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Agreements for the financial or material support of a non-commercial clinical trial in Germany

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Abstract

The following article outlines the essential clauses within agreements about the funding of German Universities or German clinical trial sites in order for them to conduct a non-commercial clinical trial on their own, a so-called Investigator-Initiated-Trials or Investigator-Sponsored-Trials. The authors explain the basic legal principles and clauses for such an agreement and clarify certain German Law specialities, which any funder should be aware of, if they were to fund an Investigator-Initiated-Trial in Germany. It becomes clear, that it is very important for the funding pharmaceutical company or foundation, not to be confused with the regulatory sponsor of the given clinical trial. Unclear wording in the funding agreement could lead to the actual transfer of a sponsor's responsibilities from the University or clinical trial site to the funding pharmaceutical company or foundation, with all legal and monetary risks. In order to avoid unwanted penalties and costs, it is imperative for the funding entity to draft the essential clauses carefully. This article aims to help with that.

Keywords: Clinical Trials, Contract, non-commercial clinical trials, ICH-GCP, Declaration of Helsinki, General Data Protection Regulation (DSGVO), investigator, clinical trial participants, Sponsor

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1. Introduction

Clinical trials are essential for the development and research of medicinal products since the benefit-risk assessment that is normally necessary before approval can only be carried out based on the data gathered in these trials by the various bodies entrusted with the development and approval of medicinal products. (1) First of all, the pharmaceutical company has an interest in getting approval because it intends to make a commercial profit from the medicinal products. It is not uncommon, however, that approval or its prolongation is not in sight and that the knowledge gain associated with a clinical trial does not provide a benefit that can outweigh the financial expenses of sponsoring a clinical trial.

On the other hand, patients may have a vested interest in the conduct of the clinical trial, for example, in such areas as an "off-label" use or the treatment of rare diseases. (2) Then, so-called non-commercial clinical trials (known as IIT, so-called Investigator-Initiated-Trials or IST, so-called Investigator-Sponsored-Trials) are conducted, for which the scientific gain of knowledge rather than economic interests are in the foreground. Nevertheless, such clinical trials are only very rarely conducted without the pharmaceutical industry's support. (3) Even without participation in the traditional sense, many non-commercial clinical trials are sponsored in some way by the pharmaceutical industry. (3) The following section discusses in more detail what should be considered when drafting an agreement for such financial or material support of a non-commercial clinical trial.

2. Recitals

Each agreement's generic introductory portion first names the parties, followed by their designation in the agreement's subsequent section.

In the context of every clinical trial, there must be a sponsor. There is no single fixed definition of this term. Thus, according to Section 4 (24) of the Medicinal Products Act (AMG), the sponsor is 'a natural or legal person who assumes responsibility for the commissioning, organisation and financing of a clinical trial on human beings'. By comparison, this is the narrowest definition. Furthermore, the so-called ICH-GCP Guideline (Guideline for good clinical practice

E6(R2), Step 5) is authoritative, and its Section 1.53 defines a sponsor as an individual, a company, an institution, or an organization that takes responsibility for the initiation, management, and/or financing of a clinical trial. Most commonly, it is about a medical institution, such as a hospital or a university clinic.

However, the ICH-GCP Guideline also provides for the figure of the "Sponsor-Investigator", a quasi-sponsor-investigator. As the name suggests, this possible party to an agreement combines the obligations of both the sponsor and the clinical trial site. Thus, in addition to the task of a sponsor to ensure the responsible conduct of research, the supervision of the application to the trial subject is also his duty.

If the financial support is stipulated in the agreement, the second party to the funding agreement (the pharmaceutical company) acts solely as a provider of funds and is also identified as such in the Recitals.

As in the agreement for the clinical trial itself, it is possible to include not only the trial site, which is typically the medical institution, but also the specific investigator in the agreement. If this person is already an employee of the respective trial site, it will most commonly be sufficient if investigator receives the corresponding order from there to carry out trials. In addition, investigator is thus shielded from a direct contractual claim. (4)

3. Preamble

Then, to govern any interpretation or amendment of the agreement that may be required at a later stage, it is useful to briefly describe the basic "distribution of roles" and intentions in a preamble. The sponsor, as an institution or private individual, intends to conduct a clinical trial and to assume full responsibility for the fulfilment of all those obligations that classically befall it in the conduct of clinical trials.

In return, it is stated that a pharmaceutical company acts as a funder and does not act as both the sponsor and the client of the clinical trial, as is common in the context of commercial clinical trials. It is interested in the research results but does not influence the procedure of a clinical trial.

If it has been decided to include the investigator contractually in a funding agreement, it is ensured that the principal investigator has the necessary expertise for conducting clinical trials in general and for treating patients with the very disease whose treatment is to be researched in particular.

The name of the specific clinical trial for which funding is to be contracted is then given, along with a brief description of whether the investigational medicinal product or medical device already has marketing approval, and if so, to what extent.

4. Terms

It is best to define the terms used in the agreement to avoid ambiguity. For clarity and quick reference, terms are placed outside the brackets. Furthermore, it serves the transparency of the agreement to name the corresponding definition not only when a term is used for the first time. (5) The content of the definitions according to the ICH-GCP Guideline can be used as a basis. It is not legally binding and originally only served to harmonise standards and the way clinical trials are conducted between the USA, Europe, and Japan. (6) Nevertheless, parts of it, or rather of the original version, have found their way into European guidelines, and they now serve as an international standard for the planning and conducting of trials. (7) In any case, it makes sense to define what is to be assessed as an "adverse" and as a "serious adverse event". According to Article 42 (2) of Regulation (EU) No. 536/2014, the investigator shall report all serious adverse events to the sponsor without delay, if they are not excluded from the reporting requirement according to the protocol. There is also a reporting obligation for "only" adverse events. According to Article 2 (2), no. 32(m) of that Regulation, an adverse event is "any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment". A serious adverse event is "any untoward medical occurrence which, regardless of the dose, requires either inpatient hospitalization or the prolongation of hospitalization, results in a persistent or significant disability or incapacity, results in a congenital anomaly or a birth defect, is life-threatening or results in death" (Article 2 (2), No. 33(o) Regulation (EU) No. 536/20214). Both terms can be included in the agreement.

A separate contractual regulation is agreed upon regarding the confidentiality of the information obtained during the clinical trial. A joint determination of what constitutes "confidential information" is required for its implementation. It is also necessary to determine what constitutes intellectual property rights.

5. Clinical trial descriptions and responsibilities

Following that, more detailed descriptions of the funded clinical trial are required. In addition to the clinical trial's title and registration number, additional information must be provided. (8) Declaratively, it should be mentioned that it is the objective of the parties to conduct a clinical trial that falls under the notion of non-commercial sponsors as defined in point 81 and Article 78 (4) of the Regulation (EU) No 536/2014.

The medical institution/ investigator undertakes to research following the research protocol. Although the need to include this in the annex to the agreement is understandable per se, a dynamic link to the respective valid version of the study protocol seems to be more practical. This is based on the idea that the protocol is usually modified multiple times during the clinical trial. On the one hand, the investigator is obliged to adhere to the current protocol medically, but in terms of liability, he or she is bound by an agreement that refers to the outdated protocol. A dynamic link serves to avoid this contradiction. (4)

To avoid the impression that the funder influences the concrete content of the clinical trial, it also makes sense not to refer the agreement to a protocol that is contractually defined in terms of content. (9) In the worst

case, this could lead to the consequence that the funder is considered to be the one who takes "responsibility for initiating and organising", i.e., is considered to be a sponsor. In this case, the conduct of the clinical trial would be incorrect, as the participants' consent refers to the medical institution/the investigator. (10) The problem can be solved by attaching a "study outline", which is essentially a sketch of the clinical trial. This section outlines the main points of the clinical trial as well as a detailed description of the planned implementation, as well as the scientific basis and research objective. This also gives the investigator the freedom to design a clinical trial. (10)

The funder undertakes to provide advice, support, or information about the medicinal product, but without having any influence on the clinical trial. The sponsor provides the funder with a clinical trial report, which must meet certain standards, which must also be defined. From the funder's perspective, it is obvious that a deadline for this must be specified in the agreement. He can compel the medical institution/investigator to provide him with interim reports on a regular basis and keep him updated on the clinical trial's progress. According to the safety data, both parties should be required to provide each other with all clinical trial safety information.

If desired, it should be specified at whose expense the quantity of an investigational product will be provided for the conduct of the clinical trial.

The conduct of clinical trials must comply with several defined framework conditions. To ensure that these conditions are met, it should be defined which laws and guidelines should be followed in particular. (11) The following should be listed:

- The ICH-GCP Guideline
- European Regulation (EU) No. 536/2014; Implementing Regulation (EU) 2017/556
- The applicable national law, to which concrete reference is ideally made, in Germany, for instance, the Medicinal Products Act /AMG/
- The requirements of the respective ethics authorities
- The Declaration of Helsinki as amended in 1996, which in turn is referred to in Directive 2005/28/EC in conjunction with the Implementing Regulation (EU) 2017/556.
- Regulation (EU) 2016/679 General Data Protection Regulation,
- Anti-corruption laws, if applicable
- All applicable rules of professional and business ethics

Although it is also possible just to state that all applicable laws must be followed when conducting a clinical trial. It appears to be the safer option to include a more detailed list in the agreement.

6. Duties of the institution/investigator

In a separate clause of an agreement, further obligations of the sponsor, i.e. the medical institution or the investigator, are specified: Thus, compliance with the above-mentioned laws, guidelines, etc. is a part of the sponsor's area of responsibility. The start of the clinical trial depends on the complete granting of approval by the respective competent authorities, about which the funder must also always be informed. The duty to inform also refers to planned changes in the conduct of the clinical trial. (12)

While it is specified and important for the classification of research as non-commercial that the funder has no influence over the trial's content, it is clear from his perspective that provision should be made for termination if the changes prove to be so severe as to significantly affect the original project.

The position of the sponsor, as such, should also be made clear once more to provide a clear demarcation of the legal areas of responsibility: implementation, planning, and all related activities within the scope of the clinical trial must be clearly subject to the sponsor's area of responsibility. (11) The funds made available to carry out the clinical trial may only be used for this purpose; ideally, a cost calculation can be included as an annex to the agreement. (13) The possibility of reimbursement to the funder should also be excluded. As a further specification of previously agreed information obligations, it could be agreed that if the nature of the research changes to a commercial trial, the funding organisation (the funder) and the competent authorities must be notified.

The specific primary responsible investigator must be indicated, and it must be ensured that the investigator possesses all of the required vocational qualifications, see Section 40 Clause 1 No. 5 of the Medicinal Products Act. Furthermore, the clinical trial's progress may depend on his or her participation as primary responsible investigator, as investigator agreement may be terminated if he or she leaves the institution, and investigator is the one most likely to have the most experience in the subject matter of the trial at that trial site. However, to avoid jeopardizing the clinical trial's success unnecessarily, it makes sense to first impose a duty on the institution to look for a proper successor and then, if no adequate substitute is found, to grant a right of termination. (10)

The institution/investigator also writes a study report, which the funder is not allowed to influence, in order to avoid the funder being considered the sponsor in the end. (9) Only the possibility to inspect the report in advance and to point out errors should be granted. (14)

In addition, it is the sponsor's responsibility to report any side effects.

7. The investigational medicinal product

A clause in which the funder provides the investigational medicinal product and guarantees that it was produced in accordance with applicable laws and rules can be included. Irrespective of this insurance, the pharmaceutical company, i.e. the funder, bears responsibility for the manufacture, marketing and

labelling of medicinal products anyway under Sections 13, 19, 9, 10 of the Medicinal Products Act. However, goods that have already been labelled are not necessarily distributed. The sponsor has the option of labelling the product as an investigational medicinal product. Section 13 (II) No. 1, 2 of the Medicinal Products Act is only applicable if there is a state pharmacy or a hospital pharmacy for this purpose. (15)

It must be clear who is responsible for the cost of delivering the medicine. It is permissible to deliver the medicine directly to the sponsor under Section 47 (I) No. 2(g) of the Medicinal Products Act, as long as it is labeled as such and provided free of charge as part of a clinical trial. Otherwise, only delivery to a pharmacy (hospital pharmacy) is possible. The sponsor must document the supply as well as the current inventory. The product may only be used by the sponsor to conduct a clinical trial following the established study protocol.

It should also be specified whether the funder supplies the verum and placebo or only the verum.

It is also necessary to plan for what happens to medicines that are not dispensed. Residual quantities cannot be used elsewhere. They must be disposed of in accordance with the disposal guidelines or returned to the funder. To avoid potential liability on the part of the funder, the obligation of mandatory careful documentation must be agreed upon. (16)

8. Provisions concerning intellectual property and ownership of data obtained

When determining which party has rights to the obtained results and data, the ultimate result will always be based on negotiation on a case-by-case basis. The contracting parties' interests are always to become the owners of the rights: the investigator/ medical institute as the active researcher, but also the funder, counting on service in return.

The development stage of an investigational medicinal product at the start of a clinical trial can be critical for distribution. In the case of an already approved, relatively well-developed product, it is obvious that the funder should also be granted rights to further development. (17) In general, it appears that to protect the interests, differentiation should be made based on whether the rights that have arisen are related to the sponsor's product, and in other cases, the intellectual property should be left to the sponsor who provides the research services.

The alternative configuration follows a similar pattern, distinguishing whether only one party to the agreement was involved in the discovery or whether both parties jointly have a share in it. (18)

If necessary, the investigator must make a declaration under the Employees' Inventions Law to rule out the possibility that he or she is a sole owner of any inventions' intellectual property. (17)

It is unclear whether a clause allowing the use of data for regulatory or marketing purposes is admissible, or whether it has any impact on the assessment as a non-commercial clinical trial. A never-implemented guideline stated that this must not be the case if the clinical trial is to be classified as "non-commercial".(19) According to an "Announcement of the Federal Institute for Drugs and Medical Devices (BfArM) of the Paul Ehrlich Institute (PEI) and the Federal Ministry of Health of 21 October 2009, Non-commercial Clinical Trials - Summary of Regulatory Requirements", the opposite is more likely to be inferred, which states that it is "ethically unacceptable" if a clinical trial has to be repeated only to meet the formal requirements. In any case, a corresponding clause does not seem to exclude the classification as non-commercial. (17)

9. Publications

The medical institution and the investigator are also contractually granted the right to publish the results of their research. Again, it should be remembered that the agreement of too much influence by the funder may possibly lead to his absolutely undesirable classification as a sponsor of the clinical trial, which is why it is not advisable to grant him a right to prevent publication, for example. (20) Furthermore, the impermissible restriction on the freedom of publication arising from Article 5(3) of the Basic Law of the Federal Republic of Germany (21) results in a breach of good morals and thus to the nullity of the agreement clause under Section 138(1) of the German Civil Code. (22) However, to avoid undermining the agreed-upon confidentiality rules, the possibility of publication may be subject to certain conditions.

For example, the funder may be granted the right to review the content within certain, preferably specifically defined period before publication. However, the aim of this review must not be to influence the content, but solely to prevent the publication of information that should be subject to secrecy. If such information is contained, the funder may then demand that it be removed. The need to contractually define certain terms becomes apparent here as well. To ensure the quality of the publication, an obligation can also be introduced to set a contractually defined standard at the time of publication, for example, by referring to a specific guideline such as "Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals" available from: http://www.icmje.org/recommendations. (10, 23)

10. Confidentiality rules

Furthermore, it would be in the parties' best interests to enter into bilateral confidentiality agreements. The agreement requires each party to refrain from disclosing confidential information unless prescribed by administrative regulation. In this context, any form of receiving information, whether in conversation, electronically, or in writing, should be included as far as possible to avoid gaps in regulation. In terms of content, there is, of course, room for design. For example, it could be agreed that any information exchanged will be treated as confidential or that separate marking will always be required. In this option, however, there is a risk that throughout prolonged cooperation, the regulations will be virtually forgotten or that persons who were not aware of them will not use the marking.

(24) This would have the consequence that there would be no contractual duty of confidentiality concerning information that per se requires confidentiality.

11. Data protection regulations

Data protection regulations are indispensable. The implementing parties, i.e. the investigator when he or she is included in the agreement, as well as the medical institute, in particular, are the ones who gain access to personal data of the clinical trial participants. Their responsibility should therefore be to ensure that data subjects have been fully informed about how their personal data will be used and have given their consent before the data reaches the funder or its partners, where it can be processed within certain limits. (25)

How exactly the contractual arrangement is then made depends largely on who is the "responsible person" within the meaning of Art. 4 (7) of the General Data Protection Regulation (DSGVO). This will usually be the relevant medical institution, which must then oblige its employees, including the investigator, to comply with data protection requirements. (26) The situation is different if, for example, there is joint liability within the meaning of Article 26 of the General Data Protection Regulation. In this case, a supplementary agreement must be concluded stating who has to fulfil which obligation in accordance with the Regulation, see Art. 26 part 1 of the General Data Protection Regulation. If one of the parties has its registered office in a non-EU country that does not have a level of data protection comparable to European data protection, it is necessary to conclude a data processing agreement for which an EU template exists. (4)

12. Compensation

Of central importance is, of course, the amount with which the funder wants to support the clinical trial. There are no regulatory requirements for this per se. However, it should be noted that the company wishes to be a funder rather than a sponsor of the trial. However, as stated in Art. 2(e) of Directive 2001/20/EC, the sponsorship status is also significantly associated with the financing of a clinical trial. (11) However, the concerns raised by this may be alleviated because the Directive's incorporation into the Medicinal Products Act requires taking responsibility for initiating and organising clinical trials in addition to funding, as stated in Section 2 (XXIV) of the Medicinal Products Act. (27) The exclusion of potential criminal liability under anti-bribery laws must also be considered. This would be ruled out in any case if the benefit of financial support and the reward of gaining knowledge, i.e., data and research results, were adequately balanced. (28) However, the clinical trial costs themselves should represent the maximum amount of possible funding and, in addition, a restriction should be made to the costs that are actually related to the performance of the clinical trial. (29) To avoid accusations of fraud from the start, it makes sense to include the planned cost calculation in the appendix.

In addition to the general agreement on financial support, the payment modalities must be precisely regulated. An instalment plan should be created as an annex to the agreement for this purpose, to which the agreement clause can refer.

It clearly stipulates that payments must be made in the exact amount and on the dates specified therein. Any other cash flow is excluded. Payment timing may be subject to some discretion. In the case of VAT, an arrangement must be made so that it is not included in the payment plan but is shown separately. (16)

13. Agreement duration

A contractual term is also to be agreed upon if this has not already been done.

Both parties may include termination clauses in the text of the agreement. In addition, an extraordinary termination of the agreement can also be made possible based on designated reasons for termination. Examples may include significant changes to the trial's process, risk, or benefit-risk assessment. A right to terminate should also be agreed upon if the study's hypothesis is confirmed or refuted, or if the data is proven to be unusable for any other reason. (20) In these situations, it is advisable to agree on the continued treatment of the participants concerned despite the termination of clinical trial, if discontinuation an investigational medicinal product is inadvisable in the particular case. (30)

In the event of termination, it must also be determined how the parties' intellectual property rights will be affected, whether documents must be returned, and how payments will be refunded.

14. Compensation of damage

Finally, a clause for damage compensation must be included. According to this clause, the donor, who does not want to be a sponsor and to bear the responsibility that goes with it, is largely exempted from the obligation to pay damages. The only exceptions are gross or even intentional breaches of duty in the manufacture, labelling or delivery of the drug. (9) This does justice to the fact that the responsibility for manufacturing, placing on the market and labelling of medicinal products intended for a clinical trial lies with the respective pharmaceutical company, which is usually the funder. This arises from Sections 9, 10, 13 and 19 of the Medicinal Products Act.

15. Standard contractual clauses

The place of jurisdiction and the applicable law must be specified, as is customary. A severability clause, as well as a preservation clause for unenforceable or void agreements and a replacement clause, should be included. It is also advisable to agree that changes to the agreement must be made in writing. It is possible to make stipulations in this regard to avoid ambiguity as to who the respective contact person should be.

The agreement then ends as usual with the signatures of the contracting parties.

16. Addendums

The clinical trial outline, cost planning, and payment schedule, as well as the data-sharing agreement, are all

attached to the agreement for clarity and the ability to refer to previously agreed points.

The latter, in particular, is relevant for the fulfillment of legal obligations for both contracting parties. Section 40 of the Medicinal Products Act, the GCP Directive, and Section 5.16 of the ICH GCP Guideline impose extensive notification and documentation obligations on the sponsor that can only be met if relevant information is exchanged on a regular basis.

If an investigational medicinal product is already approved, the funder must follow the regulations for approved medicinal products, while the sponsors must follow the regulations for clinical trials. (9) For serious adverse events, there is an immediate reporting obligation, Art. 42 (2) of the Regulation EU No. 536/2014. Otherwise, adverse events will be finalised later. (31) This demonstrates the importance of defining when these events occur in each case. Furthermore, a specific time frame within which the reporting obligations must be met precisely should be agreed upon. A clause requiring stricter reporting obligations if an embryo or foetus comes into contact with the medicinal product, in particular, should be included. This is based on Section VI.B.6.1.(a) of the Guideline on Good Pharmacovigilance Practices. (32)

The numerous reporting and documentation obligations demonstrate the importance of paying close attention to how the obligations are structured here.

17. Conclusion

When negotiating an agreement to fund a non-commercial clinical trial, several potentially fatal parameters must be correctly set for the desired classification of the clinical trial. Thus, it is always necessary to specify in an agreement draft that, while financial support is provided, the investigator/his or her medical institution bears primary responsibility for implementation. Otherwise, the funder company may be classified as a research sponsor, which would have far-reaching, including legally binding, consequences. As a result, it is especially important, among other things, to delineate the areas of responsibility of the parties and, for example, to leave the preparation of the study protocol to the investigator, while only basic objectives and cornerstones of the clinical trial are contractually determined. Under no circumstances should the funder be allowed to influence the content of the study design.

To avoid future ambiguities and conflicts, the funder's general responsibilities should be clearly stated, including how, when, and to what extent the agreed funding sum must be paid out. It makes sense, including from a legal standpoint, to balance the amount of funding with the expected knowledge acquisition.

The primary goal of any clinical trial is to gain scientific knowledge. It should come as no surprise that attention must also be paid to who is ultimately entitled to the data and scientific knowledge gained. It is advisable to differentiate according to whether these affect the already existing product. In the case of data sharing, confidentiality agreements are usually required to protect both parties from unwanted information reaching third parties. This also applies to later publications: Researchers' freedom to publish may not be restricted, but it may be made subject to certain conditions, for example, to provide additional safeguards to confidentiality agreements.

Depending on the constellation, compliance with data protection rules also requires additional agreements. Documentation and information obligations must also be defined so that both parties can comply with the applicable legal requirements. In other cases, the funder shall not be held liable. In the event of major changes to clinical trial progress, the unreasonableness of the clinical trial, and things like that, the mutual termination options and the resulting consequences should be finalised before the relevant final provisions are determined.

On the one hand, discretion is severely limited with regard to certain aspects, the observance of which is all the more important. On the other hand, there are still many points on which there are ample opportunities for negotiation, the most important of which have been briefly described in the previous sections to simplify the drafting of the relevant agreements.

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Conflict of interest

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