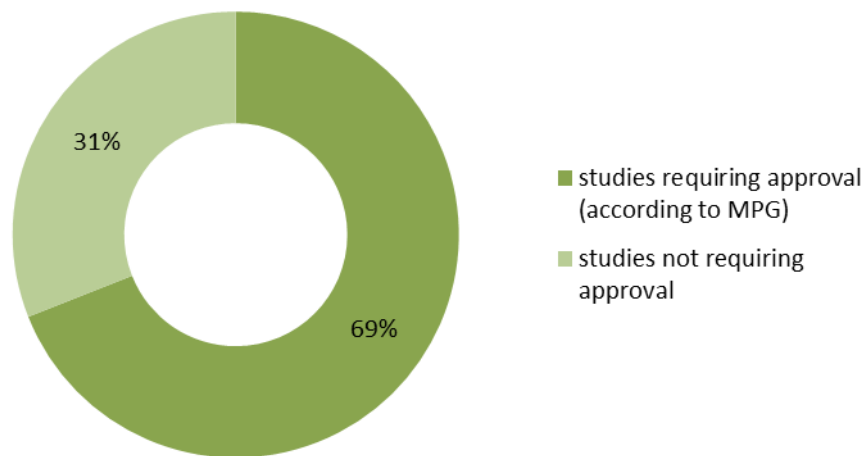


29% of the KKS stated to perform risk adapted monitoring. Within the scope of the ADAMON (adapted monitoring) project funded by the BMBF (see <http://www.adamon.de/ADAMON/Projektbeschreibung.aspx>, last accessed on 30.05.2012) reduced on-site monitoring strategies for non-commercial trials were examined in comparison to comprehensive “full” monitoring according to the ICH

GCP. The intention is to develop an instrument to deduce a monitoring strategy which is adapted to the particular (investigator-initiated) trial and which is optimized with regard to the available and required resources, but which at the same time ensures the adherence to the GCP principles. A document provided on the above mentioned web page describes procedures for the derivation of risk adapted quality assurance strategies within the scope of non-commercial clinical trials [3].

#### **4.3 Involvement and opinions of the ethics committees**

The ECs affiliated with universities or university hospitals handle IITs and investigations within the scope of section 23b MPG equally regarding the application for and conduct of advice on professional ethics and legal regulations. On the web pages of the ECs application forms and checklists are available for so called “research projects”, “other studies (which do not underlie the AMG or MPG)”, “free studies” or “non-AMG/Non-MPG-studies” covering both types of investigations, IITs and section 23b MPG studies. The ECs were asked about the numbers of applications for advice respectively for opinion involving medical devices. A total of 2061 applications were in process during the requested time period. 69% thereof dealt with studies within the scope of the MPG which required approval respectively an approving opinion. 31% of the applications dealt with studies which were not subject to approval, but sought for advice, including IITs and studies according to section 23b MPG (see figure 8). 12% of the studies not requiring approval had an industrial (commercial) sponsor. Though one EC annotated that studies not requiring approval and with a commercial sponsor would not have been possible since 21<sup>st</sup> March 2010. But it is the case for studies according to section 23b MPG. As the KKS, the ECs were asked if there were trials not requiring approval with medical devices without a CE-mark. Most ECs (six out of eight) answered that no trials with medical devices without CE-mark were advised. One EC stated that four such studies were handled, but it was not possible to find out details about these studies. One EC again annotated that studies of that kind would not have been possible since 21<sup>st</sup> March 2010.

**Figure 8 Applications for approval or advice from an Ethics committee**

In the second part of the questionnaire the ECs were asked about handling the application and conduction of an advice on professional ethics and legal regulations within the scope of medical device clinical investigations which not require approval. The majority of the ECs (63%) appraise the current handling as satisfying, 25% as very satisfying and 13% as less satisfying. A look to the web pages of the different ECs points up, that the application forms and the documents which have to be submitted differ strongly. In contrast the documents for clinical investigations requiring approval are clearly specified in section 3 subsections 1, 2 and 3 MPKPV. The Permanent Working Group of Medical Research Ethics Committees offers on its web page checklists and letter templates for clinical investigations within the scope of the MPG and seeks for harmonization of advisory and evaluation processes of the ECs. With the 4<sup>th</sup> MPG Amendment coming into effect, for MPG studies the applications for authorization by the higher federal CA and for the favourable opinion from the EC, and the respective documents have to be submitted electronically at the German Institute of Medical Documentation and Information (*Deutsches Institut für Medizinische Dokumentation und Information*, DIMDI). Details are provided in section 3a and Annex 4 of the Ordinance on the Database-assisted Information System of Medical Devices of the German Institute for Medical Documentation and Information (*Verordnung über das datenbankgestützte Informationssystem über Medizinprodukte des Deutschen Instituts für Medizinische Dokumentation und Information*, DIMDIV) [45]. The survey revealed that 63% of the ECs think, that the

documents and forms for the application for advice on professional ethics and legal regulations within the scope of studies not requiring approval should be harmonized, 13% think they should not be harmonized and 25% are neutral. Six out of the seven ECs which answered the respective question dislike submission of the application and documents for such studies electronically at the DIMDI.

A question concerning harmonization of assessment criteria in the context of the advice on professional ethics and legal regulations was answered as follows: five out of eight ECs think that the assessment criteria should be harmonized, two out of eight ECs think that they should not be harmonized and one EC is neutral. In case of harmonization of the assessment criteria, four of six ECs think that the criteria should be adapted to those listed in section 5 subsection 4 of the MPKPV. One EC thinks the criteria should not be adapted to those of the MPKPV and one EC is neutral.

The advice on professional ethics and legal regulations from the EC leaves the investigator (or sponsor-investigator) with uncertainty regarding the matter, if the respective trial requires approval or not. In contrast, the opinion given for MPG studies is a legal act and provides legal certainty for the sponsor (investigator), because the ECs decide bindingly about the legitimacy of the respective trial [36]. A statement on the web page of the EC of the faculty of medicine of the *Christian-Albrechts-Universität zu Kiel* makes this circumstance clear: “ECs advice, they don’t authorize; the responsibility remains with the physician respectively the one working in the medical field who conducts the study” [29]. In the case that clinical investigations which do not serve a conformity assessment procedure were covered by the MPG, all ECs are in agreement that a favourable opinion instead of advice on professional ethics and legal regulations should be required. This would implicate that the decision of the EC is an administrative act and hence privately organized ECs affiliated with universities or university hospitals would not be allowed to perform this task. The implementation of a favourable opinion would also implicate unavoidably a harmonization with regard to the documents for submission, the assessment criteria and the assessment process.

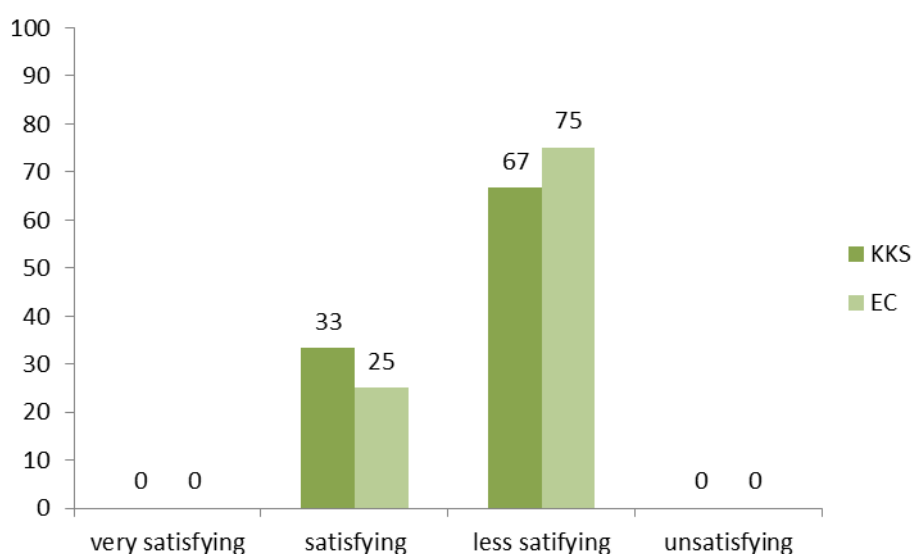
In a survey performed by the BMBF involving KKS a suggestion for improvement of clinical investigations of medical devices was to establish a national particularly for medical devices (respectively the MPG) qualified EC [35]. This idea was

addressed in the survey of this master thesis with following result: all ECs consider such a particular EC as unrealizable and undesirable. Two out of eight ECs consider the establishment to be reasonable and the other six ECs not. One EC commented that a particular EC would not be feasible because of the amount of clinical investigations of medical devices and the circumstance that especially for monocentric trials the feasibility of the respective trials, e.g. concerning patient population for recruitment, suitability of investigators and sites, may only be assessed locally.

#### 4.4 Particular stipulations of the legal and regulatory framework

Both involved parties, the KKS and the ECs, were asked about their general opinion regarding the current legal and regulatory framework for non-commercial clinical trials of medical devices. The majority (67 % of the KKS and 75% of the ECs) answered to be less satisfied with it (see figure 9).

**Figure 9** Appraisalment of the current legal and regulatory framework for non-commercial clinical trials of medical devices  
(% of n = 9 KKS, % of n = 8 EC)



To identify specific possibilities for improvement of the legal and regulatory framework, the third part of both questionnaires (see Annexes 1 and 3) comprised questions which picked up suggestions of Wachenhausen H (2011) [50].

##### 4.4.1 Definition of the term “clinical investigation”

One of the questions was about the entry of a definition of the term “clinical investigation” into the MPG. A definition is still lacking in the MPG even though the



government explicitly stated that with the 4<sup>th</sup> Amendment of the MPG via the *Gesetz zur Änderung medizinprodukterechtlicher Vorschriften* the law concerning medical devices “will be adapted to the basic and formal requirements for clinical investigations of medicinal products” [12]. Furthermore the omission of the definition is not comprehensible as with the 4<sup>th</sup> MPG Amendment definitions of the “sponsor” and the “investigator” were included in section 3 subsection 23 and 24 MPG, who are essential participants in clinical investigations. The survey revealed that all KKS and all ECs agree that a definition of the term “clinical investigation” should be included into the MPG. All ECs and eight out of nine KKS are in agreement that this definition should also cover non-commercial clinical investigations, one KKS disagrees. In contrary to the current MPG, the definition of the clinical investigation given in section 4 subsection 23 (sentence 1) AMG applies, regardless if it is a commercial or a non-commercial trial of a medicinal product, which implicates that all provisions of the AMG regarding clinical trials have to be applied for IITs.

#### **4.4.2 Special provisions regarding quality standards**

One possibility to set IITs in the MPG could be, to include special provisions for clinical investigations which do not serve the conformity assessment (including non-commercial trials). These special provisions ensure that quality standards were maintained and that the protection of the trial subjects is equally to that in studies underlying the MPG, especially for minors and persons who are incapable of giving their consent to the clinical trials (see also chapter 4.4.5). Almost all KKS and ECs think that such special provisions should be included in the MPG, and one of nine KKS as well as one out of eight ECs thinks that such special provisions should not be included.

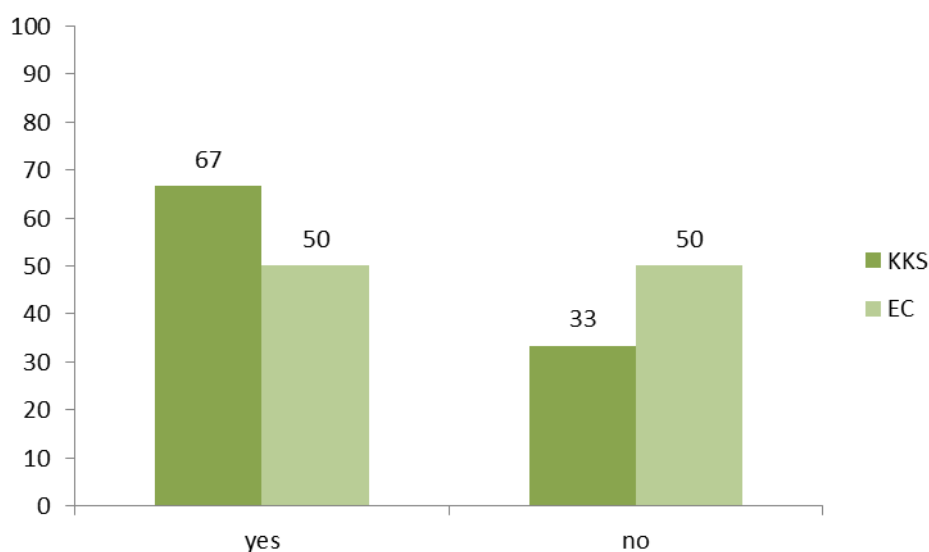
#### **4.4.3 Inclusion of non-commercial clinical trials in the MPG**

Another possibility to set IITs in the MPG is, to include clinical investigations which do not serve the conformity assessment (including non-commercial trials) in the scope of the MPG.

Then legal facilitations could be allowed for non-commercial trials, e.g. for the submission of information and documents. The sponsor may refer to the technical documents of the manufacturer; respectively the reference to the instructions for use of the medical device may be sufficient. The survey showed that one half of

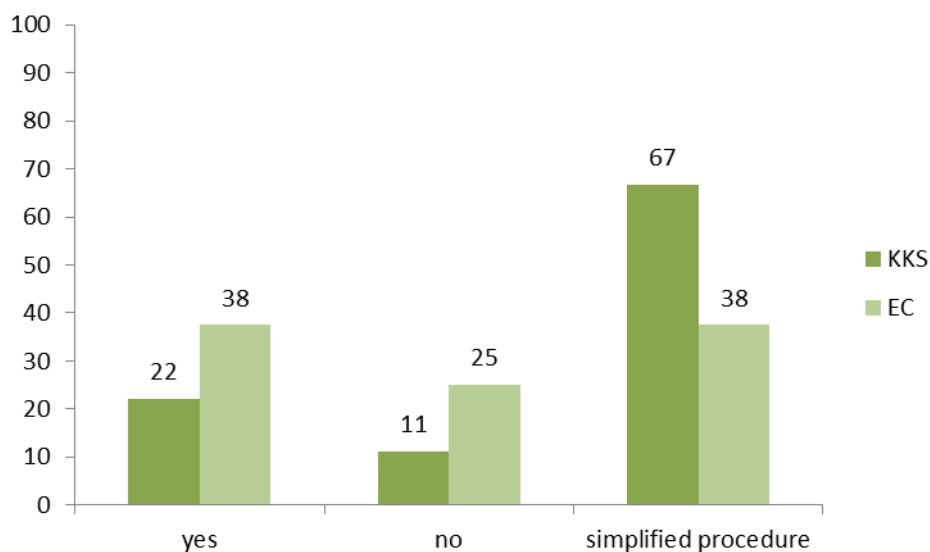
the ECs think, that legal facilitations should be provided for clinical investigations which do not serve the conformity assessment, in the case that such trials are covered by the MPG (see figure 10). The other half of the ECs was not of that opinion, that means these ECs would not support facilitations for non-commercial trials. More as the half of KKS support legal facilitations for non-commercial clinical investigations (see figure 10).

**Figure 10** Legal facilitations for non-commercial trials within the MPG  
(% of n = 9 KKS, % of n = 8 EC)



Another question was, if a mandatory authorization by the national CA should be introduced, in the case that clinical investigations which do not serve the conformity assessment (including non-commercial trials) are included in the scope of the MPG. Most of the KKS (67%) and 38% of the ECs answered that a simplified authorization procedure (e.g. abbreviated and implicit) should be introduced. 38% of the ECs and 22 % of the KKS think that a full authorization procedure should be introduced and 25 % of the ECs as well as 11 % of the KKS think that a mandatory authorization by the national CA should not be introduced (see figure 11). In the course of the introduction of a mandatory authorization for non-commercial clinical investigations the national CA, the BfArM, would be involved in IITs and perform an assessment of the scientific and technical safety aspects of the trial and of the device, which would implicate increased protection and safety of the trial subjects.

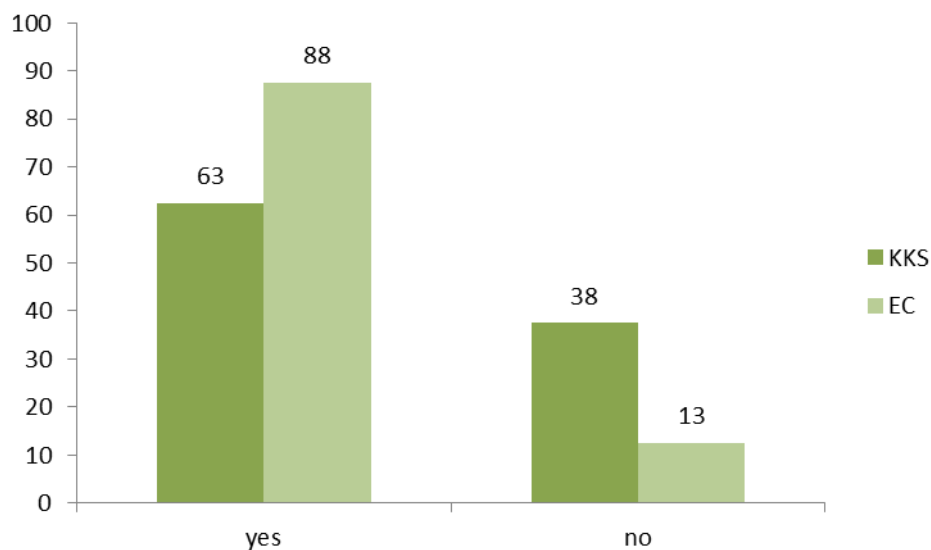
**Figure 11 Introduction of a mandatory authorization by the national CA**  
(% of n = 9 KKS, % of n = 8 EC)



#### 4.4.4 Insurance of trial subjects

Currently the conclusion of an insurance of the subjects of IITs is not legally defined as the MPG is not applicable. Section 20 subsection 3 MPG clearly stipulates the conclusion of an insurance policy with the person affected by the clinical investigation as beneficiary. Neither the standard ISO 14155 nor the DoH, both applicable for IITs, makes a statement concerning an insurance of the trial subjects. The questionnaires asked about the numbers of trials with or without clinical trial insurance. The KKS stated that in 80% of the non-commercial clinical investigations of medical devices in the years 2010 and 2011 an insurance of the trial subjects was procured and in 20% of the trials it was not. The ECs stated that for 48% of the studies not requiring approval an insurance of the study subjects was existent and for 52% of the studies it was not. The ECs were additionally asked if they recommend the conclusion of an insurance of the trial subjects if there is none existent with the following result: three out of eight ECs recommend in either case the conclusion of an insurance policy and five of eight ECs recommend the conclusion of an insurance policy in some cases. Furthermore the polled parties should give their opinion regarding the legal provision of a risk dependent insurance of clinical trial subjects in non-commercial clinical trials. The majority of both parties (63 % of the KKS and 88% of the ECs) agree that a risk dependent insurance of subjects of non-commercial trials should be legally defined, 38% of the KKS and 13% of the ECs disagree (see figure 12).

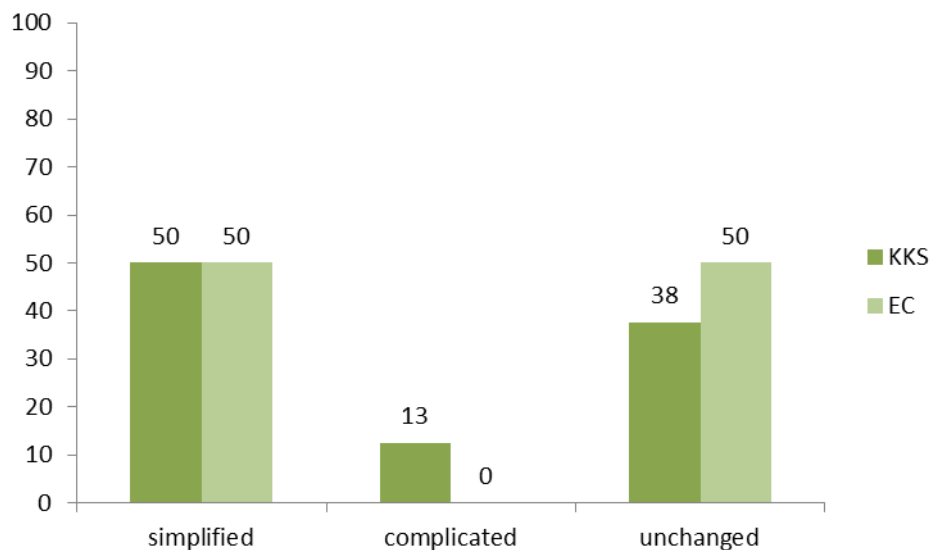
**Figure 12** Introduction of a risk dependent insurance of the trial subjects  
(% of n = 8 KKS, % of n = 8 EC)



One KKS mentioned that a risk dependent insurance should not be introduced in the MPG generally, but should be in individual cases. One KKS did not answer the question but noted the question who would decide about the risk (insurer?). One solution for the issue concerning the insurance of trial subjects would be, to insure academic trials through the national public health system comparable to other countries [16]. This option would improve the protection of trial subjects and in addition alleviate the financing of IITs.

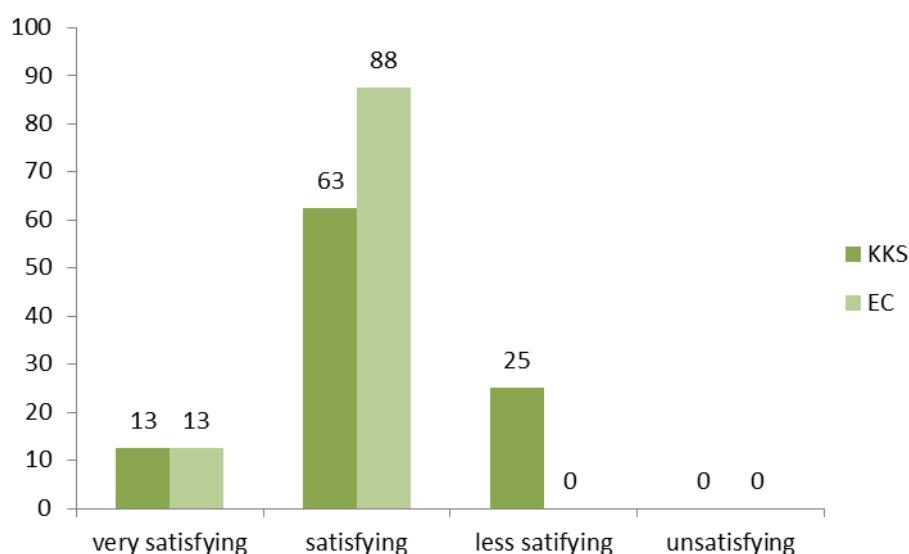
Summing up all the above described modifications (chapter 4.4.1 to 4.4.4) the KKS and ECs should indicate their opinions concerning different aspects of non-commercial clinical investigations with medical devices. One half of the KKS as well as the ECs think, that the conduction of non-commercial clinical trials would be facilitated through the modifications of the legal and regulatory framework discussed above (see figure 13). 38% of the KKS and the other half of the ECs think, that the modifications would have no impact on the conduction of non-commercial trials (see figure 13). 13% of the KKS suppose, that the conduction of non-commercial trial would even be more complicated (see figure 13). All KKS and the majority (75%) of the ECs consider that the safety and protection of trial subjects would improve and 25% of the ECs think that the safety and protection of trials subjects would not improve but remain unchanged.

**Figure 13** Conduction of non-commercial clinical trials taking into account the proposed modifications (% of n = 8 KKS, % of n = 8 EC)



Finally both involved parties, the KKS and the ECs, were asked again about their general opinion regarding the legal and regulatory framework for non-commercial clinical trials of medical devices with the implementation of the discussed modifications. In contrary to the current situation (see figure 9) most of the KKS and ECs consider the framework then to be satisfying or even very satisfying (see figure 14).

**Figure 14** Appraisal of the legal and regulatory framework for non-commercial clinical trials of medical devices implementing the discussed modifications (% of n = 8 KKS, % of n = 8 EC)



#### **4.4.5 Complete assimilation of sections 20 and following MPG to sections 40 and following AMG**

During the preparation of the 4<sup>th</sup> MPG Amendment the *Deutsche Bundestag* stated, that the legislator undertakes an appropriate assimilation of the provisions for medical devices to the relevant provisions concerning clinical investigations of medicinal products on behalf of patient safety [12]. The comparison of the relevant chapters concerning clinical investigations of the AMG and the MPG reveals striking differences [21]. The first crucial difference shows the title of the respective chapters: in the AMG chapter six is named “Protection of human subjects in clinical trials” whereas chapter four of the MPG is simply named “Clinical evaluation, performance evaluation, clinical investigation, performance evaluation assessment” unrelated to the protection of trial subjects. Requirements regarding the information of the person concerned by an investigator and regarding the consent given by the person concerned differ between the AMG and MPG. Section 40 subsection 2a of the AMG defines that the person concerned shall be informed of the purpose and scope of the recording and use of personal data, especially medical data, and lists special provisions concerning the use and storage of recorded data. Equivalent stipulations are still completely absent in the MPG. Section 41 AMG covers special conditions for clinical trials. According to subsection 2 thereof the AMG enables inclusion of underage patients in trials e.g. if the trial is of direct benefit to the group of patients suffering from the same disease. Requirements for inclusion of patients of legal age that are incapable of comprehending the nature, significance and implications of the clinical trial are given in subsection 3. In contrast in section 21 MPG concerning special conditions for clinical investigations, requirements are neither for the inclusion of underage patients suffering from the respective disease are, nor for the inclusion of patients of legal age, who are incapable of giving their consent, provided. According to section 21 number 2 MPG clinical trials on persons who are incapable of contracting require the consent given by the legal representative, even if the respective persons are able to comprehend the nature, significance and implications of the clinical trial. Another difference is, that according to section 20 subsection 4 number 3 MPG, clinical trials on minor persons require that clinical trials performed on adults (capable of giving informed consent) cannot be expected to produce satisfactory test results. The AMG contains a similar

requirement also for persons of legal age who are incapable of comprehending the nature, significance and implications of the clinical trial (section 41 subsection 3 number 3 AMG). This provision could be implemented in the MPG. The AMG requires, that if clinical trials are to be performed on minor persons, the minor shall be informed by an investigator, who is experienced in dealing with minors, about the trial, the risks and the benefits, taking into account the minor's age and mental maturity (section 40 subsection 4 number 3 AMG). A correspondent requirement should be implemented in the MPG. Finally section 42b AMG stipulates the publication of the results of clinical trials. An analogy is currently missing in the MPG.

To estimate the necessity of a complete assimilation of the requirements for clinical trials of medical devices and medicinal products, the KKS and ECs were asked about the opinion with regard to a complete assimilation of sections 20 and following MPG to sections 40 and following AMG. The answers were differing. About one half of the KKS (n = 8) believe a complete assimilation to be reasonable and desirable and as well as feasible. The ECs had difficulties with the question and answered partly. The majority of the ECs (six out of seven) believe a complete assimilation to be reasonable, all of five ECs that answered the question think that assimilation is desirable, one EC thinks that a complete assimilation could be realized and two ECs think that it is not feasible. One KKS noted that a complete assimilation is not possible due to the peculiarities of medical devices. Another KKS mentioned that a complete assimilation would ignore the significant differences between medicinal products and medical devices. One EC commented that a complete assimilation would result in increased certainty of the regulation and assessment of trials with medical devices. Another EC stated, that the MPG contains too many "loopholes".

#### **4.5 Comments of KKS and ECs given in the survey**

The questionnaires offered the possibility to note suggestions for improvement of the legal and regulatory framework concerning clinical investigations of medical devices. The given suggestions are presented here:

- There should be more space for the scientific quality of trials and the safety of patients and subjects. An increase of regulation via forms which have to be filled in and other measurements would not lead to the desired result.

- Protection of the patients respectively trial subjects has to be assured constantly.
- Non-commercial clinical investigations should be within the scope of the MPG without exceptional provisions. Simplified procedures according to the MPKPV should also be applicable for application for the favourable opinion from the EC.
- Reporting of serious adverse events (SAE) should be adapted to the AMG (concerning the timelines and only for SAEs with regard to the clinical trial).

#### **4.6 Aspects which were not outlined in the survey**

Some aspects concerning clinical investigations of medical devices were not outlined in the survey and cannot be discussed in detail within the scope of this master thesis but are mentioned in the following. The questionnaires did not enquire data distinguishing monocentric and multicentric and/or multinational trials. Furthermore the risk classes of the medical devices were irrelevant. The opinions and experiences concerning the safety reporting were also not objects of the survey. As presented in chapter 2.2.2 the scope of the MPSV includes medical devices which are used in clinical investigations (with authorization or waiver or according to section 23b MPG). The DoH specifies in section B number 15 that the researcher (investigator) must provide monitoring information within the research protocol especially information about any SAE. For IITs the reporting of SAEs to the EC is determined through the vote of the EC. This provision is also defined in number 4.5.4 a) of the ISO 14155. In addition according to the above mentioned number of the DoH as well as numbers 4.5.4 d) and 6.5.1 of the ISO 14155 no modifications to the research (trial) protocol may be made without consideration or approval by the EC. Another essential aspect is that “every clinical trial must be registered in a publicly accessible database before recruitment of the first subject” (section B number 19 DoH). In Germany IITs can be registered in the German Clinical Trials Register (*Deutsches Register klinischer Studien*, DRKS) or in the European Databank on Medical Devices (EUDAMED). Clinical trials requiring authorization according to the MPG need to be registered in EUDAMED since 1<sup>st</sup> May 2011. The DRKS cooperates with the Permanent Working Group of Medical Research Ethics Committees with the purpose to interlink the application for the opinion or the advice from the EC with the trial registration procedure at the DRKS [25].



## 5. Conclusion and outlook

The need for non-commercial clinical trials as IITs exists without any doubt for improvement of the public health. The Clinical Trials Directive [14] states that “non-commercial clinical trials conducted by researchers without the participation of the pharmaceuticals industry may be of great benefit of patients concerned”. The “great benefit” is independent from the fact, if the clinical trial is about a medicinal product or a medical device. Therefore it is indispensable to establish a definite legal basis for non-commercial trials as IITs with medical devices. Currently the discrimination of the legal and regulatory framework and handling of trials with medical devices in Germany bases upon the reason for the clinical investigation and the persons who take over the sponsor responsibility. Clinical trials which underlie the MPG were conducted for commercial reason, namely to gain data for the conformity assessment and therefore for the marketability, and the manufacturer takes over the sponsorship. On the other hand, IITs were performed due to medical and scientific reasons and with non-commercial, e.g. academic, sponsors. By comparison, a glance at the current legal basis for IITs of medicinal products in Germany shows that clinical trials within the scope of the AMG are closely connected to the marketing authorization procedure of medicinal products but they are not limited to it. Chapter six of the AMG concerning clinical trials is definitely applicable for all other clinical trials which were performed for other reasons than to gain data for the marketing authorization [50].

The different handling of both types of medical device trials, commercial versus non-commercial, is not justifiable. Theoretically both trial types differ with respect to the utilization of the achieved clinical data: commercial use for the conformity assessment versus medical and scientific knowledge for use within the health care. In practice this difference may become indistinct. Researchers have the duty, to make the results of their research on human subjects publicly available (section B number 30 DoH, [51]). Although the data sovereignty remains with the non-commercial sponsor, manufacturers may use clinical data from IITs to support the marketability of the respective medical device either for the conformity assessment of a new or extended intended use or for the update of the clinical evaluation (post market) to maintain marketability. One cannot refuse the manufacturer to use post market clinical data of his medical device, actually he is obliged to update regularly the clinical evaluation (Annex X number 1.1c of the MDD [11]) what he can do by

using scientific literature. Hence the data of non-commercial trials may be used commercially. For medicinal products it is considered that appropriate results of non-commercial trials may flow into marketing authorization documentation, because a rerun of the same clinical trial on human subjects (for formal reasons within the scope of a marketing authorization application) would not be ethical justifiable [2]. This should also be the case for medical devices. Clinical data which was gathered by IITs may also be used otherwise by manufacturers, for example findings within the scope of IITs could lead to modifications of the instructions for use of medical devices or may impact commercial product information such as brochures of medical devices.

In practice the distinctions between IITs and trials according to section 23b MPG are merging. As shown in chapter 4, KKS and mainly the ECs are handling both types of trials equally. There is no clear demarcation between both trial types in practice. Actually, Germany is actively contributing to the merging of both trial types. With the Federal Ministry of Education and Research (*Bundesministerium für Bildung und Forschung*, BMBF) funding measure for the BMBF's "KMU-innovative: Medical Technology" initiative, the cooperation between manufacturers, small and medium-sized enterprises in the medical technology industry, and scientific institutions, such as universities or university hospitals, shall be encouraged. The objective of the KMU-innovative scheme is "to target and promote the innovative potential of cutting-edge research at small and medium-sized enterprises", and to produce synergies between economy and science [28]. According to the notification of the BMBF concerning the initiative, the term "Medical Technology" refers to research and development of medical devices (according to Directive 2007/47/EC) and others. The notification explicitly states that clinical investigations of medical devices within the scope of a clinical evaluation for a conformity assessment procedure are not objects for funding [28]. It leaves one wondering which legal basis such trials within the scope of the funding measure have when the trials are not for a conformity assessment and are performed in cooperation of manufacturers and (academic) research institutes.

Another important factor for the use of IITs and the clinical data thereof is the Health Technology Assessment (HTA). HTA is a scientific, systematic and multidimensional assessment of health-relevant technologies (e.g. medical devices, respectively methods of examination or treatment involving medical

devices) with the aim to provide decision-makers a valid basis of information for their decisions e.g. concerning assumption of costs [35]. For this assessment clinical data of IITs e.g. about the effectiveness of medical devices under routine conditions during the post-market phase may be used.

The analyses of the current situation by means of the questionnaires and of relevant publications indicates, that it is evident, that an assured legal basis for IITs of medical devices should be provided, which eliminates the discrimination of “commercial” and “non-commercial” trials with medical devices. On the other hand the discrimination of trials with medicinal products and with medical devices should be cleared as far as possible considering the peculiarities of medical devices. One possibility to fulfill this would be, to include special provisions for clinical investigations which do not serve the conformity assessment (including non-commercial trials as IITs) into the MPG, to ensure the safety and protection of human subjects. Personally preferred is to enter clinical investigations which do not serve the conformity assessment (including non-commercial trials as IITs) in the scope of the MPG, to ensure not only the safety and protection of human subjects, but also to ensure the quality of all clinical investigations and their resulted data for whatever reason they are performed, and to provide all parties involved in clinical trials with legal certainty. Then alleviations for IITs may be allowed comparable to the handling of trials with low risk medical devices. The common practice as shown in chapter 4 reveals, that the majority of IITs would then underlie section 23b MPG and all other IITs would undergo a technical, scientific and safety-related assessment by the BfArM as well as an ethical legal assessment by an EC. In particular following main actions should be implemented for non-commercial trials into the MPG:

- Entry of a definition of the term “clinical investigation” into the MPG, including non-commercial clinical investigations
- Introduction of a mandatory authorization by the national CA (BfArM) with a simplified procedure
- Requirement of a favourable opinion by the EC
- Requirement of a (risk dependent) insurance of clinical trial subjects
- Legal facilitations could be allowed for non-commercial trials, e.g. for the submission of information and documents
- Waiver or reduction of fees for IITs

All things considered, it can be concluded that the 5<sup>th</sup> Amendment of the MPG with attention to its chapter four is inevitable.

## **6. Summary**

With the 4<sup>th</sup> Amendment of the Medical Device Act (MPG) on 21<sup>st</sup> March 2010 tightened authorization procedures for clinical investigations with medical devices were introduced targeting improved safety and protection of patients and trial subjects, improved quality of clinical investigations and of resulting clinical data. One of the most important changes was the introduction of a mandatory authorization of clinical investigations by the national competent authority (Federal Institute for Drugs and Medical Devices, BfArM). Additionally a clinical investigation can only be commenced when a favourable opinion from an ethics committee has been obtained. Also the MPG stipulates the conclusion of an insurance policy with the trial subject as beneficiary. These provisions are applicable for clinical investigations within the scope of a conformity assessment of medical devices to gain marketability. As such clinical investigations are conducted for commercial reasons they are called “commercial” trials. Clinical investigations for other reasons, such as medical or scientific questions, are not liable to the MPG neither to the Ordinance on clinical investigations of Medical Devices (MPKPV). Sponsors of such clinical investigations are not the manufacturers of medical devices but the director of a hospital or a physician for example and they are called “investigator-initiated trials” (IITs), respectively “non-commercial” trials. Analysis of the experiences and positions of two organizations (Coordination Centres for Clinical Trials, ethics committees), who have to deal with the legal and regulatory framework of IITs and of clinical investigations within the scope of conformity assessment, identified possibilities of improvement concerning the legal and regulatory framework for IITs. An assured legal basis for IITs should be provided, which eliminates the discrimination of commercial and non-commercial trials of medical devices. This should best be achieved by incorporation of clinical investigations which do not serve the conformity assessment (including non-commercial trials as IITs) in the scope of the MPG.

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Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

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Datum, Pia Helfrich

## **Annexes**

- 1 Questionnaire KKS
- 2 Cover letter KKS
- 3 Questionnaire EC
- 4 Cover letter EC
- 5 MDRA confirmation

Fragebogen zu nicht-kommerziellen klinischen Prüfungen – Medizinprodukte  
Masterarbeit – Pia Helfrich

## 1. Anzahl von klinischen Prüfungen (in den Jahren 2010 und 2011)

1.1 Bitte nennen Sie die **Anzahl aller klinischen Prüfungen** (kommerziell und nicht-kommerziell, Arzneimittel und Medizinprodukt), in denen Ihr Koordinierungszentrum in den Jahren 2010 und 2011 zentrale Aufgaben übernahm:

\_\_\_\_\_ (Anzahl)

- a) Von diesen Prüfungen waren \_\_\_\_\_ (Anzahl) **Arzneimittelstudien** (kommerziell und nicht-kommerziell)
- b) Von diesen Prüfungen waren \_\_\_\_\_ (Anzahl) **nicht-kommerzielle Arzneimittelstudien**
- c) Von diesen Prüfungen waren \_\_\_\_\_ (Anzahl) **Medizinprodukte-Prüfungen** (kommerziell und nicht-kommerziell)
- d) Von diesen Prüfungen waren \_\_\_\_\_ (Anzahl) **nicht-kommerzielle Prüfungen mit Medizinprodukten**

1.2 Wie viele klinische Prüfungen mit Medizinprodukten aus 2010 und 2011 wurden zum **Zwecke der Konformitätsbewertung (Nachweis der Verkehrsfähigkeit)** gemäß Medizinproduktegesetz (MPG) durchgeführt?

\_\_\_\_\_ (Anzahl)

- a) Von diesen Prüfungen waren \_\_\_\_\_ (Anzahl) mit **Medizinprodukten ohne CE-Kennzeichnung**
- b) Von diesen Prüfungen waren \_\_\_\_\_ (Anzahl) mit **Medizinprodukten mit CE-Kennzeichnung** (z.B. neue Zweckbestimmung / Indikation)

Fragebogen zu nicht-kommerziellen klinischen Prüfungen – Medizinprodukte  
Masterarbeit – Pia Helfrich

1.3 a) Wie viele der **nicht-kommerziellen klinischen Prüfungen** wurden mit **CE-gekennzeichneten (innerhalb ihrer Verkehrsfähigkeit)** Medizinprodukten durchgeführt?

\_\_\_\_\_ (Anzahl)

b) Gab es **nicht-kommerzielle klinischen Prüfungen** mit Medizinprodukten **ohne CE-Kennzeichnung**? Wenn ja, wie viele?

nein  ja \_\_\_\_\_ (Anzahl)

1.4 Gab es **nicht-kommerzielle klinischen Prüfungen** mit Medizinprodukten, für die beim Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) eine Genehmigung eingeholt wurde? Wenn ja, wie viele?

nein  ja \_\_\_\_\_ (Anzahl)

1.5 Wie schätzen Sie die Anzahl an klinischen Prüfungen mit Medizinprodukten nach der 4. MPG-Novelle (Einführung der zwingenden Genehmigungspflicht) ein?

- gleichbleibend
- steigend
- sinkend

1.6 a) Wie viele **Beratungen** hat Ihr Koordinierungszentrum in den Jahren 2010 und 2011 bezüglich nicht-kommerzieller klinischer Prüfungen mit Medizinprodukten durchgeführt?

\_\_\_\_\_ (Anzahl)

b) Wurde im Zuge dieser Beratungen wissenschaftlicher Rat beim BfArM eingeholt, um über die Anwendbarkeit der §§ 20ff MPG zu entscheiden? Wenn ja, in wie vielen Fällen?

nein  ja \_\_\_\_\_ (Anzahl)

c) Wie viele dieser Beratungen führten tatsächlich zu einer nicht-kommerziellen klinischen Prüfung mit Medizinprodukten?

\_\_\_\_\_ (Anzahl)

d) Bitte geben Sie an welche Probleme/Hemmnisse dazu führten, dass nach der Beratung die nicht-kommerzielle Prüfung nicht durchgeführt wurde:

- Klinische Prüfung fällt unter §§ 20ff MPG
- Finanzierung
- Regulierungsrahmen
- Sponsorenverantwortung
- Studiendurchführung
- Monitoring
- Qualitätsmanagement
- Qualifikation des Personals
- Rekrutierung von Probanden
- Ethikkommission
- Überwachungsbehörde
- Probanden-/Patientensicherheit
- Sonstige: \_\_\_\_\_ (Bitte nennen)

Fragebogen zu nicht-kommerziellen klinischen Prüfungen – Medizinprodukte  
Masterarbeit – Pia Helfrich

## 2. Durchführung der klinischen Prüfungen

2.1 Wer übernahm die **Sponsorenverantwortung** in den nicht-kommerziellen klinischen Prüfungen mit Medizinprodukten aus 2010 und 2011:

*Bitte Anzahl nennen*

Universität \_\_\_\_\_

Institut/Fakultät \_\_\_\_\_

Universitätsklinik \_\_\_\_\_

KKS \_\_\_\_\_

Prüfarzt \_\_\_\_\_

Wissenschaftler/Ingenieur \_\_\_\_\_

Sponsor-GmbH \_\_\_\_\_

Sonstige \_\_\_\_\_ *(Bitte nennen)*

2.2 Welche **Qualitätsstandards** werden im Rahmen von nicht-kommerziellen klinischen Prüfungen mit Medizinprodukten eingehalten?

ISO 14155

GCP-Verordnung

ICH-GCP-Leitlinie E6

Deklaration von Helsinki

Sonstige: \_\_\_\_\_ *(Bitte nennen)*

2.3 In welchem Umfang erfolgt das **Monitoring** von nicht-kommerziellen klinischen Prüfungen mit Medizinprodukten?

nach KKS-einheitlichen Qualitätsstandards

gemäß ICH-GCP-Leitlinie E6

vereinfachtes Monitoring

Sonstige: \_\_\_\_\_ *(Bitte nennen)*

Fragebogen zu nicht-kommerziellen klinischen Prüfungen – Medizinprodukte  
Masterarbeit – Pia Helfrich

2.4 Bitte geben Sie an in wie vielen nicht-kommerziellen klinischen Prüfungen mit Medizinprodukten in den Jahren 2010 und 2011 eine **Probandenversicherung** abgeschlossen wurde und in vielen nicht:

\_\_\_\_\_ (Anzahl) mit Probandenversicherung

\_\_\_\_\_ (Anzahl) ohne Probandenversicherung

### 3. Rechts- und Regulierungsrahmen

3.1 Wie schätzen Sie, ganz allgemein, den **derzeitigen Rechts- und Regulierungsrahmen** für nicht-kommerzielle klinische Prüfungen mit Medizinprodukten ein?

- sehr zufriedenstellend
- zufriedenstellend
- weniger zufriedenstellend
- unbefriedigend

3.2 a) Soll Ihrer Meinung nach eine **Definition der klinischen Prüfung** in das MPG aufgenommen werden, um eine klare Einordnung zu ermöglichen und Rechtssicherheit zu schaffen?

- ja
- nein
- egal

b) Wenn ja, sollte diese Definition auch nicht-kommerzielle klinische Prüfungen umfassen?

- ja
- nein
- egal



3.3 a) Sollte Ihrer Meinung nach eine **Sonderbestimmung** für klinische Prüfungen, die nicht dem Zweck der Konformitätsbewertung dienen (einschließlich nicht-kommerzielle klinische Prüfungen), in das MPG aufgenommen werden, die sicherstellt, dass die **Qualitätsstandards** nicht unterschritten werden und für die Prüfungsteilnehmer (z.B. Minderjährige und Einwilligungsunfähige) die gleichen **Schutzkriterien** gelten wie bei MPG-Studien?

- ja
- nein
- egal

c) Sollte Ihrer Meinung nach eine risikoabhängige **Probandenversicherung** bei nicht-kommerziellen klinischen Prüfungen gesetzlich vorgesehen sein?

- ja
- nein
- egal

3.4 Wenn klinische Prüfungen, die nicht dem Zweck der Konformitätsbewertung dienen (einschließlich nicht-kommerzielle klinische Prüfungen), im MPG erfasst werden, sollten dann Ihrer Meinung nach

a) **gesetzliche Erleichterungen** vorgesehen werden, z. B. bei der Vorlage von Unterlagen?

- ja
- nein
- egal

b) eine Genehmigungspflicht durch die Bundesoberbehörde eingeführt werden?

- ja
- nein
- vereinfachtes Genehmigungsverfahren (z.B. verkürzt und implizit)
- egal

3.5 Würde die Implementierung der von Ihnen in Frage 3.2, 3.3 und 3.4 genannten gesetzlichen Änderungen Ihrer Meinung nach

a) die Durchführung von nicht-kommerziellen klinische Prüfungen mit Medizinprodukten

- erleichtern
- erschweren
- gleich bleiben

a) den Schutz von Probanden und Patienten

- verbessern
- nicht verbessern

c) Wie würden Sie, ganz allgemein, den Rechts- und Regulierungsrahmen für nicht-kommerzielle klinische Prüfungen mit Medizinprodukten nach der Implementierung der von Ihnen Frage 3.2, 3.3 und 3.4 genannten gesetzlichen Änderungen einschätzen?

- sehr zufriedenstellend
- zufriedenstellend
- weniger zufriedenstellend
- unbefriedigend

3.6 Was halten Sie von einer **vollständigen Angleichung** der §§ 20 ff MPG an die §§ 40 ff AMG (Arzneimittelgesetz)?

- |               |                             |                               |
|---------------|-----------------------------|-------------------------------|
| sinnvoll      | <input type="checkbox"/> ja | <input type="checkbox"/> nein |
| wünschenswert | <input type="checkbox"/> ja | <input type="checkbox"/> nein |
| realisierbar  | <input type="checkbox"/> ja | <input type="checkbox"/> nein |

Kommentar:

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Fragebogen zu nicht-kommerziellen klinischen Prüfungen – Medizinprodukte  
Masterarbeit – Pia Helfrich

3.7 Haben Sie weitere Anmerkungen, was Ihrer Meinung nach den Rechts- und Regulierungsrahmen für nicht-kommerzielle klinische Prüfungen mit Medizinprodukten entscheidend verbessern würde?

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Ich würde mich freuen, wenn Sie mir einen Ansprechpartner für eventuelle Rückfragen nennen:

Name \_\_\_\_\_

Telefon \_\_\_\_\_

E-Mail \_\_\_\_\_

Sind Sie an der Masterarbeit oder an den Ergebnissen der Befragung interessiert?

- Masterarbeit
- Ergebnisse der Befragung

an folgende E-Mail \_\_\_\_\_

Anmerkung: Aufgrund der Abgabe- und Bewertungsfristen kann die Masterarbeit frühestens im Herbst/Winter 2012 zur Verfügung gestellt werden.

**HERZLICHEN DANK FÜR DAS AUSFÜLLEN DES FRAGEBOGENS!**

Pia Helfrich, Anschrift

**KKS**

Darmstadt, 20.02.2012

**Masterarbeit zu nicht-kommerziellen klinischen Prüfungen (IITs) mit  
Medizinprodukten**

Sehr geehrte Damen und Herren,

als Absolventin des weiterbildenden Studiengangs „Master of Drug Regulatory Affairs“ der Deutschen Gesellschaft für Regulatory Affairs und der Universität Bonn (Bestätigung anbei), wende ich mich heute mit einer Bitte an Sie.

Im Rahmen meiner Masterarbeit möchte ich den derzeitigen Rechts- und Regulierungsrahmen für **nicht-kommerzielle klinische Prüfungen (IITs) mit Medizinprodukten** sowie dessen Optimierungsmöglichkeiten untersuchen.

Ich wende mich gezielt an die Koordinierungszentren für Klinische Studien, da Sie sehr viel Erfahrung mit diesen Studien haben. Der Fragebogen enthält Fragen zu Fakten und Zahlen, zur Durchführung von IITs und zum Rechts- und Regulierungsrahmen. Dadurch kann es notwendig sein, dass mehrere Mitarbeiter Ihres KKS aufgrund ihres Fachwissens zur Beantwortung der Fragen hinzugezogen werden müssen. Ich würde mich sehr freuen, wenn Sie sich die Zeit nehmen würden, um den beiliegenden Fragebogen auszufüllen.

**Zur Erläuterung:**

Bitte beantworten Sie die Fragen aus der Sicht Ihres KKS. Alle Ihre Informationen werden unter Einhaltung des Datenschutzes vertraulich behandelt, aus der Darstellung von Ergebnissen wird kein Rückschluss auf einzelne Teilnehmer möglich sein.

**Nicht-kommerzielle klinische Prüfungen (IITs) mit Medizinprodukten im Sinne dieser Untersuchung sind Prüfungen, bei denen**

- Medizinprodukte (ausgenommen In-vitro-Diagnostika) am Menschen geprüft werden, wobei
- der Sponsor eine nicht-gewinnorientierte Person oder Einrichtung ist.

Die Angaben beziehen sich auf Prüfungen, bei denen ihr KKS im **Zeitraum vom 21.03.2010 bis Ende 2011** zentrale Aufgaben übernahm.

Ich danke Ihnen schon jetzt recht herzlich für Ihre Mitarbeit und bitte um Rücksendung des ausgefüllten Fragebogens bis zum **09.03.2012**. Ein adressierter und frankierter Rückumschlag liegt bei.

Für eventuelle Rückfragen stehe ich Ihnen natürlich gerne zur Verfügung:

Telefon:    Mobil:    E-Mail: -

Mit freundlichen Grüßen,

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Pia Helfrich

Fragebogen zu nicht-kommerziellen klinischen Prüfungen – Medizinprodukte  
Masterarbeit – Pia Helfrich

### Anzahl von klinischen Studien/Prüfungen

1.1 Bitte nennen Sie die **Anzahl aller Anträge auf Bewertung bzw. Beratung, die mit Medizinprodukten** befasst waren:

\_\_\_\_\_ (Anzahl)

a) davon waren \_\_\_\_\_ (Anzahl) **genehmigungspflichtige MPG-Studien**

b) davon waren \_\_\_\_\_ (Anzahl) **genehmigungspflichtige MPG-Studien** mit Beteiligung eines **KKS** (Koordinierungszentrum für Klinische Studien)

c) davon waren \_\_\_\_\_ (Anzahl) **nicht-genehmigungspflichtige Studien mit Medizinprodukten**

d) davon waren \_\_\_\_\_ (Anzahl) **nicht-genehmigungspflichtige Studien mit Medizinprodukten** mit Beteiligung eines **KKS**

1.2 Gab es **nicht-genehmigungspflichtige Studien** mit Medizinprodukten **ohne CE-Kennzeichnung**? Wenn ja, wie viele?

nein  ja \_\_\_\_\_ (Anzahl)

1.3 Gab es **nicht-genehmigungspflichtige Studien** mit Medizinprodukten mit einem industriellen (kommerziellen) **Sponsor** (im Sinne des MPG)? Wenn ja, wie viele?

nein  ja \_\_\_\_\_ (Anzahl)

1.4 a) Bitte geben Sie an bei wie vielen **nicht-genehmigungspflichtigen Studien** mit Medizinprodukten eine **Probanden-/Patientenversicherung** vorlag und bei wie vielen nicht:

\_\_\_\_\_ (Anzahl) mit Versicherung

\_\_\_\_\_ (Anzahl) ohne Versicherung

b) Empfehlen Sie den Abschluss einer Versicherung sofern keine vorliegt?

nein  ja  in manchen Fällen: \_\_\_\_\_

Fragebogen zu nicht-kommerziellen klinischen Prüfungen – Medizinprodukte  
Masterarbeit – Pia Helfrich

- 1.5 Wie schätzen Sie die **Anzahl** an klinischen Studien/Prüfungen mit Medizinprodukten nach der **4. MPG-Novelle** (Einführung der zwingenden Genehmigungspflicht) ein?
- gleichbleibend
  - steigend
  - sinkend

## 2. Antrag auf Beratung und Durchführung der berufsrechtlichen Beratung durch die Ethikkommission

- 2.1 Wie schätzen Sie, ganz allgemein, die **derzeitige Handhabung für die berufsrechtliche Beratung** (Antrag auf Beratung und Durchführung der Beratung) für **nicht-genehmigungspflichtige Studien** mit Medizinprodukten durch die Ethikkommissionen ein?
- sehr zufriedenstellend
  - zufriedenstellend
  - weniger zufriedenstellend
  - unbefriedigend

- 2.2 a) Sollten Ihrer Meinung nach die **Unterlagen und Antragsformulare** für den Antrag auf berufsrechtliche Beratung für **nicht-genehmigungspflichtige Studien** mit Medizinprodukten **vereinheitlicht** werden?
- ja
  - nein
  - egal
- b) Wenn ja, sollte dann der Antrag über das **DIMDI** (Deutsches Institut für Medizinische Dokumentation und Information) gestellt werden?
- ja
  - nein
  - egal

Fragebogen zu nicht-kommerziellen klinischen Prüfungen – Medizinprodukte  
Masterarbeit – Pia Helfrich

- 2.3 a) Sollten Ihrer Meinung nach die **Bewertungskriterien** für Anträge auf berufsrechtliche Beratung **vereinheitlicht** werden?
- ja
  - nein
  - egal
- b) Wenn ja, sollten dann die Bewertungskriterien an die Bewertungskriterien **für MPG-Studien** (§5 Abs. 4 MPKPV) angepasst werden?
- ja
  - nein
  - egal

- 2.4 Was halten Sie von der Einrichtung einer **bundesweit besonders qualifizierten Ethikkommission**, die für Medizinprodukte zuständig ist?
- |               |                             |                               |
|---------------|-----------------------------|-------------------------------|
| sinnvoll      | <input type="checkbox"/> ja | <input type="checkbox"/> nein |
| wünschenswert | <input type="checkbox"/> ja | <input type="checkbox"/> nein |
| realisierbar  | <input type="checkbox"/> ja | <input type="checkbox"/> nein |

Kommentar:

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### 3. Rechts- und Regulierungsrahmen

- 3.1 Wie schätzen Sie, ganz allgemein, den **derzeitigen Rechts- und Regulierungsrahmen** für nicht-kommerzielle klinische Prüfungen mit Medizinprodukten ein?
- sehr zufriedenstellend
  - zufriedenstellend
  - weniger zufriedenstellend
  - unbefriedigend

Fragebogen zu nicht-kommerziellen klinischen Prüfungen – Medizinprodukte  
Masterarbeit – Pia Helfrich

- 3.2 a) Soll Ihrer Meinung nach eine **Definition der klinischen Prüfung** in das MPG aufgenommen werden, um eine klare Einordnung zu ermöglichen und Rechtssicherheit zu schaffen?
- ja
  - nein
  - egal
- b) Wenn ja, sollte diese Definition auch nicht-kommerzielle klinische Prüfungen umfassen?
- ja
  - nein
  - egal

- 3.3 a) Sollte Ihrer Meinung nach eine **Sonderbestimmung** für klinische Prüfungen, die nicht dem Zweck der Konformitätsbewertung dienen (einschließlich nicht-kommerzielle klinische Prüfungen), in das MPG aufgenommen werden, die sicherstellt, dass die **Qualitätsstandards** nicht unterschritten werden und für die Prüfungsteilnehmer (z.B. Minderjährige und Einwilligungsunfähige) die gleichen **Schutzkriterien** gelten wie bei MPG-Studien?
- ja
  - nein
  - egal
- b) Sollte Ihrer Meinung nach eine risikoabhängige **Probandenversicherung** bei nicht-kommerziellen klinischen Prüfungen gesetzlich vorgesehen sein?
- ja
  - nein
  - egal



Fragebogen zu nicht-kommerziellen klinischen Prüfungen – Medizinprodukte  
Masterarbeit – Pia Helfrich

- 3.4 Wenn klinische Prüfungen, die nicht dem Zweck der Konformitätsbewertung dienen (einschließlich nicht-kommerzielle klinische Prüfungen), im MPG erfasst werden, sollten dann Ihrer Meinung nach
- a) **gesetzliche Erleichterungen** vorgesehen werden, z. B. bei der Vorlage von Unterlagen?
- ja
  - nein
  - egal
- b) eine **Genehmigungspflicht** durch die Bundesoberbehörde eingeführt werden?
- ja
  - nein
  - vereinfachtes Genehmigungsverfahren (z.B. verkürzt und implizit)
  - egal
- c) die **zustimmende Bewertung (anstelle einer berufsrechtlichen Beratung)** der Ethikkommission gefordert werden?
- ja
  - nein
  - egal

- 3.5 Würde die Implementierung der von Ihnen in Frage 3.2, 3.3 und 3.4 genannten gesetzlichen Änderungen Ihrer Meinung nach
- a) die Durchführung von nicht-kommerziellen klinische Prüfungen mit Medizinprodukten
- erleichtern
  - erschweren
  - gleich bleiben
- b) den Schutz von Probanden und Patienten bei nicht-kommerziellen klinischen Prüfungen
- verbessern
  - nicht verbessern
- c) Wie würden Sie, ganz allgemein, den Rechts- und Regelungsrahmen für nicht-kommerzielle klinische Prüfungen mit Medizinprodukten nach der Implementierung der von Ihnen Frage 3.2, 3.3 und 3.4 genannten gesetzlichen Änderungen einschätzen?
- sehr zufriedenstellend
  - zufriedenstellend
  - weniger zufriedenstellend
  - unbefriedigend

Fragebogen zu nicht-kommerziellen klinischen Prüfungen – Medizinprodukte  
Masterarbeit – Pia Helfrich

3.6 Was halten Sie von einer **vollständigen Angleichung** der §§ 20 ff MPG an die §§ 40 ff AMG (Arzneimittelgesetz)?

sinnvoll  ja  nein

wünschenswert  ja  nein

realisierbar  ja  nein

Kommentar:

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3.7 Haben Sie weitere Anmerkungen, was Ihrer Meinung nach den Rechts- und Regulierungsrahmen für nicht-kommerzielle klinische Prüfungen mit Medizinprodukten entscheidend verbessern würde?

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Fragebogen zu nicht-kommerziellen klinischen Prüfungen – Medizinprodukte  
Masterarbeit – Pia Helfrich

Ich würde mich freuen, wenn Sie mir einen Ansprechpartner für eventuelle Rückfragen nennen:

Name \_\_\_\_\_

Telefon \_\_\_\_\_

E-Mail \_\_\_\_\_

Sind Sie an der Masterarbeit oder an den Ergebnissen der Befragung interessiert?

- Masterarbeit
- Ergebnisse der Befragung

an folgende E-Mail \_\_\_\_\_

Anmerkung: Aufgrund der Abgabe- und Bewertungsfristen kann die Masterarbeit frühestens im Herbst/Winter 2012 zur Verfügung gestellt werden.

**HERZLICHEN DANK FÜR DAS AUSFÜLLEN DES FRAGEBOGENS!**

Pia Helfrich, Anschrift

EK

Darmstadt, 05.03.2012

## **Masterarbeit zu nicht-kommerziellen klinischen Prüfungen (IITs) mit Medizinprodukten**

Sehr geehrte Damen und Herren,

als Absolventin des weiterbildenden Studiengangs „Master of Drug Regulatory Affairs“ der Deutschen Gesellschaft für Regulatory Affairs und der Universität Bonn (Bestätigung anbei), wende ich mich heute mit einer Bitte an Sie.

Im Rahmen meiner Masterarbeit möchte ich den derzeitigen Rechts- und Regelungsrahmen für **nicht-kommerzielle klinische Prüfungen (IITs) mit Medizinprodukten** sowie dessen Optimierungsmöglichkeiten untersuchen.

Zu diesem Zweck habe ich einen Fragebogen erstellt, um den aktuellen Stand der öffentlich-rechtlichen medizinischen Ethik-Kommissionen der Universitätsklinik zu erfassen. Der Fragebogen enthält Fragen zu Fakten und Zahlen bezüglich Beratungen bzw. Bewertungen durch Ihre Ethikkommission, zur Antragstellung und Durchführung von Beratungen und zum Rechts- und Regelungsrahmen von nicht-kommerziellen klinischen Prüfungen. Ich würde mich sehr freuen, wenn Sie sich die Zeit nehmen würden, um den beiliegenden Fragebogen auszufüllen.

Bitte beantworten Sie die Fragen aus der Sicht Ihrer Ethikkommission. Alle Ihre Informationen werden unter Einhaltung des Datenschutzes vertraulich behandelt, aus der Darstellung von Ergebnissen wird kein Rückschluss auf einzelne Teilnehmer möglich sein.

### **Zur Erläuterung:**

**Nicht-kommerzielle klinische Prüfungen (IITs) mit Medizinprodukten** im Sinne dieser Untersuchung sind Prüfungen, bei denen

- Medizinprodukte (ausgenommen In-vitro-Diagnostika) am Menschen geprüft werden, wobei
- der Sponsor eine nicht-gewinnorientierte Person oder Einrichtung ist.

Bitte beziehen Sie die Angaben auf Prüfungen/Studien, bei denen Ihre Ethikkommission im **Zeitraum vom 21.03.2010 bis Ende 2011** beraten bzw. bewertet hat.

Ich danke Ihnen schon jetzt recht herzlich für Ihre Mitarbeit und bitte um Rücksendung des ausgefüllten Fragebogens bis zum **23.03.2012**. Ein adressierter und frankierter Rückumschlag liegt bei. Sollten Sie aus organisatorischen Gründen den angegebenen Abgabetermin nicht einhalten können, bitte ich Sie, mich per E-Mail zu informieren und den ausgefüllten Fragebogen zu einem späteren Zeitpunkt zurückzuschicken.

Für eventuelle Rückfragen stehe ich Ihnen natürlich gerne zur Verfügung:

Telefon:

Mobil:

E-Mail:

Mit freundlichen Grüßen

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Pia Helfrich



„Master of Drug Regulatory Affairs“ Adenauerallee 15 53111 Bonn

Frau  
Pia Helfrich  
Elisabeth-Schumacher-Str. 29  
64295 Darmstadt

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des weiterbildenden Studienganges  
**„Master of Drug Regulatory Affairs“**

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Bonn, 17.02.2012


**M.D.R.A. Studiengang - Bescheinigung**

Frau Diplom-Biologin **Pia Helfrich**  
geboren am 24. April 1974 in Annweiler am Trifels

bearbeitet im Rahmen des weiterbildenden Studiengangs „Master of Drug Regulatory Affairs“ als schriftliche Prüfungsarbeit das folgende Thema:

**„Investigator-Initiated Clinical Research on Medical Devices - Legal Basis  
and Regulatory Aspects“**  
- vorläufiger Arbeitstitel -

Mit freundlichen Grüßen



Barbara Nägel  
Dipl.-Kauffrau  
Geschäftsführerin M.D.R.A.