UNIKLINIK KÖLN

# Study Protocol

FUNGISCOPE
GLOBAL FUNGAL INFECTION REGISTRY

## A Global Fungal Infection Registry

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# 1. Introduction

Invasive fungal diseases (IFD) remain a challenging problem with increasing incidence rates worldwideand significant regional and local variations. Although the etiology of this epidemiological development is not fully understood, the widening of indications for intensive chemotherapy and the growing number of transplantations seems to be important contributing factors.

Patients with hematological malignancies and profound, prolonged neutropenia (defined as <500 cells/µl >10 consecutive days), solid organ transplant recipients and otherwise immunocompromised patients are at a high risk of contracting IFD [1]. Apart from *Candida albicans and C. glabrata*, *Aspergillus fumigatus* and *Cryptococcus neoformans*, which are the most frequent causative pathogens for IFD, the so-called "emerging fungi" are gaining importance, for example *C. auris*, *A. terreus*, Mucorales, *Fusarium* and other less common fungi such as*Acremonium* spp.*, Lomentospora* spp., *Penicillium* spp.*, Paecilomyces* spp.*, Scedosporium* spp.and *Trichoderma* spp. [2-7]. Intrinsic resistance of many emerging fungi to approved antifungals remains a therapeutic challenge and has been associated with treatment failure and thus, high mortality rates [8-10].

Therapeutic standards have been established for aspergillosis [11] and cryptococcosis [12], and detailed guidelines for diagnosis and management of *Candida*-related diseases have been developed in 2012 [13-18]. In 2014 an international team of experts, including members of EFISG-ESCMID and ECMM, developed clinical guidelines for the diagnosis and management of rare and emerging fungi [19] covering rare hyalohyphomycosis [20], invasive yeast infections [21], mucormycosis [22], and systemic phaeohyphomycosis [23]. Current recommendations largely rely on a collection of case series, single-center studies and expert opinions [24]. In order to establish evidence-based treatment recommendations analyses of a comprehensive cohort is required.

# 2. Objectives

The objective of this study is to overcome the lack of knowledge on epidemiology, clinical course, and molecular characteristics of invasive infections due to emerging

fungal pathogens, in order to develop evidence-based diagnostic and therapeutic recommendations. The specific objectives are:

### 1. Epidemiology

- To define risk groups
- To describe the global incidence of emerging fungal infections
- To monitor trends over time

### 2. Clinical course

- To describe the clinical pattern of disease
- To document diagnostic procedures performed for confirmation of diagnosis
- To describe first-line and salvage treatment regimens applied, their efficacy and impact on patient survival

### 3. Recommendations for diagnosis and treatment

- To inform consensus guidelines
- To develop clinical screening procedures
- To identify treatment approaches for first-line and salvage therapy

## 3. Study Period

Start date of study: January 1st, 2003

Start date of amendment for protocol 7.0: March 10th, 2026

End date: not determined

## 4. Patient Population

### 4.1 Inclusion criteria

- Cultural, histopathological, antigen or DNA evidence of an invasive fungal infection

### 4.2 Exclusion criteria

- Infections due to endemic fungi, e.g., *Coccidioides* or *Histoplasma*

- Colonization or other non-invasive infection, including superficial skin infections irrespective of causative pathogen

Within the FungiScope registry, patients retrospectively diagnosed with a proven or probable IFD within the past 20 years prior to the day of the signed agreement with the respective study siteare enrolled retrospectively.

### 4.3 Specified patient populations within defined sub-projects

In order to address specific questions in the context of evolving epidemiology and increasing data availability, targeted sub-studies may be conducted within the framework of FungiScope®.

These sub-studies may focus on specified patient populations and utilize purpose-specific electronic Case report forms (eCRFs) with detailed information provided in dedicated study synopses. All sub-studies adhere to the FungiScope® umbrella study objectives and the defined ethical considerations and data privacy protection regulations provided under Appendix 1 - Ethical Considerations and Data Privacy Protection.

## 5. Case Report Form

The study protocol, the full electronic Case Report Form (eCRF) as portable document file, the ethics committee´s approval of the study, the specified sub-study synopses including the respective, targeted eCRFs and information on defined sub-studies will be available for download on the following website:

www.fungiscope.net..

The following clinical information of each eligible patient will be collected:

1 Epidemiological data: country where initial diagnosis of IFD was made, institution
2 Demographic data: age-group, weight, height, sex, ethnicity
3 Data of fungal infection: year of infection, species identification, site of infection, co-infections with other fungi, clinical characteristics upon diagnosis, antifungal susceptibility testing

4 Data of concomitant diseases: diagnosis, duration of disease, current status and treatment
5 Potential risk factors for developing fungal infection: immunosuppressive therapy, chemotherapy, biopharmaceuticals, use of corticosteroids, radiotherapy, solid organ or human stem cell transplantation, chronic pulmonary disease, diabetes mellitus, renal failure and dialysis, trauma and major surgery, HIV/AIDS, neutropenia, mucositis, and other risk factors
6 Diagnostic measures and findings (CT, MRI, endoscopy, ultrasound, micro- and molecular biological analyses, pharmacological analyses)
7 Antifungal prophylaxis and treatment: drug, route of administration, duration, side effects, main reason for stop
8 Treatment response at day 14, 28, 42, 84 and status at the last follow-up
9 Treatment outcomes

Participants wishing to contribute cases will receive individual account details for login. Account details are requested via email from the FungiScope study team. Full name, institution and email address have to be supplied.

Data entry is carried out via an interactive macro created by the software that can be accessed via any internet browser. All documented data are automatically collected in a database. Detailed information on the software platforms and data protection regulations are provided under Appendix 1.

## 6. Data Analysis

Data will be analyzed using descriptive statistical methods using IBM SPSS™, Stata, and R software.

## 7. Specimen Collection and Laboratory-Based Research

In addition to clinical data, partners can contribute clinical fungal isolates for formal species identification and susceptibility testing done by the FungiScope central laboratory in Cologne, Germany. Isolates will be stored and may bemade available for research projects after written consent by the contributor of the respective isolate(s). The following laboratory-based research will be conducted:

1 Strain identification by micro- and macromorphology, culture and by using molecular biological methods,
2 In vitro susceptibility testing according to EUCAST and CLSI [25]
3 Sequencing for genetic alterations associated with antifungal resistance (e.g. *cyp51A* and others)

## 8. Budgetary Information

For evaluable patient documentations entered by the participating center a compensation of € 100 incl. VAT per valid case will be paid. If the documentation workload is too high, centers are encouraged to ask the study office for personnel to be sent to the site. For isolates made available to the central laboratory an additional S&P compensation of € 50 will be paid.

## 9. Authorship Policy

Authorship will be restricted to those centers contributing clinical/microbiological data or translational work. For each contributing center, there will be authorship positions available. The individual input relative to the overall project will be reflected in the order of the authors. An additional collaborator list may be included to appropriately highlight the respective contribution of each partner.

## 10. Contact Information

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# Appendix 1 - Ethical Considerations and Data Privacy Protection

The eCRF is currently hosted by two separate platforms, the GDPR compliant survey software EFS Survey™ (clinicalsurveys.net, TIVIAN XI) and the GDPR and HIPAA compliant platform Carelane (https://www.carelane.io/). There will be a transition period during which both platforms will operate simultaneously until all activities in the platform TIVIAN will be discontinued by the end of 2032.

## 1. Documentation of Clinical Data

Only data created during standard medical care will be documented in the CRF. There is no interventional aspect to this study. Therefore, there are neither associated risks nor benefits for the patient when participating in the study. The digital documentation of the clinical data will take place in an anonymized, retrospective fashion. No identifiable data, e.g., name will be entered into the database. Dates that are entered by the participants (e.g. month and year of birth, hospital admission date) are not accessible and visible to the sponsor and are only used to calculate age groups or timelines. Clinical data collected refers to common conditions and treatment modalities in medical care, such that no re-identification of the individual case on the basis of these data will be possible.

The FungiScope® study team has no access to this information at any time. Under these circumstances, we consider an informed consent of the patient not necessary. If partner sites require a Patient Information Pamphlet (see 1.1) for their patient due to local requirements, an information sheet will be provided. Signed forms and medical records remain at the partner site, no copy will be sent to the study team nor will any patient-related information be shared that would allow re-identification of that patient.

FungiScope® currently uses the General Data Protection Regulation (GDPR) compliant platform EFS Survey™ (clinicalsurveys.net). EFS Survey™ is hosted by TIVIAN XI (formerly QuestBack) on servers in Cologne, Germany as part of a software-as-a-service agreement. Study participants log into the system with username and password including letters, numbers, and symbols. Participants can only view and modify their own contributions. All data transmissions are encrypted via TLS 1.2 with an AES 256 GCM bit key and ECDHE RSA key exchange; certificate provided by COMODO RSA Domain Validation Server.

From 2026, the documentation of patient data of new collaborators will be hosted on the GDPR and HIPAA-compliant Carelane platform. During the transition phase, both EFS Survey™ and Carelane will be used simultaneously for this study until the end of 2030. Ultimately, only Carelane will be used. The new repository is maintained by Carelane GmbH, the vendor of the Carelane Platform. Carelane uses the high-availability GCP/firebase infrastructure in two main regions - EU or US. The sponsor entity has selected GCP eur3 Multi Region (Europe). Servers are distributed on two primary locations for failover purposes. The cloud provider has no access on the data (double encrypted) and all data is also encrypted in transit.

Data is only documented anonymously, no directly identifying data other than the investigator names and sites are stored on TIVIAN and Carelane servers. Administration of the eCRF is limited to selected and named administrators at the University Hospital Cologne (UHC), who receive comprehensive training in the systems before access is granted. Secure passwords are also enforced for administrators and they have to regularly change their passwords. Any data manipulation by users and administrators is logged in an audit trail allowing complete data reconstruction. For TIVIAN, server administration is performed by the company, and includes regular updates of the linux-based servers, rigid firewall configuration, current virus and threat detection, and daily backups (on-site and off-site with secure storage). Contracts between the UHC and TIVIAN XI GmbH and Carelane GmbH regulate ownership and responsibility for data and eCRFs. Regular on-site audits of security and data protection measures are performed at TIVIAN Cologne by UHC. For Carelane, server administration is performed by Carelane GmbH, Bremen, Germany. The system is configured for automated daily backups and Point-in-Time Recovery (PITR) with binary logging enabled for Recovery Point Objective (RPO) management. It utilizes multi-region replication for high availability and SOC 2 compliant measures for security. Real-time monitoring and continuous auditing of roles and permissions are performed to respond to suspicious activities and maintain access control.

All study procedures are liable to Good Epidemiological Practice (GEP) requirements of German and European legislation. All clinical data fall under medical confidentiality. All data and results will be stored for at least 10 years after publication of results.

### 1.1 Patient Information Pamphlet

While the study does not involve direct patient contact or require patient informed consent, it is acknowledged that local regulations in some regions may necessitate providing patients or their guardian with information about the study. To address this, an information pamphlet detailing the study's objectives, methods, and data protection measures in simple language is available upon request.

## 2. Work with Clinical Fungal Isolates

To ensure anonymity of all patients in the context of microbiological reference analyses, these analyses must have been completed and the results must have been included into the respective patient file, before the entire case is documented into the database as described in 1). This procedure aims to ensure anonymous documentation of patient data. The microbiological analyses of isolates of emerging fungi does not require an information for the patient, as there is no patient material involved.