Table 1. Study summary

<table>
<thead>
<tr>
<th>Study title</th>
<th>Multicenter prospective study to determine the usefulness of systematic 18F-FDG PET-CT in the management of invasive fungal infection (PET-IFI Project)</th>
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<tbody>
<tr>
<td>Design</td>
<td>Multicenter prospective cohort study. 18F-FDG PET-CT will be performed systematically at the onset and follow-up of invasive fungal infection (IFI). Findings and changes in the IFI management pre- and post-18F-FDG PET-CT will be compared. In addition, the association of the quantitative parameters of the initial 18F-FDG PET-CT with the response to treatment will be analyzed.</td>
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<td>Participants</td>
<td>224 patients with invasive fungal infection.</td>
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<td>Participating centres</td>
<td>14 Spanish tertiary centres.</td>
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<td>Tracking</td>
<td>The patient’s outcome will be evaluated at 100 days and 6 months after inclusion.</td>
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<td>Duration</td>
<td>The duration of the study is expected to be 24 months.</td>
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</table>
| Main objective | To compare the performance of 18F-FDG PET-CT with standard management of invasive fungal infection without 18F-FDG PET-CT:  
 a. In the initial assessment 
 b. In the monitoring of response to treatment. |
| Secondary objectives | 1. To assess the impact of 18F-FDG PET-CT results on the management of patients with IFI (added value) in terms of:  
 a. Diagnostic tests  
 b. Modifications of treatment  
 c. Outcome  
 2. To determine the value of the different quantification parameters of 18F-FDG PET-CT and the characteristics of the uptake in IFI, and their prognostic capacity regarding the metabolic response/outcome of the patient with IFI. |
| Primary variables | 1.a. Change in the proportion of patients classified as localized IFI and disseminated when comparing pre-PET and post-PET evaluation (adding information from 18F-FDG PET-CT). Likewise, the % of patients in whom new lesions are detected with the PET scan, or detection of lesions in organs that were previously not involved, even if it does not involve a change of staging, will be evaluated.  
 1.b. Changes in the assessment of outcome after follow-up 18F-FDG PET-CT compared to pre-PET will be analyzed. |
| Secondary variables | 2.a. The impact (added value) of 18F-FDG PET-CT on the management of IFI will be analyzed, both at the time of initial staging and in the monitoring of the response using follow-up 18F-FDG PET-CT (proportion of patients in whom 18F-FDG PET-CT represents a change of management). In addition, the characteristics of patients who benefit from 18F-FDG PET-CT will be compared with those who do not benefit.  
 2.b. The prognostic value of the parameters of 18F-FDG PET-CT in the IFI will be analyzed, comparing the baseline characteristics of the
parameters of 18F-FDG PET-CT in patients who achieved complete metabolic response with those who did not.

**Inclusion criteria**

Adult patients 18 years admitted with a diagnosis of invasive fungal infection able to undergo a 18F-FDG PET-CT and give their informed consent.

For inclusion in the study, two types of IFIs will be considered:

- **Fungemia**: detection of fungal growth in blood cultures.
- **Focal** IFI with tissue invasion: patients with a diagnosis of IFI proven or probable based on criteria established according to the type of patient (hematological and other ID: European Organization for Research and Treatment of Cancer (EORTC)/Mycoses Study Group Education and Research Consortium (MS GERC) consensus definitions; solid organ transplantation: 2010 International Society for Heart and Lung Transplantation (ISHLT) consensus statements for the definitions of infections in cardiothoracic transplant recipients; ICU/COPD: Bulpa; COVID-19: ECMM/ISHAM).

**Exclusion criteria**

Concomitant active bacterial infection likely to produce uptake in organs and tissues

Recent surgery in the IFI area (within the previous 3 months)

Other medical conditions that interfere with the conduct of the study (e.g., inability to tolerate testing for the required time, pregnancy)

Terminal situation.

**Intervention**

In addition to the usual management, 18F-FDG PET-CT will be systematically performed, to evaluate:

- Extension/staging to diagnosis: in the first week after diagnosis (preferably in the first 48 hours of initiation of antifungal treatment).
- Response monitoring/follow-up: will be performed on the same equipment as the initial 18F-FDG PET-CT
  *in the case of fungemia, at 2 weeks of the 18F-FDG PET-CT of initial staging.
  *for focal IFIs, at 2-4 and 12 weeks of initial staging 18F-FDG PET-CT.

**Statistical analysis**

1. The NRI (net reclassification index) between the pre-PET and post-PET classification will be estimated. A study of the agreement between the pre-PET and gold standard evaluation, and the post-PET vs gold standard evaluation (both in terms of staging and response monitoring) will be carried out using a weighted kappa index.

2. A multivariate predictive model will be constructed to identify patients who would potentially benefit from performing systematic 18F-FDG PET-CT. The dependent variable will be benefit (yes or no). To account for the effect on the variability of the benefit by center, mixed models will be used.

3. The prognostic value of the initial PET parameters will be compared by binary logistic regression. An analysis will also be performed using ROC curves (receiver operator characteristic) to determine if the metabolic parameters allow to discriminate
which patients will have complete metabolic response in the final examination.