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Clinical Trial Agreement – Eliminate legal problems when conducting clinical trials in Germany

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Abstract

The possibilities of structuring clinical trial agreement are far reaching. Especially regarding the question, who the contract partner will be, an initial, also liability-related, positioning is possible; by either including or not including the respective examining physician in the agreement. The agreement has in large parts a clarifying function regarding the contractual obligations of both parties, as the AMG, the ICH-GCP guideline and various european regulations and directives stipulate a wide range of requirements for the performance of clinical trials. Inclusion in the agreement allows for a clear division of responsibilities and liability in the event of non-compliance with the requirements. It is also necessary that the sponsor is obligated to carry out quality assurance measures and the modalities of their implementation, including the remuneration of the time spent for this purpose.

A central question is also, who is entitled to the results of the clinical trial or to inventions based on them, whereby the ArbnErfG also must be taken into account. Whether there are at least rights of use for non-commercial purposes for the other party, should also be regulated. Also relevant is the agreement of confidentiality agreements and the answer to the question, when and to which extent publications on the results of the tests in question are permissible, in order to ensure an appropriate balance of the parties' interests.

In terms of data protection law, special attention must be paid to the question which party is the controller within the meaning of the GDPR - depending on the answer to this question, complicated and extensive regulations must be made. In addition to the regulation of the remuneration and its payment modalities, regulations regarding the liability, at least within the legal ramifications are possible and necessary. Conclusively – as always - general cancellation rights and other possibilities of terminating the agreement can be added.

The preceding explanations show how complex and comprehensive the aspects to be taken into account are. Numerous possibilities have been highlighted above, in order to provide an overview and to simplify the drafting, in hope that the contribution may aid as an orientation.

Keywords: Clinical Trial Agreement, Academic Research, IP-Rights, Liability, GDPR

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1. Introduction

Clinical trials bridge the gap between patients and laboratories by testing the safety and efficacy of drugs according to Art. 2 para 2 no. 1 REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014 on clinical trials on medicinal products for human use and repealing Directive 2001/20/EC and § 4 para. 23 sentence 1 Medicinal Products Act (AMG) or the safety or performance of medical devices according to Art. 2 no. 45 REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC. In 2021 alone, 603 license applications were submitted to the Federal Institute for Drugs and Medical Devices. (1) Furthermore, the importance of the Federal Republic of Germany in clinical trials can hardly be underestimated compared to the rest of Europe. (2) The basis for clinical trials here is the cooperation of pharmaceutical companies or medical device manufacturers, contract research organisations, medical institutions, and physicians. However, due to the public law bottleneck at the international and national levels, as well as technical aspects, this can be complicated or confusing from a legal standpoint. ICH-GCP (clause 5.9) therefore rightly requires that the essential elements of (financial)

cooperation are clearly spelled out in contracts between the parties, in particular between the research client (usually the "sponsor") and the implementer (i.e. the trial site/investigator). This contract, known as a clinical trial agreement, is the basis of today's medical research, as it authorises a hospital/a private practice/a physician to conduct study-specific trials. Which legal points should be regulated in such a clinical trial agreement is the subject of the following and closer examination. In particular, it is recommended that the subject matter of the clinical trial agreement, the duties of the parties, the remuneration and liability are clearly defined and agreed upon. It is by clearly defining the respective rights and obligations in the clinical trial agreement that any misunderstandings can be eliminated at an early stage.

Generally, studies are divided into commercial and non-commercial, although this does not affect the applicable rules. Non-commercial studies are usually not related to the market approval of a new product but aimed at improving existing treatments. (3) They are mainly initiated by university organisations or other primarily non-commercial organisations, (3) whereas commercial clinical trials are usually initiated and conducted by commercial enterprises. Regardless of this semantic distinction, the rules and regulations that apply in both cases are the same; for example, the general contractor as the so-called sponsor according to Art. 2 para 2 no. 14 REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC) or according to § 4 no. 24 Medicinal Products Act (AMG) takes responsibility for initiating, organising and funding the clinical trial. Even in the case of collaborative research with its various agreement variants, clinical trials must ultimately identify one sponsor. The contractual structure also leads to clearly defined responsibilities in the case of scientific collaboration.

In this article, the authors would like to continue the theme of the previous publication (4) by describing the structure and explaining the basic regulatory content of clinical trial agreements with trial sites. This article is intended for anyone interested in contractual relationships within clinical trials and serves as a kind of mental checklist.

2. Material and methods

A. Structure of a clinical trial agreement

A clinical trial agreement with a trial site typically consists of an agreement text and various annexes that, when combined, constitute the legally binding will of the parties involved. The text of the agreement primarily contains the legal and factual framework conditions for cooperation, while agreements on specific projects are contained in annexes. (5) In order to comply with the principle of legal certainty, it is advisable to present the final agreed text of the agreement as an executed document with a handwritten signature on each page, the so-called Initials, and to staple the individual sheets of the document as well as the annexes firmly together.

B. Agreement Text

Recitals

The Recitals is the introductory paragraph and serves to simply classify the content and clearly identify the contracting parties. In this context, the question of who is the proper contracting party in the first place should be considered. Three configurations usually come into consideration. (6) First, an agreement could be signed directly between the sponsor and the principal investigator. This is only beneficial, in our opinion, if the physician conducting the trial works in private practice. It is not advantageous to conduct a clinical trial using the material and human resources of a hospital or a group practice, (7) because the individual physician (the so-called investigator according to Art. 2 para 2 no. 15 and 16 REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC) or § 4 no. 25 sentence 1 Medicinal Products Act (AMG) is usually not free to dispose of these resources. The sponsor, as the general contractor with ultimate responsibility, may thus find himself obligated to carry out the wrong activity. Therefore, if there is an organisational unit acting as a so-called "trial site" defined in the Guideline for good clinical practice E6(R2), step 5, Number 1.59 Trial site alongside the physician actually performing the investigator's functions, this should by no means go unnoticed in the agreement. Against this background, in such cases, a tripartite agreement is sometimes concluded between the sponsor, the trial site, and the investigator. In our view, this makes sense, especially if the investigator himself is not an employee of the trial site, but merely its owner or an external, independent consultant. If, on the other hand, the investigator is an employee of the trial site, we believe that the investigator's own participation in the agreement is unnecessary. On the one hand, the investigator's rights and obligations are directly derived from German law; on the other hand, it is sufficient if the investigator simply takes note of the agreement and approves it. As the employer, the trial site gives the recruited investigator a formal order to conduct this clinical investigation on its behalf. For the investigator, this has the advantage that the trial site becomes the sole responsible contractual partner vis-à-vis the sponsor, allowing the investigator to focus solely on the research. (6) For the investigator, this has the added benefit of shielding him or her from direct contractual liability. (6) The sponsor receives a solvent counterpart, and the trial site, particularly university institutions, fulfills its obligations to its employees and investigators. Therefore, as a rule, a bilateral agreement is made exclusively between the sponsor and the trial site.

In addition, the names of the contracting parties, their representatives and their addresses shall be stated. The recitals serve a clarifying function in this context. In particular, appropriate service providers, so-called Contract Research Organisations (CROs), sometimes appear on the sponsor's side. The latter may negotiate the agreement on their own behalf or by authority, i.e. on behalf and in the name of the sponsor. What is actually meant is not always clear from the definitions of recitals,

so it is always preferable for the trial site to have a relevant *Power of Attorney* [PoA] in this case. The agreement must not contain a direct obligation of the sponsor if the CRO is acting on its own behalf. This would be an unacceptable agreement that would impose a burden on a third party. Two parties, for example, cannot legally bind themselves to agree that a third party that is not a party to the agreement must accept responsibility for certain breaches of contractual obligations. In such a case, in addition to the agreement with the trial site, a letter of guarantee from the sponsor, the so-called *Letter of Indemnification* (LoIn), must be obtained.

In addition, the parties' descriptions should be entered abbreviated so that they can be inserted in brackets after the name. Abbreviations are then used throughout the agreement and serve to avoid misunderstandings. The functions of the parties, such as "sponsor", "trial site" or "institution", and "investigator", are typical for the choice of abbreviation.

Preamble

The following preamble introduces the text of the agreement. The preamble uses the agreement's subject matter as a heading and announces that the parties named herein have entered into the following agreements. Besides that, a brief description of the parties involved is provided, indicating the precise background to the study and the purpose of the agreement. It should also be remembered that sponsors from outside the European Community must appoint according to Art. 74 and Art. 75 REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC a "legal representative" within the EU who will also take full responsibility for the sponsorship.

Subject matter of the agreement

In the next paragraph, the subject matter of the agreement must be clearly named and described. In addition, for reasons of legal certainty, clarity and materiality, this should be done in a separate section and not included in the preamble. The agreement with the trial site covers the conduct of a clinical trial in accordance with the relevant applicable clinical trial protocol and within the framework of the relevant legal regulations. (8) Unlike the UK Anti-Bribery Act and the US Foreign Corrupt Practices Act, Germany does not require separate anti-bribery clauses in agreements. However, the agreement could do with additional wording that applies alongside the provisions of the law or simply reproduces them.

The current clinical trial protocol, in turn, serves here to clarify the subject matter of the agreement. Contrary to the widespread belief that the clinical trial protocol should be kept as an annex, (6, 8-10) we recommend a different procedure in terms of administrative practice. The clinical trial protocol will most likely be changed several times during the course of the study, based on previous experience. If it is attached as an annex to the agreement, an attachment to the agreement must be created for each new version of the clinical trial protocol in which the old clinical trial protocol is replaced by the new one within the scope of the agreement. Otherwise, the contractual obligations arising from the agreement with the trial site would differ from the new clinical trial protocol's current ethically approved implementing instructions. When this is not the case, the physician must apply the current clinical trial protocol following medical and ethical guidelines, which contradicts the agreement and activates its liability provisions. Especially when collaborating with a large number of participating research centres, this would result in a large number of agreements having to be adapted by the participating administration. Therefore, in our opinion, this approach can only be recommended to those who are interested in creating as many agreements as possible, e.g. in monetary terms. Thus, from a pragmatic point of view, so-called dynamic references, in which the subject of the agreement becomes the respective valid version of the clinical trial protocol, are much better in this context. However, we should not forget to regulate the hierarchical relationship between the clinical trial protocol (which only the investigator has to sign) and the agreement (which is signed by the person in charge of the trial site). It has been proven that the agreement takes precedence in legal matters and the study protocol in medical matters.

Furthermore, against the conclusions to the contrary, (11) the definition of the type of agreement is irrelevant. Essentially, agreements with trial sites are a special case of research and development agreements that combine elements of various types of agreements listed in the German Civil Code (BGB), such as service agreements, work agreements and loan agreements. The full correspondence is not possible, because on the one hand they impose an obligation to treat patients according to the study design and on the other hand there is a specific obligation to correctly transfer the data thus obtained from medical records to the study documents (the so-called Case Report Form [CRF]). In turn, patient treatment frequently involves the use of equipment loaned from the sponsor, and the trial site/investigator, as part of the reporting obligations, must prepare reports, etc. The trial site agreement is thus a hybrid form, i.e. an agreement of its own kind or, to put it in German legal terms, a *sui generis* agreement. Therefore, the determination of the provisions applicable to the agreement under the German Civil Code (11) cannot derive directly from the assignment of an agreement to a particular type of agreement. For this reason, to be on the safe side, certain provisions from the field that the practicing lawyer considers necessary should be directly included as clauses in the agreement.

Contractual obligations

A basic component of the agreement with a trial site is an enumeration of the specific rights and obligations of the contracting parties, which are crucial for the cooperation. At this stage, it may be useful to write down the responsibilities of the sponsor as customer separately from the responsibilities of the trial site as implementer. Against the evidence, all relevant legal provisions relating to the tasks and responsibilities of the parties

involved can be included in the agreement to remind the parties concerned about them once again. (6) On the other hand, the specification of work as well as the timetable can be placed in annexes.

a. Obligations of the sponsor

According to the legal definition, the sponsor takes responsibility for initiating, organising and funding a clinical trial. The sponsor therefore bears all responsibility. Further individual services must be specified and accurately named in the agreement. For example, according to Sections 40 (para. 1) of the Medicinal Products Act (AMG), the sponsor must obtain approval of the higher federal authority and approval from the ethics committee. Additional approvals, for example from the Federal Office for Radiation Protection, must not be disregarded if X-rays are used. Furthermore, the storage of essential documents for at least 25 years is one of the tasks according to Art. 58 Regulation (EU) 536/2014 of the European Parliament and of the Council. Finally, the sponsor has to prepare all necessary test products and documents under his own responsibility and hand them over to the trial site free of charge.

b. Obligations of the trial site and the investigator

In particular, the trial site must be obliged to comply with the clinical trial protocol specified by the sponsor and the prescriptions on adverse event reporting. In the case of a two-party agreement (a sponsor and a trial site), the trial site is, of course, also responsible for the activities of the investigator employed by it. On the other hand, the investigator is responsible for the work of the qualified team and for ensuring that this work is completed in accordance with the terms of the agreement. (8) The same also applies when third-party services are used by the trial site and/or investigator. In addition, he must guide and supervise the work of the team. (8) In addition, the investigator should choose a deputy with comparable qualifications. (12) Eventually, the investigator and the trial site will not be able to use the documents, materials, and equipment provided for any purpose other than conducting the trial. A unique feature in Germany is the notification to the local health authority responsible for the trial site of the activities (or termination) of the physicians participating in the clinical trial as investigators. In the case of drug studies according to Section 67 AMG, this obligation is formulated as an obligation of the investigator. However, the possibility of transferring this obligation to the sponsor or the CRO is usually used. What appears to be extra work for the sponsor at first glance turns out to be the only practical way, as this is the only way the sponsor can ensure that these tasks are completed on time. If he does not make the notifications himself, he will have to carefully check compliance with all the local inspection authorities for his own records.

Quality assurance measures

In addition, the sponsor is obliged to carry out quality assurance activities as part of its organisational commitment to ensure that the study is conducted properly. It is necessary to follow the clinical trial protocol's obligations and to ensure the validity of the data obtained in the study. (13) Thus, access to the trial site and site files should be included in the agreement on a mandatory basis within the frame of the monitoring and auditing clause. In our experience, the missing of such clauses is regarded as a so-called *Major Finding* by auditors and inspectors, which could easily be avoided by drafting the agreement accordingly. Therefore, the agreement should include a clear description of the monitoring and communication strategy. (14)

It is also usually stipulated that audits are carried out on a jointly agreed date and only in time consistent with normal business practice, without disturbing the clinic's daily routine. (15) At least the inclusion of time consistent with normal business practice is recommended in Germany, mainly for the reasons of transparency and the aspects described in clause 3 at the end, as this is already regulated by Section 358 of the German Commercial Code (HGB). From the point of view of the trial site, this disruption to the hospital's daily routine must be compensated, at least in the case of an audit, because the staff assigned to the audit does not work with patients at that time.

In addition, the competent authorities may arrange for the inspection of the study covered by the agreement as part of the study or as part of the subsequent approval process, so provisions should also be made in this regard. The sponsor would like to be informed regularly about these without delay in order to accompany them. (15) It is important for the trial site that the obligation to transfer such an inspection (cf. Section 66 AMG) allows the inspection authority to charge the corresponding inspection fee directly to the trial site instead of a possibly distant (foreign) sponsor. The agreement with the trial site must therefore include appropriate clauses on assumption of costs. (13)

3. Research Results

In terms of clinical research findings, a distinction should be made between research results (including the raw data on which the results are based and the information storage environment) and inventions based on those results. For this purpose, it should already be taken into account during agreement negotiations whether the project realisation leads to significant innovations or not. In the context of purely agreement research conducted by a trial site for a sponsor, it is usually beyond reasonable doubt that all the results obtained, documents, data and materials belong to the sponsor. As a general contractor, the latter also bears global responsibility and must have the necessary access rights in order to be able to fulfil its information obligations towards the authorities. In this context, it should be noted that the sponsor is required by Section 42 b (2) of the AMG to report all clinical trial results to the authorities. The relevant patient records as raw data (which in turn serve as the basis for the raw data described above) are an exception to the transfer of ownership and must remain the property of the relevant hospital or practice. Otherwise, at least in Germany, the obligations of the hospital and the relevant practice to

inform patients according to Section 630a et seq. of the German Civil Code (BGB) cannot be fulfilled at all.

Another unique feature of German law must be considered when regulating (patentable) inventions by trial site employees. Employees' inventions are regulated by a separate law, the Law on Employees' Inventions (ArbnErfG). This law applies to all employers, and it cannot be overturned by contractual agreements between the employer and the employee-inventor (cf. Section 22 ArbnErfG). The trial sites must now be careful in their external relationship with the sponsor not to ignore the regulations that are imposed on them internally in relation to their employees. Rather, the trial site must harmonise the sponsor's requirements with the legal requirements; otherwise, the trial site risks falling into extensive liability traps. Sections 5 and 6 ArbnErfG require employees to report tied inventions to their employers (in this case, a trial site), which can then claim them. (16) Tied inventions or service inventions are inventions made during the term of employment which either (1) arose from the employee's work in the enterprise or in the public administration or (2) are substantially based on the experience or work of the enterprise or the public administration (§4 para. 2 ArbnErfG). Therefore, a trial site may only transfer a service invention to the sponsor after it has claimed it itself. In most cases, it will want to leave the evaluation of the payoff of the service invention to the sponsor, and will only take appropriate steps if the sponsor agrees to the takeover. When proceeding in this manner, it should be noted that the trial site's time limit for claiming an invention is only four months (Section 6(2) ArbnErfG). If the trial site does not reject the claim within this time frame, it is required to claim the service invention (Section 6(2) ArbnErfG) and pay the corresponding remuneration to the employee-inventor (cf. Section 9 ArbnErfG or Section 42 (4) ArbnErfG for inventions made by employees at a university). In this case, trial sites insist on being exempt from employee remuneration because no profit can be expected once the rights to the invention have been transferred to the sponsor. Should this happen, the employee's remuneration will be based on the university's theoretical income. (17)

On the other hand, if the investigator is at the same time employed at a university, he has a so-called negative right of disclosure under Section 42 (2) ArbnErfG, which allows him to initially remain silent about his invention. Consequently, the investigator would then have to refrain from publishing, applying for the grant of a patent or exploiting the invention. (18) However, in many cases, it is stipulated that this right is waived in relation to the sponsor, so that the service invention made in the course of the research should be reported to the employer without delay.

Universities should, at the very least, ensure that they retain free rights to use tied inventions for non-commercial purposes such as research and teaching, in accordance with the various requirements of higher education legislation or EU State aid law.

Data protection

At this point, the parties should agree that the collection, processing and publication of any data relating to an identifiable person ("Personal Data" within the meaning of Art. 4 (1) of the EU General Data Protection Regulation [GDPR] and "Health Data" within the meaning of Art. 4 (15) GDPR) can only be carried out in compliance with the relevant national and local data protection laws. It is then essential for the contractual adjustments to be made in the further course on this subject, who is to be considered as the "person responsible" within the meaning of Art. 4 (7) of the GDPR. If this responsibility lies first and foremost with the sponsor, then in accordance with Article 28 of the GDPR in relation to the collection of patient data in the context of the research, the trial site must be considered as the processor of this data, so a clause must be included or a separate agreement for data processing must be concluded. On the contrary, if the sponsor and the trial site are to be treated as joint controllers under Article 26 of the GDPR, they must enter into a so-called Joint Controller Agreement, either as an annex to the agreement or as a separate agreement. The situation becomes even more complicated if the sponsor is registered in a third country that lacks a level of data protection comparable to that of the EU and to which the trial site is contractually obligated to send the data. In this case, a corresponding data protection agreement must be concluded between the trial site and the sponsor. The EU has developed a non-negotiable template for this. (19)

Publications and Confidentiality

According to Art. 5 para. 3, every investigator is entitled to the right of exploratory and scientific activities, whereby the distribution of publications and other doctrinal disseminations is also protected. (17) However, premature publication, for example, can jeopardise the patent application and the sponsor's interest in nondisclosure, so a contractual agreement is often required. It should be noted that the dependence of the publication right on the approval of the sponsor would be immoral (17) or illegal because it would be a violation of a fundamental right protected by Section 242 of the German Civil Code. This problem is solved by a so-called review right, which requires the investigator to submit a manuscript to the sponsor prior to publication. (20) Thus, the sponsor may make comments to be taken into account within a certain period of time, provided that these do not limit the scientific character of the text. (20) It is also possible to postpone publications until the publication of the overall study or until another negotiated date (21) as well as in the event that the sponsor has to file corresponding patent applications.

Research funding, remuneration

Although the remuneration of the trial site is another obligation of the sponsor, the regulations on research funding and remuneration should always be listed separately from the performance obligations. The remuneration is based on the medical services to be provided per visit per patient in accordance with the clinical trial protocol. It is recommended that the remuneration is not paid in a lump sum at the beginning

or at the end, but that it is made conditional on the clinical trial protocol and the achievement of certain milestones. The starting point for the remuneration is the proper preparation of a CRF per patient, (22) which is controlled by the so-called monitors of the sponsor during a Source Data Verification. The fact that this monitoring takes place and must be approved by the trial site is a contractual obligation of the trial site, so that it should take into account the necessary costs for this (provision of the premises for the test, time for query resolution) as well as the time required by the respective test group members for the transfer of the source data from the patient file to the CRF in the calculation.

Furthermore, possible overhead costs, a start-up fee, payment for screening failures, costs for emergency treatment, costs for advertising measures or for unscheduled visits as well as the modalities of patient compensation/transport reimbursement should already be discussed here.

Additionally, it is advisable to include the invoice addresses, agree on invoicing dates, and set payment deadlines for speedy cost processing. It should be noted that the payment period may not exceed 30 days in form agreements (Sections 307 and 308 (1a) of the German Civil Code).

Finally, the agreement must include a so-called Disconnection Clause, which ensures that the clinic does not participate in the sponsor's profits. This means that the trial site/investigator must not receive any payment, value, offer, or value transmission to a third party, either directly or indirectly.

Agreement validity period and termination

As a rule, the agreement comes into force on the date of the last signature. The agreement ends when all obligations or rights granted have been fully performed or executed, unless terminated under other provisions of the agreement. This will primarily be the end of the study as specified in the protocol. However, other terminal time closes, such as the Close-Out Visit or the Data Base Lock, are also possible in the individual agreement. Whatever agreement is reached, it is advisable to accurately name the terminating event. Because the archiving obligation only begins after the agreement expires, this is the only way to avoid later disputes over the length of the archiving period.

Provision should be made for a mutual termination of the agreement with more details on the terms and conditions. (23) It should be noted that in Germany, each party has the right to terminate the agreement for cause. Depending on which provisions one ultimately considers applicable (or declares applicable in the agreement), this results either from §626 of the German Civil Code (BGB) or §314 German Civil Code (BGB). This right cannot be contractually waived, but it can be contractually structured, which is advisable for reasons of transparency. A breach of agreement that has not been remedied by the guilty party within a reasonable period of time after notification by the affected party, for example, may be grounds for extraordinary termination. In this context, another unique feature of the German legal system should be mentioned: a contracting party's insolvency does not automatically entitle it to terminate the agreement (cf. Sections 103 and 119 German Law of Insolvency Statute (InsO)).

What remains to be recompensed in the event of agreement termination should also be regulated. It is unclear, however, whether the provision of Section 628 German Civil Code (BGB) also applies to a *sui generis* agreement. With the exception of significant breaches of agreement, the amounts payable by the sponsor are frequently paid based on the actual services provided up to the date of termination, with any unused funds being refunded. In accordance with anti-corruption regulations, the clinic must not be given any financial advantage for services that were not rendered. (22) In this regard all data, documents and materials provided must also be returned to the sponsor, with the exception of documents to be kept by the investigator according to legal requirements.

Liability

In general, the sponsor is the central figure of a clinical trial of a medicinal product and bears overall responsibility, according to the legal definition and as the addressee of the regulations in the Medicinal Products Act and Medical Devices Act. (24) The sponsor can even be compared to a general contractor, as in the case of construction projects, which, by the way, would lead to the application and thus the ultimate responsibility under the Minimum Wage Act (MiLoG) for economically active sponsors in Germany through Section 13 MiLoG in conjunction with Section 14 of the German Employee Secondment Act (AEntG). However, each contracting party usually has an initial interest in avoiding liability for any incidents and in delimiting its area of responsibility. In order to balance interests, fair rules of responsibility are needed for the internal relationship between the sponsor and the trial site. (25) As a matter of fact, they only regulate the internal relationship between the contracting parties, as the sponsor, the sponsor's EU representative, the CRO, the trial site, the investigator, the trial product manufacturer, etc. are all jointly and severally liable from the perspective of the affected patient. Against this background, the sweeping statement that the sponsor must always accept responsibility for a damaging event (24) is not correct. The corresponding internal balance is then a matter of the liability provisions regulated in the agreement. This is the main area of regulation in this section, along with ordinary agreement breaches (for example, a sponsor not paying remuneration or a trial site not fulfilling its reporting obligations). As a rule, this means that the sponsor is liable for damages resulting from faulty clinical trial protocols or study drugs, and the trial site or a physician is liable for incorrect information or treatment of the patient. (24) Against this background, it is important to note that the sponsor's proband insurance, which is mandatory in Germany, applies only after the patient has been included in the study, i.e. after signing the declaration of consent. The prior counseling interview is therefore still a matter for the physician's standard personal liability insurance. In most cases, this section discusses the contracting parties' warranty and liability

limitations. But additional declarations of exemption also attract attention. For example, the trial site has to use the appropriate templates for the sponsor's patient consent (so-called Informed Consent Forms [ICF]). This declaration of consent legally constitutes the treatment agreement between the trial site and the patient. However, the particularity of the study is that the trial site is no longer allowed to negotiate the treatment agreement, but simply has to use the template approved by the Ethics Committee. If this template states, for example, that the patient does not incur any costs due to participation in the study, but the patient is now admitted to the trial site's emergency room due to a study-related emergency situation, the trial site is not permitted to bill the patient for the emergency measures. This is prohibited by the treatment agreement stipulated by the sponsor. Instead, the sponsor must then be obliged to absorb these costs through corresponding regulations in the agreement.

Another method of regulating liability is to refer to the relevant provisions of the applicable law, which is sometimes suggested as a better solution when applying German law. (24) However, this should be done with caution, because there are significant liability risks here, at least in the context of clinical trials conducted in accordance with the Medicinal Products Act and the Medical Devices Act. To the best of the authors' knowledge, there is no medical malpractice insurance in Germany that covers clinical trial activities, with the exception of a few individual cases. This means that the usual risk in the case of negligent misconduct is no longer insured, so an appropriate limitation of liability, both general and value-based, should be urged, at least in the case of legal advice.

Final provisions

The final provisions typically include a written request for any agreement changes, as well as a so-called Severability clause (consisting of a so-called preservation part on the one hand and a so-called replacement part on the other), which takes effect in the event of ineffective provisions. (26) In particular, in the case of cooperation with foreign parties, it should also be considered which is the applicable law for the agreement and thus also the place of jurisdiction. (27) Because the testing facilities in Germany are required to conduct the study in accordance with German regulations, they must also ensure that the agreement complies with these regulations. In purely factual terms, this is only possible if the agreement is concluded under German law. Furthermore, the differences between the Civil Law and Common Law System must be known in order to avoid misunderstandings. (28) It is recommended that the law of the trial site be declared applicable. (29) Regulations relating to the law governing the use of names may also be included.

4. Summary and Conclusion

As a result, we believe that a trial site agreement, which governs the collaboration between a study's client (the sponsor) and the contractor (the trial site/the investigator), should include a clear designation of the contracting parties in the Recitals. It should also be ensured that the correct contracting parties are represented. The preamble that follows briefly describes the parties involved as well as the exact background of the study and the agreement's objective. The implementation of the clinical study in accordance with the respective current study protocol within the framework of the relevant legal provisions is then described in detail under the clause "Subject matter of the agreement", and the subject matter of the agreement is thus clearly specified. Furthermore, the next clause of the agreement should include a list of the contracting parties' concrete rights and obligations. It is best to separate the obligations of the sponsor from those of the trial site. It should also be stated that the sponsor is required to implement quality assurance measures. These ensure that the study is carried out properly. During agreement negotiations, it is important to consider whether a project involves an invention or not, because research results differentiate between results obtained during the course of a study and inventions based on the results. Furthermore, the parties should agree that the collection, processing and publication of any personal data can only be done in compliance with the relevant national and local data protection laws. In this context, particular attention must be paid to who is the "person responsible" within the meaning of Article 4(7) of the General Data Protection Regulation. Since premature publications jeopardise the patent application, it is advisable to include a so-called review right in the agreement. The investigator would thus be obliged to provide the sponsor with a manuscript before publication. The regulations on research funding and remuneration should always be listed separately from the performance obligations. The remuneration is based on the medical service to be provided per visit per patient according to the study protocol. It makes sense to make the payment of the remuneration dependent on the study protocol and the achievement of certain milestones. In addition, a Disconnection Clause should be included to ensure that the clinic does not share in the sponsor's profits. In most cases, the agreement ends when all obligations have been fulfilled in full. However, other individual terminal time is possible, so a provision for the duration of the agreement should be included. Furthermore, the agreement should include a more detailed provision for both parties to terminate the agreement. It should also be regulated what still has to be rewarded in the event of premature termination of the agreement. Furthermore, the agreement should reflect the fair liability regulations agreed upon in the internal relationship between the sponsor and the trial site. Finally, the agreement should include a Severability Clause as well as the agreement's applicable law and place of jurisdiction.

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Conflict of Interest

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