Register for long-term observation of participants in cancer studies

GBG 71

Version 2.0

07.11.2025

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CONFIDENTIAL

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APPROVAL SIGNATURES

Register for long-term observation of study participants

Study#: GBG 71

Protocol Version: 2.0

Protocol Version Date: 07.11.2025

I, the undersigned, have read this protocol and confirm that to the best of my knowledge it accurately describes the planned conduct of the study.

Signature: Date:

Sibylle Loibl (Nov 7, 2025 16:44:53 GMT+1)

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Prof. Dr. med. Sibylle Loibl,
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Rationale

Over the past 45 years, more than 70,000 patients with breast cancer (BC) have been included in GBG studies. These prospective clinical trials consistently evaluate long-term outcomes such as recurrences, deaths, and late-onset toxicities as primary or secondary objectives. However, for administrative and financial reasons, follow-up is typically limited to 1–5 years. Moreover, clinical trials increasingly demand significant effort from trial sites yet are challenged by limited resources[1]. Recent publications have revealed that, in early BC setting, regular follow-up duration in clinical trials is not sufficient to capture late events, especially in Estrogen Receptor (ER)-positive disease[2,3]. This is caused by the intrinsic characteristics of the disease and the increasing complexity of adjuvant endocrine therapies, as well as enhanced treatment options in the metastatic setting[4,5,6].

Unlike many other diseases, breast cancer recurs at a significant rate (approximately 2-4% per year) even 20 years after initial treatment. The effects of therapy are often only evident after a long period of observation, particularly in patients with ER-positive tumors[2,3]. For example, the improvement in survival rates achieved through breast radiation therapy only becomes apparent after 15 years. This underlines the importance of long-term follow-up to fully capture treatment efficacy and late side effects. The relevance of long-term observation has been repeatedly emphasized by international research groups, such as the Early Breast Cancer Trialists' Collaborative Group. Although the long-term course with the collection of data on recurrences, deaths, and late toxicities is the primary or at least secondary endpoint in all prospective treatment studies conducted by the GBG, follow-up observation is usually limited to 1-5 years for administrative reasons.

National and international experience shows that contact with study participants is often lost during the follow-up phase of a clinical trial without them expressly withdrawing their consent. Due to the decentralized healthcare structure and increasing staff and financial constraints, primary care clinics are no longer able to fulfill the task of long-term follow-up care. This is also not considered to be the responsibility of the cost bearers.

In this respect, other options must be sought to enable long-term observation. Breast cancer patients show above-average compliance with medical and therapeutic measures. In addition, they have a very high level of knowledge about the course of this disease and their individual medical history. A large proportion of patients keep their own patient files, in which they collect all findings relating to their disease, because the highly interdisciplinary nature

of breast cancer means that patients are repeatedly required to report their medical history to new doctors themselves. In this respect, it seems possible to obtain the information necessary for long-term observation through self-reporting by patients.

Evidence also supports the integration of register data with clinical trial results. For example, Shi et al. demonstrated a high level of concordance between cancer register data and randomized trial data, including a 99.0% agreement in disease-free status, thereby indicating the potential of register-based long-term follow-up as a complementary tool to collect data after regular follow up in randomized trials[7]. There have been several initiatives calling for pragmatic clinical trials that put patient engagement in the center, address clinically relevant questions in broad, representative populations and are embedded in clinical practice. Such trials may offer a valuable framework for addressing the limitations of traditional explanatory trials, particularly in oncology where long-term, patient-centric outcomes are essential. These trials are designed to reflect routine clinical practice, using broad eligibility criteria, decentralized settings, and streamlined data collection methods, making them well-suited for long-term follow-up and real-world evidence generation[8,9,10].

To address these gaps, the GBG established a multicenter, non-interventional, long-term cancer register study to follow-up former clinical trial participants collecting patient-reported outcomes and other relevant data beyond the end of the original study protocol. By leveraging patient engagement and longitudinal data collection, this initiative aims to generate real-world evidence for improved clinical decision-making.

Objectives and endpoints of the survey

The primary objective of the register study is to collect long-term follow up data from clinical cancer trial participants beyond the end of study to evaluate long-term survival outcomes. These outcomes will be evaluated with the following endpoints:

- Disease-free survival (DFS) which is defined as the time from randomization to the first occurrence of local (invasive or DCIS) or regional recurrence of the original cancer, contralateral breast cancer (invasive or DCIS) distant recurrence, diagnosis of a second primary invasive cancer (other than the index cancer type), or death from any cause, whichever occurs first.
- Invasive disease-free survival (iDFS) which is defined as the time from randomization to the first occurrence of any invasive local or regional recurrence, invasive contralateral breast cancer, distant recurrence, diagnosis of an invasive second

primary cancer (other than the index cancer type), or death from any cause, whichever occurs first.

- Distant disease-free survival (DDFS) is defined as the time from randomization to the first occurrence of distant recurrence, diagnosis of a second primary invasive cancer (other than the index cancer type), or death from any cause, whichever occurs first.
- Locoregional invasive recurrences-free interval (LRRFI) is defined as the time from randomization to the first occurrence of any invasive loco-regional recurrence (including recurrence in the primary tumor site or associated regional lymph nodes), or any invasive contralateral breast cancer, whichever occurs first; distant recurrence, invasive second primary cancer (other than the index cancer type), or death from any cause are considered competing events.
- Overall survival (OS) is defined as the time from randomization to death of any cause.
- Other study-specific or adapted long-term survival endpoints may be defined in the respective study protocol or statistical analysis plan (SAP), tailored to the study population and tumor type.

Secondary Endpoints may include:

- Long-term side-effects associated with study therapy.
- Subsequent anti-cancer therapies administered after study completion.
- Pregnancies occurring after study participation and evaluate their outcomes.
- Quality of life (QoL) post-study.
- Additional study-specific long-term outcomes as defined in the respective study protocol or statistical analysis plan (SAP), tailored to the study population and tumor type.

Population

Investigators should consider each of the eligibility criteria outlined below when selecting a patient for this register study. In general, participation in a clinical cancer trial thereby meeting the inclusion criteria of the clinical trial where patients were initially enrolled is the essential prerequisite for enrolment into this register study. Further inclusion criteria for participating in the Register for long-term observation are listed below. In connection with participating in clinical cancer trials, patients will be offered to participate in the Register for long-term observation of study participants. Patients may participate in the study regardless of their native language, provided that understanding of the study's purpose is ensured and unequivocal written informed consent can be obtained. It is aimed at including a maximum number of former trial participants in a continuous manner. Therefore, the number of participants enrolled in this register study is dependent on the number of participants in the

initial cancer trials. Because the register study will be analyzed in a descriptive manner, a sample size calculation defining a minimum of participants required is not applicable. An amount of more than 10.000 participants is expected.

Inclusion Criteria

Patients will be eligible for study participation only if they comply with the following criteria:

1. Participation in a cancer clinical trial.
2. 18 years of age or older
3. Provision of written informed consent

Exclusion Criteria

1. History of significant neurological or psychiatric disorders or any other condition that would prohibit the understanding of the study purpose and giving informed consent.

Finance and Insurance

The study will be funded by GBG Forschungs GmbH.

Since there are no study-specific interventions or on-site visits in this study, insurance is not applicable.

Expense Allowance

There will be no expense allowance paid to participants.

Methods

Study Overview

This is a prospective and retrospective, multicenter, register study with a non-interventional design. The study will collect clinical data on long-term patient reported outcomes and further parameters, including but not limited to, pregnancies of former study participants of prospective cancer clinical trials. It is aimed at including a maximum number of former trial participants in a continuous manner. A definite timepoint for the end of this register study is not planned and dependent on the end of the last clinical cancer with participants to be enrolled in self-reporting.

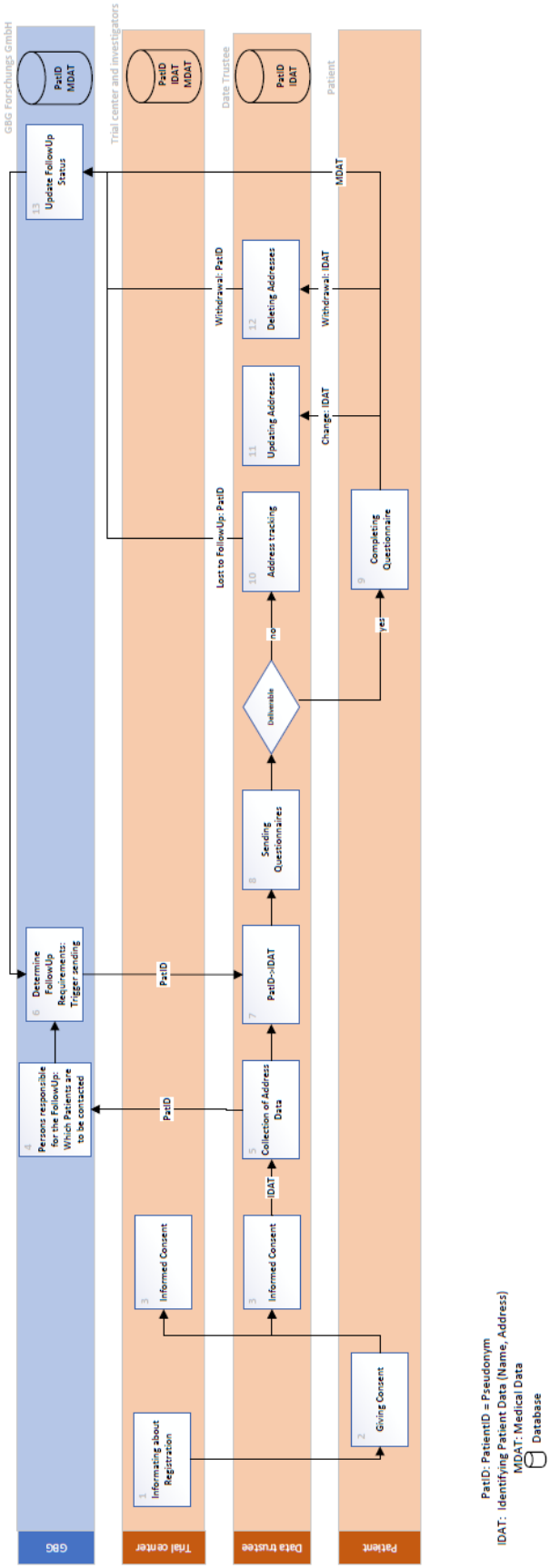
The register study is designed to enable the systematic collection of self-reported long-term follow-up data from patients previously enrolled in clinical cancer trials. The task of maintaining contact with former patients is to be transferred from the trial centers to an independent central data trustee. The process is structured to ensure compliance with data protection regulations and to maintain data integrity throughout the follow-up period. The workflow includes the following key steps:

1. Patients will be informed about the register study by their treating physician at the study site, and written informed consent for data collection will be obtained.
2. Upon consent, identifying patient data (IDAT), such as name and contact details, are collected and linked to a pseudonymized patient identifier (PatID) which is performed by the site and shared with the data trustee. This enables secure and compliant communication with participants while protecting their identity. Only the data trustee, who is legally and organizationally independent from the GBG, has access to IDAT and is responsible for it.
3. Follow-up questionnaires are sent to participants via trustee to collect relevant medical and quality-of-life data. Completed pseudonymized questionnaires are returned and used to update the patient's follow-up status and medical data (MDAT) in the GBG Electronic Data Capture (EDC) system.
4. If a patient cannot be reached by trustee, contact tracking procedures are initiated. Updated contact details are recorded and outdated, or incorrect data are deleted by trustee. Participants who remain unreachable are classified as lost to follow-up by trustee.

The inclusion and registration may occur immediately after consent is obtained.

Data flow is coordinated between the trial siter, data trustee, and GBG Forschungs GmbH. Questionnaires may be sent in print or in electronic form.

Participants may authorize a relative or acquaintance to provide information about their state of health, who will then be contacted in place of the participant. Participants may withdraw their consent at any time.


GBG Forschungs GmbH
Trial center and investigators
Data Trustee
Patient
PatID MDAT
PatID IDAT MDAT
PatID IDAT
13 Update FollowUp Status
12 Deleting Addresses
11 Updating Addresses
10 Address tracking
9 Completing Questionnaire
8 Sending Questionnaires
7 PatID->IDAT
6 Determine FollowUp Requirements: Trigger sending
5 Collection of Address Data
4 Persons responsible for the FollowUp: Which Patients are to be contacted
3 Informed Consent
3 Informed Consent
2 Giving Consent
1 Informating about Registration
MDAT
Withdrawal: PatID
Withdrawal: IDAT
Change: IDAT
Lost to FollowUp: PatID
PatID
PatID
IDAT
Deliverable
no
yes
GBG
Trial center
Data trustee
Patient
PatID: PatientID = Pseudonym
IDAT: Identifying Patient Data (Name, Address)
MDAT: Medical Data
Database

Risk Benefit Assessment

As described above, long-term courses with the collection of data on recurrences, deaths and toxicities are primary or at least secondary endpoints in most prospective clinical cancer treatment trials. Yet follow-up observation is usually limited to 1-5 years for administrative reasons. Moreover, clinical information on i.e. late recurrences, quality of life data years after treatment and following pregnancies (as an indicator for fertility) are also extremely valuable for counseling patients when deciding on neoadjuvant or adjuvant treatments. Also, local therapy trials investigating treatment like radiotherapy or surgical procedures may have impact on long-term oncologic and quality of life outcomes[11,12]. It is a dilemma that, particularly for local therapy studies, there is often insufficient funding available to collect this long-term data. The collection of this long-term data as part of a pragmatic long-term register study based on self-reported information provides future patients and their treating physicians with valuable consultation content that would otherwise not be available at all. In this respect, the findings from the register study have the potential to have a direct impact on medical care. As there are no study specific procedures or investigations or on-site visits there is no potential harm in participating. Even if individual study participants do not personally benefit from participating in the study, the benefits of register study participation clearly outweigh the risk of participating. As the information that is stored and analyzed within the register study is reported by the respective participants themselves, additional individual medical information is not generated within the register study. Participation in the register study continues until withdrawal of consent, death or lost to follow up. The register study may be prematurely terminated in case of lower patient accrual or lower questionnaire return rate for a longer period that does not allow reliable analysis of the study's objectives.

Statistical Methods

This is an observational study for collection of long-term outcome parameters of former study participants. Analyses will be performed in a descriptive manner.

Baseline characteristics, short-time efficacy, toxicity parameter and follow-up data already collected in the clinical trials will be merged with the register study data, to assess their impact on long-term patient reported outcomes.

Data protection aspects

Responsibility

GBG Forschungs GmbH is responsible for data processing.

Pseudonymization

In order to ensure the data protection rights of participants, identifying contact details are kept separate from pseudonymized medical data by a data trustee. Each participating patient is assigned a unique GBG reference number (PatID), as part of their inclusion in any GBG clinical trial. Instead of the true patient identity, the pseudonym is used for all communication purposes between the trial site and the GBG. Only the data trustee, who is legally and organizationally independent of the GBG, will link identifying patient data (IDAT), such as name and contact details, to this register study PatID and thereby has access to and responsibility for the contact details. A qualified data trustee will be engaged under a contractual agreement to manage IDAT in accordance with applicable data protection laws, including the GDPR. The trustee will be selected based on professional standards and data security requirements.
The medical data relevant to the study is stored only in pseudonymized form and only at GBG.

User Access Control

A role and rights concept for data processing and storage ensures data protection and integrity. Access control to systems and applications is intended to ensure that access to data and information is always limited to the need-to-know principle. Those authorized to use a data processing system can only access the data subject to their access authorization.

Data collected

The names and contact details of the participants in the long-term observation study will be recorded by the data trustee. At the participant's request, the name and contact details of a contact person of her/his choice can also be recorded, who will be contacted instead and provided with information about the participant's state of health (see "Change of address"

form). Only the data trustee has access to this data. Data will be stored until withdrawal of consent.
The participants are asked to provide information about their health status with regard to their long-term outcomes of their cancer disease and associated medical data. Among other questions they are asked about relevant medical follow up information related to the cancer diagnosis or cancer treatment received e.g. any recurrences or distant metastases,any new cancers or pregnancies (see the "Medical data" form).

Data transfers

The transfer of data collected in the register study is currently not planned, yet data transfer across national borders for the purpose of analysis within the intended scope cannot be ruled out. In such cases, it will be ensured that any transfer of personal data, including pseudonymized medical data, to countries outside the European Union or European Economic Area complies with the applicable data protection regulations. Appropriate safeguards will be implemented to ensure an adequate level of data protection in the receiving country, in line with the requirements of the General Data Protection Regulation (GDPR).

Administrative Execution

Patient Informed Consent

The legal basis for data collection is § 6 Abs. 1 lit. a DSGVO. Prior to the inclusion in the register study, the patient is informed about the nature of the data collected and the intended purpose. Informed consent form will be obtained for each participant. No undue influence, including that of a financial nature, shall be exerted on patients to participate in the register study. Moreover, the patient may, without any resulting detriment and without having to provide any justification, withdraw from the register study at any time by revoking his/her informed consent. Upon withdrawal of consent or wish to end participation, IDAT data stored at the data trustee will be deleted and thereby data will be anonymized. Moreover, no further data will be collected.

Ethics and Regulatory Considerations

The initial protocol (Version 1.3, 16.02.2009) and the informed consent form will be submitted for review by the responsible ethics committee. The study will only be started in case the committee does not raise concerns against the study.

Declaration of Helsinki

This study is to be performed in accordance with the Declaration of Helsinki.

Publication

The results of the register study will be published according to GBG SOPs.

Miscellaneous

Telemedicine

Optionally, the questionnaires may be sent out to participants in electronic form.

Biomaterials

Not applicable. Collection of biomaterials is not planned within the register study.

Use of Radiation

Not applicable. No Radiation will be applied within the register study.

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