DZHK
DEUTSCHES ZENTRUM FÜR
HERZ-KREISLAUF-FORSCHUNG E.V.

Clinical studies in the DZHK

Legal and administrative implementation - information for applicants and study leader

Preamble

The DZHK is a non-profit association, in which university and non-university research institutes come together in a research alliance on the subject of cardiovascular research. In the DZHK area clinical research, scientists organise themselves into projects and working groups that receive (partial) funding from the DZHK. The association's Main Office is located in Berlin and supports the Board of Directors in carrying out the tasks of the association. The DZHK is funded by the German Federal Ministry of Education and Research (BMBF) and the German states in which it is represented. The most important goal of the DZHK is to generate new research results and bring their benefits to the patient more quickly, i.e. the "translation" of research results into clinical practice. The therapies as well as the diagnosis and prevention of cardiovascular diseases are to be improved.

For the funding of clinical *investigator initiated trials* (IIT), the DZHK has a similar funding construct as the BMBF has for the funding of "clinical studies with high relevance for patient care". The rules and regulations of GCP and the Declaration of Helsinki are applied to the situation of IIT studies in the principles and responsibilities in the conduct of clinical studies of the BMBF and widely apply analogously to clinical DZHK studies. Yet while individual projects are funded independently of each other in the case of BMBF funding, where study management or the sponsor has sole responsibility for their design, the DZHK ties its funding approval to provisions regarding the use of the clinical-scientific infrastructure, contribution to the DZHK collection of biomaterial and application of the Use and Access Policy.

With these provisions, a strategically desirable opportunity is opened up for using samples and data collected in studies multiple times beyond answering the study-specific question. This is directed by a committee of the association established for this purpose. The association thereby sees its role as a "disinterested facilitator" and, in line with its mission, would like to generate a clear added value with respect to its research funding. The DZHK does not sell data or samples.

Moreover, the standardisation/harmonisation of multiple study collections associated with the provisions (Fig. 1) contributes to ensuring the quality and homogeneity of data in every project.

To our knowledge, this construct is unprecedented in Germany.

Modul*	TORCH-DZHK1	TransitionCHF-DZHK2	VAD-DZHK3	TOMAHAWK-DZHK4	FAIR-HF2-DZHK5	APPROACH-ACS-AF-DZHK7	SMART-MI-DZHK9
Klinischer Basisdatensatz	X	X	X	X	X	X	X
Biobanking Basis Set	X	X	X	X	X	X	X
Anamnese	X	X	X	X	X	X	X
Labor	X	X	X		X	X	X
Medikation	X	X	X			X	X
6MWT	X	X	X		X		
Echokardiographie	X	X	X				
Spiroergometrie	X	X	X				
EKG	X	X	X		X		X
Herzkatheter, Hämodynamik	X	X	X	X			X
Kardiomyopathie-Diagnostik	X	X				X	
Depression	X	X				X	
MRT	X						

* Module zum Teil nur partiell in einzelnen Studien genutzt

Fig. 1: The standardisation of study collections (blue ellipses) enables the combined secondary use of samples and data beyond individual studies (red ellipse).

1. Legal and administrative implementation of the features of the DZHK construct

The responsibilities when conducting DZHK studies are fundamentally envisaged analogously to funding through the BMBF or DLR Project Management Agency. The DZHK member institution of the applicant assumes responsibility as sponsor

- for clinical studies pursuant to AMG (German Medicinal Products Act)/MPG (German Medical Devices Act) or BO (German Professional Code), and coincidentally
- for study-related “basic” biobanking (see below)

in accordance with the construct described in the funding lines for clinical DZHK studies by signing a GCP declaration (Funding document CR.4a).

In accordance with the Use and Access Policy (Section 4), the DZHK has the property and unlimited usage rights of the study’s data and samples. Study participants are informed to this effect, and their consent is obtained. Ethics committees and data protection officers agree to this provision for a DZHK study. By adopting the Use and Access Policy, the study sponsor has co-drafted this provision and backs it as well.

For conducting the study project, the respective study management are granted a protection period, during which they have an unlimited right to use the data and samples collected for the purpose of the study (U&AP Section 4(5) and 4(6)).

Samples from DZHK “basic” biobanking are not at the disposal of the study leader for study purposes and there is no time limit for these samples (U&AP Section 4(7)). This DZHK biobanking occurs within the framework of the study to the extent that all study participants must be given the opportunity to participate. The same medical study data is used for both projects. Informed consent is either joint or separate, depending on the stipulation of the central ethics committee of a study (the nationwide

working group of ethics committees meanwhile places value on obtaining consent for study participation and for biomaterial donations separately). Compilation in the system using personally identifying information is done jointly. Funds (for patient fees as well as coordination tasks) are allocated by the DZHK for this study-related DZHK biobanking (collection, management, transport) through a separate, study-related application in addition to the study application. From the point of view of funding, a study application and the study-related "basic" biobanking application are therefore administratively conceived as two separate projects, but are mutually dependent.

2. Questions and answers regarding the construct

a. Is it possible to use biological samples from DZHK "basic" biobanking and associated medical data (basic dataset and further data) before the end of the protection period of a study project for research purposes beyond the study context?

The sponsor may publish data from a study while it is being conducted; there is no known law that would prohibit this. This is the result of legal advice obtained by the DZHK Main Office in 2017 from a law office specialised in the conduct of clinical studies and applies to both study projects supervised by government authorities and study projects conducted in accordance with rules of professional conduct.

Access to the data during the conduct is necessary. A sponsor is thus obliged, for example, to monitor the development of data or appoint an appropriate committee for this purpose (DMSC).

For the DZHK to use the data and samples in this sense, however, it is important that the sponsor approves of it. Aside from the agreement of all members of the DZHK e.V. to implement funding subject to terms of use pursuant to the DZHK Use and Access Policy, the application of the Use and Access Policy in funding guidelines for *Early Clinical Studies* and *Guideline-relevant Studies* (cf. 2.2.2.) as well as in the funding contract as conditions for funding are adverted to.

In accordance with U&AP Section 4(7), the use of samples obtained from DZHK "basic" biobanking is not subject to time restrictions. Even though every sponsor of a DZHK study thus gives its prior consent, the DZHK biological samples from DZHK "basic" biobanking and associated medical data are only made available beyond the study context if the sponsor has explicitly consented to this once quality-assured data and samples exist.

b. How does the DZHK ensure that the use of biological samples from DZHK "basic" biobanking and associated medical data for research purposes beyond the study context does not compromise the study purpose or the novelty value of the study result?

The Feasibility Explorer available online is the tool for selecting collectives in order to make a usage application for data/samples at the DZHK. Applicants can use the Feasibility Explorer to obtain an overview of data and biomaterials available at the DZHK. Using different filter settings, the population can be limited and a collective can be formed, and its suitability for examining the scientific problem underlying a potential usage application can be reviewed.

Pursuant to a decision of the DZHK Board of Directors on 10.10.2017, the Feasibility Explorer accesses a selected data basis that has been released for secondary use (provided as soon as quality assurance is carried out according to DZHK-SOP-P-01 Clinical Data Review). Only cleansed data of participants with valid consent are used. The following characteristics are currently enclosed in the data basis: a clinical basic dataset comprising 42 items (see Data Catalogue), values directly derived from this (e.g. age, BMI), information about the availability of samples of basic biobanking and special information about consent status. The data basis is updated regularly.

The most important protection against the premature publication of data or release of samples that investigate potential study content in a compromising manner is that a study-specific search or allocation of data cannot be done in the Feasibility Explorer. Since factually anonymised data are provided to the data user – without information regarding in which study the data was collected –, the purpose of the study generating the data (e.g. publication 'altitude') is effectively protected at any time.

DZHK studies are academic sponsorships, in which secrecy agreements are generally not common or necessary. Moreover, the DZHK commits itself to transparency in reporting, for example, regarding recruitment status (website).

In accordance with freedom of research (Basic Law for the Federal Republic of Germany (GG) Section 5(3)), data that are of fundamental importance for the study leaders' research are exclusively at their disposal to a scientifically reasonable extent in order to avoid a parallel investigation by others of the scientific problem to be researched. The two-year protection period provided in the Use and Access Policy (U&AP Section 4(6)), the study leaders' right to veto registers/cohorts (U&AP Section 4(6)) and the right to be heard (U&AP Section 5(3)) in the case of use and access applications (in accordance with U&AP Section 4(5)) sufficiently cover these circumstances.

Compliance with the German Federal Data Protection Act (BDSG) is ensured with the patient's informed consent form. Documents that have received a positive ethics vote ensure the validity of the patient's will.

c. Does the DZHK become the co-sponsor of DZHK studies with its provisions (e.g. Use and Access Policy, SOPs, compulsory use of the DZHK infrastructure and the use of the association's technical acquisitions such as LIMS and BDMS IT systems)?

In AMG studies, only one sponsor is currently allowed in Germany (until the EU regulation takes effect). The actual performance of responsibilities is decisive for sponsorship. Who the applicant is when obtaining approval, for example, from ethics committees and BFARM, is crucial. Since these typical responsibilities (e.g. also monitoring) are evident from the project plan and included in funding, there is clearly little ground for argumentation in favour of a co-sponsorship of the DZHK or a pseudo-sponsorship of the medical institution. The issue of a pseudo-sponsorship basically occurs, if at all, when the actual sponsor is no longer financially capable of supporting the project and patient safety needs to be ensured.

Following the model of the TIMI consortium, the DZHK attaches a "DZHK number" to all study acronyms in order to gain awareness and recognition as an association for its funded projects. This publicity measure, which follows the idea of a funding number, does not generate a co-sponsorship.

d. Who is responsible for ensuring the validity of the informed consent documents?

From a regulatory perspective, ensuring that all informed consent forms are legally signed is a key responsibility of the sponsor.

In the DZHK construct, the responsibility is indeed two-sided: it lies with the study site/study doctor and the Trusted Third Party, since several sites process personally identifying data (in accordance with data protection laws, the responsibility lies with each party that collects, stores and uses data). In our construct, the task of controlling the informed consent forms can be done twofold: on the one hand by the Trusted Third Party, and on the other hand by a monitor appointed by the study management. Ideally, they cooperate.

Tracking correctness on the part of the Trusted Third Party is important to the DZHK so as to work with legal certainty when it comes to the storage, sharing and use of data. In the chapter on data protection, the patient informed consent forms contain the declaration of consent on the storage and transfer of personally identifying and medical data from the study and medical files to "the DZHK" (here, the DZHK projects Trusted Third Party and Data Handling or the scientific infrastructure are primarily meant, but furthermore also the scientists who submit use and access applications). Informed consent forms are fundamentally valid after death unless otherwise indicated.

As with the handling of consent with personally identifying data, withdrawals/study exclusions are also processed by the Trusted Third Party directly with the study site at which the case occurred. In accordance with data protection laws, involving the main study centre is not allowed if this would give them access to identifying information.

The sponsor must therefore arrange a provision on who will undertake quality assurance (ensuring the correctness of the documents) and to what extent (recommendation: e.g. in the study's cooperation agreement).

e. Who is responsible for monitoring?

Fundamentally, the overall responsibility for conducting a clinical trial lies sponsor, who can delegate its tasks, but not its responsibility. The sponsor is thus responsible for correctly selecting and also supervising the person/institution to whom it assigned any tasks.

The sponsor (who usually delegates these tasks to study management) has the right to assign individuals bound to confidentiality pursuant to the patient's informed consent form for audits and monitoring. In doing so, the sponsor may not have access to personally identifying information, but a defined representative of the sponsor (monitor or auditor) has access; yet not, for example, the coordinator or

study leader (data protection laws; this does not distinguish between the BO and AMG). The relationship between sponsor and study leader is best established with an internal delegation letter: the study leader ultimately acts as an employee on behalf of the sponsor (is thereby not independent).

A right to carry out audits at the enrolling study site must be contractually agreed upon in the study site contract.

The patient consents to a monitor accessing his data: The consent form regarding data protection includes the statement: “I agree that my original medical documents [medical files] at the hospital may be accessed by an authorised representative of the study within the scope of so-called monitoring [ ].” This will be performed by an independent, commissioned individual (the monitor) who is obliged to maintain confidentiality in accordance with the respective informed consent form. For quality assurance, the sponsor will normally involve a KKS for this purpose, among others (as stipulated in the DZHK funding guideline).

f. Who signs the GCP declaration?

That the sponsor assumes responsibility is declared to the DZHK e.V. with the signing of the form “Commitment to the Guideline for Good Clinical Practice (ICH-GCP)” (funding document CR.4a). The signature of the legal representative of the medical institution that is assuming sponsorship of the study and the signature of the coordinating investigator (or the head of clinical trial) as acknowledgement are required. The legally signed form must be submitted to the Funding Management Department of the DZHK before the funding contract for the study can be concluded. If the funding management department finds uncertainties regarding the signature rules of the medical institution, the power of representation must be disclosed.

g. Who is the data protection officer of the DZHK e.V.?

Infrastructure data protection issues (Data Handling unit in Göttingen, Trusted Third Party in Greifswald) and data protection issues of the main study centres are currently resolved with the responsible DZHK member institutions, their respective data protection officers and the respective state data protection officers. There is no data protection officer for the DZHK association. The DZHK will have a specialist in data protection law review whether this is useful and satisfactory long-term.

h. Can data be transferred to third parties for the conduct of study services?

For BO studies, it is conceivable to have a (e.g. telephone) follow-up performed by a third party (agent) because of organisational benefits. For this, the agent could, if necessary, have access to the personally identifying information and medical information of the participant. Requirements for this are that the patient was adequately informed and explicitly consented to the transfer of his data as well as the consent of the competent ethics committee and, where applicable, the data protection officer of the sponsor is available.

3. Valid documents

- BMBF/DLR "Principles and Responsibilities in the Conduct of Clinical Studies" of 24.04.2013 / 20.11.2015 in adaptation for the DZHK
- Sponsor's statement on the commitment to the Guideline for Good Clinical Practice (ICH-GCP) (CR.4b)
- DZHK Use and Access Policy V1.0 Version 08/2014 with enclosures: Template for Use and Access Application/Data Use Notification, Template for Material Transfer Agreement, Flowchart Review Process
- Ethics Concept of the DZHK for the Area Clin. Research V2.0 Version 02/2016 with enclosure: Template Informed Consent Forms
- Method Description and Data Protection Concept of the Central Data Management of the DZHK in the Area Clin. Research V1.2 of 24.03.2014
- Recording instructions for 42 clinical items as basic information about every participant in Central Data Management DZHK-SOP-K-01 Basic Dataset V1.0.
- Factsheet Biobanking V1.1
- Funding guidelines Early Clinical Studies (CR.1-A), Guideline-relevant Studies (CR.1-B) Version December 2017
- As well as all updates of the stated documents
- As well as all further information available on the DZHK website https://dzhk.de/en/research/clinical-research/