Reason and reality—identifying barriers to patient enrolment for clinical trials in invasive candidiasis

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Objectives: Enrolment of subjects to clinical trials investigating novel drugs for infectious diseases is an ongoing challenge. In this study, we evaluate factors associated with non-enrolment in treatment trials for invasive candidiasis.

Methods: We conducted a retrospective review of pre-screening logs of patients that were assessed for enrolment in the three clinical trials ACTIVE (NCT00413218), APX001-201 (NCT03604705) and ReSTORE (NCT03667690), investigating novel drugs for invasive candidiasis between September 2007 and August 2021 to identify reasons for study ineligibility.

Results: Two hundred and fifty-six patients with invasive candidiasis were identified for potential study participation with \( n = 154 \) for the ACTIVE trial, \( n = 89 \) for APX001-201 and \( n = 13 \) for ReSTORE. Half of the potential participants were unable or unwilling to consent. We further identified comorbid conditions such as hepatic or renal impairment [21 hepatic and renal cases (13.6%) in ACTIVE; 12 hepatic (13.5%) and 28 renal cases (31.5%) in APX], prior antifungal treatment [11 cases (7.1%) in ACTIVE; 16 (18.0%) in APX; 7 (38.5%) in ReSTORE] and the last positive culture obtained \( \geq 96 \) h prior to dosing [1 case (0.6%) in ACTIVE; 7 (7.9%) in APX; 5 (38.5%) in ReSTORE] as relevant reasons for non-enrolment. Ultimately, 254/256 patients (99.2%) were eligible for enrolment in the respective trial.

Conclusions: This study identified barriers to enrolment in clinical trials assessing novel antifungal agents in invasive candidiasis. Identification of eligibility criteria associated with non-enrolment allows modification of future trial designs and may ultimately result in higher recruitment rates.

Introduction

Despite advances in diagnostics and treatment algorithms over the last decades, candidaemia and other forms of invasive candidiasis remain a serious threat for critically ill patients and an economic burden for the healthcare system. 1 Candidaemia is one of the most common bloodstream infections in hospitalized patients in the USA. 1,2 In Europe, both a rising incidence and increasing mortality from candidaemia have been observed between 2000 and 2019. 3 Candidaemia is the most commonly diagnosed manifestation of invasive candidiasis, but Candida spp. can also cause chronic disseminated and deep-seated infection. This includes metastatic infections of the bone, eye, kidney, liver, lung or spleen. Invasive candidiasis necessitates immediate treatment initiation, and long treatment durations are inevitable in case of organ involvement. Available treatment options are often limited by the administration route, antifungal resistance patterns, drug interactions or toxicity. This may result in hospitalization for weeks or months and adds both to reduced quality of life and economic burden.

The development of new antifungal agents with novel mechanisms of action and enhanced properties is therefore a
pressing topic. The clinical development of novel antifungals requires robust clinical trials. In the field of rare diseases, low incidences are slowing down this progress. To enrol an adequate number of cases, clinical trials depend on a multicentre design with large numbers of sites.

The small number of available participants is further diminished by strict entry criteria for clinical trials. Eligibility criteria can ensure patient safety and data homogeneity. On the other hand, candidaemia is a disease occurring in patients with multiple risk factors and complex underlying conditions. Potential participants for clinical trials are often multimorbid and exclusion of these patients due to the presence of comorbid disease and medication introduces a significant deviation from the real world. At our centre, we found that only a small fraction of patients with invasive candidiasis has been enrolled in clinical trials despite being evaluated for eligibility. On a larger scale, this delays study conduct, and ultimately delays market authorization of the urgently needed antifungal drugs.

As a foundation for modifying current clinical trial designs, it is critical to identify factors that limit patient enrolment. In this analysis, we evaluate barriers to enrolment in invasive candidiasis clinical trials by analysing reasons for ineligibility from patient pre-screening logs.

Methods
The University Hospital Cologne (UHC) is a 1540-bed teaching hospital in Cologne, Germany. Between September 2007 and August 2021, three trials investigating novel antifungals for patients with candidaemia or other forms of invasive candidiasis were conducted at UHC. All patients with invasive candidiasis who were pre-screened for trial eligibility were recorded in pre-screening logs. We retrospectively reviewed these logs and extracted and analysed the overall number of pre-screened cases, their eligibility status and—in case of ineligibility—the inclusion and exclusion criteria that led to non-enrolment.

Results
In this study, we assess factors that influence enrolment in clinical trials for treatment of invasive candidiasis by analysing pre-screening logs of three studies for reasons for ineligibility.

The first trial included in this analysis is WSA-CS-008, the ACTIVE trial (NCT00413218), by Astellas Pharma Inc. This Phase III trial was conducted as a multicentre, double-blind, randomized study to evaluate the safety and efficacy of isavuconazole versus caspofungin followed by voriconazole in the treatment of candidaemia and other invasive Candida infections. Full inclusion and exclusion criteria of this study have been provided. 

Six inclusion and 17 exclusion criteria were defined for the APX001-201 trial (Table 1, Table S1(b)). Pre-screening for enrolment was conducted in 89 cases. Similar to the ACTIVE trial, the majority of patients (46/89; 51.7%) were not included because they were not willing to give informed consent or to comply with the study restrictions. Moderate or severe renal dysfunction or haemodialysis was documented in 28 cases (31.5%) and 21 cases (23.6%) as a cause for non-enrolment, respectively. Sixteen patients (18.0%) were ineligible because they received systemic antifungal treatment for more than 48 h. Cirrhosis of the liver or defined hepatic impairment hindered enrolment in 12 cases (13.5%). Another exclusion criterion was a total bilirubin above 3-fold the upper limit of normal (ULN) in nine cases (10.1%). Life expectancy shorter than 7 days in the opinion of the investigator led to exclusion of 10 cases (11.2%). In seven cases (7.9%), the last positive culture was taken more than 96 h prior to dosing of the investigational product. Neutropenia as an exclusion criterion led to non-enrolment of seven patients (7.9%). At our centre, not a single patient was enrolled in the APX trial.

The ReSTORE trial (NCT03667690) is a Phase III, multicentre, prospective, randomized, double-blind, efficacy and safety study sponsored by Cidara Therapeutics Inc. IV rezafungin versus caspofungin followed by optional oral fluconazole step-down therapy was evaluated in patients with candidaemia or invasive candidiasis. Full inclusion and exclusion criteria are provided at ClinicalTrials.gov. At our centre, recruitment started on 26 May 2021 and ended on 16 August 2021.

Overall, 7 inclusion and 18 exclusion criteria were defined for the ReSTORE trial (Table 1, Table S1(c)). Thirteen patients were pre-screened. Again, a major reason for non-enrolment was inability or unwillingness to consent in seven patients (53.8%). In addition, five patients (38.5%) received systemic treatment with an antifungal agent for more than 48 h. In five patients (38.5%), samples for mycological diagnosis were taken longer than 96 h ago. In two cases (15.7%),
### Table 1. Eligibility criteria of three interventional candidiasis trials that led to non-enrolment and rates of non-enrolled patients at UHC

| Eligibility criteria for ACTIVE (WSA-CA-008; NCT00413218)                                                                 | Non-enrolled patients |
|-----------------------------------------------------------------------------------------------------------------------------|-----------------------|
| **Inclusion criteria**                                                                                                        |                       |
| Patients and/or legally authorized representative(s), if applicable, who have been fully informed and have given voluntary  | 77/154 (50.0%)        |
| written informed consent OR patients unable to write and/or read but who fully understand the oral information given by the   |                       |
| investigator (or nominated representative) who have given oral informed consent witnessed in writing by an independent      |                       |
| person. HIPAA authorization for US sites or equivalent privacy language as per national regulations must be obtained.         |                       |
| Ability and willingness to comply with the protocol.                                                                          | 12/154 (7.8%)         |
| Male and female patients aged ≥18 years at the time of signing informed consent.                                               | 1/154 (0.6%)          |
| Patients with candidaemia or with an invasive Candida infection who have a positive blood or tissue culture obtained within    | 1/154 (0.6%)          |
| 96 h prior to randomization, accompanied by related clinical signs and symptoms or histological or cytological changes. A     |                       |
| preliminary positive Gram stain, histology or cytology result of yeast is sufficient for randomization, and final culture results |                       |
| may still be pending at the time of first dose.                                                                               | 3/154 (1.9%)          |
| Presence of fever (on one occasion >38°C oral, or equivalent) or hypothermia (on one occasion <36°C oral, or equivalent) or    |                       |
| hypotension [systolic blood pressure (SBP) <100 mmHg or a decrease in SBP of at least 30 mmHg] or appropriate local signs      |                       |
| within 96 h prior to randomization.                                                                                          |                       |
| Subject agrees to not participate in any other clinical trial with another investigational drug.                               | 1/154 (0.6%)          |
| **Exclusion criteria**                                                                                                        |                       |
| Women who are pregnant or breastfeeding.                                                                                     | 5/154 (3.2%)          |
| Known history of allergy, hypersensitivity, or any serious reaction to any of the azole or echinocandin class of antifungal or | 1/154 (0.6%)          |
| to any component of the study medication.                                                                                     |                       |
| Patients for whom caspofungin or voriconazole is contraindicated.                                                           | 2/154 (1.3%)          |
| Patients at high risk for QT/QTc prolongation, e.g.                                                                             | 4/154 (2.6%)          |
| Baseline prolongation of QTcF ≥500 msec;                                                                                     |                       |
| Risk factors for Torsade de Pointes (e.g. uncompensated heart failure, abnormal potassium or magnesium levels that              |                       |
| cannot be corrected, any unstable cardiac condition during the last 30 days, or a family history of long QT syndrome);       |                       |
| The use of concomitant medications that prolong the QT/QTc interval.                                                         |                       |
| Patients with evidence of hepatic dysfunction with any of the following abnormalities at the time of randomization (may be    | 21/154 (13.6%)        |
| rechecked using local laboratory):                                                                                        |                       |
| Total bilirubin ≥3× upper limit of normal (ULN) or ALT or AST ≥5× ULN or                                                    |                       |
| Patients with known cirrhosis or chronic liver failure or Calculated creatinine clearance <10 mL/min or                    |                       |
| Currently on dialysis or likely to require dialysis during administration of study medication.                               |                       |
| Concomitant use of sirolimus, everolimus, efavirenz, ritonavir, astemizole, cisapride, rifampicin/rifampin, rifabutin, ergot   | 6/154 (3.9%)          |
| alkaloids, long-acting barbiturates, carbamazepine, pimozone, quinidine, neostigmine, ketoconazole, valproic acid, St. John’s |                       |
| Wort, or terfenadine in the 5 days prior to first administration of study medication.                                       |                       |
| Patients with candidaemia who failed a previous antifungal therapy for the same infection.                                   | 1/154 (0.6%)          |
| Microbiological findings (e.g. bacterial infection) or other potential conditions that are temporally related and suggest an   | 9/154 (5.8%)          |
| alternative aetiology of the clinical features in the absence of culture/histology/cytology evidence of systemic Candida       |                       |
| infection. NB: For patients with intra-abdominal infection or intra-abdominal abscess, documentation of another pathogen       |                       |
| (e.g. bacteria) would exclude the patient from enrolment.                                                                  |                       |
| Patients who have received systemic antifungal therapy for more than 48 h within 96 h prior to the first administration of    | 11/154 (7.1%)         |
| study medication.                                                                                                            |                       |

Continued
## Table 1.  Continued

### Eligibility criteria for ACTIVE (WSA-CA-008; NCT00413218)

| Inclusion criteria                                                                 | Non-enrolled patients |
|------------------------------------------------------------------------------------|-----------------------|
| Any known or suspected condition of the patient that may jeopardize adherence to the protocol requirements such as patients with fungal endocarditis, fungal osteomyelitis, fungal meningitis, or with life expectancy of <30 days. Patients with a concomitant medical condition that, in the opinion of the investigator, may be an unacceptable additional risk to the patient should he/she participate in the study. Treatment with any investigational drug in any clinical trial within 30 days prior to the first administration of study medication. | 1/154 (0.6%)         |

### Eligibility criteria for APX001-201 (NCT03604705)

| Inclusion criteria                                                                 | Non-enrolled patients |
|------------------------------------------------------------------------------------|-----------------------|
| Male or female ≥18 years of age.                                                   | 3/89 (3.4%)          |
| New diagnosis of candidaemia based on a blood sample drawn within 96 h of dosing with: | 7/89 (7.9%)          |
|   Positive blood culture for *Candida* spp., including those *Candida* spp. with suspected (in the opinion of the investigator) or documented resistance to at least one standard-of-care systemic antifungal agent. OR Positive result from a sponsor-approved rapid diagnostic blood test for *Candida* spp. infection (a rapid diagnostic test may be used to begin eligibility assessments; however, a subsequent confirmatory blood culture is required prior to dosing of APX001). |                      |
| Females of childbearing potential must have a negative urine pregnancy test within 96 h prior to baseline (i.e. pre-dose on Study Day 1). | 2/89 (2.2%)          |
| Willing to participate in the study, willing to give written informed consent, and willing to comply with the study restrictions, where permitted by local regulations. | 46/89 (51.7%)        |

| Exclusion criteria                                                                 | Non-enrolled patients |
|------------------------------------------------------------------------------------|-----------------------|
| Neutropenia defined as absolute neutrophil count <500 cells/mm³.                   | 7/89 (7.9%)          |
| Diagnosis of deep-seated *Candida*-related infections causing intraperitoneal candidiasis, septic arthritis, osteomyelitis, endocarditis, myocarditis, meningitis or CNS infection or site of infection that would require antifungal treatment to exceed maximal duration of study drug (14 days). | 1/89 (1.1%)          |
| Hepatosplenic candidiasis.                                                         | 1/89 (1.1%)          |
| Blood culture, or any other culture, positive for *Candida krusei*.                 | 3/89 (3.4%)          |
| Received >2 days (>48 h) equivalent of prior systemic antifungal treatment at approved doses to treat the current episode of candidaemia (e.g. two consecutive doses of an echinocandin). Note: ≤5 days (≤120 h) equivalent of prior antifungal treatment is permitted for patients with candidaemia caused by *Candida* spp. with documented resistance to the specific prior antifungal administered. | 16/89 (18.0%)        |
| Life expectancy of <7 days in the opinion of the investigator.                     | 10/89 (11.2%)        |
| Cirrhosis of the liver or hepatic impairment as defined by ALT or AST ≥3×ULN. Patients with AST and/or ALT ≥3×ULN and <5×ULN are eligible if these elevations are acute, not accompanied by a total bilirubin >2×ULN or international normalized ratio >1.5×ULN and documented by the investigator as being directly related to an infectious process being treated. | 12/89 (13.5%)        |
| Patients receiving haemodialysis.                                                  | 21/89 (23.6%)        |
| Known HIV, active HBV or HCV infections (defined as hepatitis B surface antigen or HCV RNA positivity). | 2/89 (2.2%)          |
| Total bilirubin >3×ULN, unless isolated hyperbilirubinaemia is directly related to an acute infection or due to known Gilbert’s disease. | 9/89 (10.1%)         |

Continued
Non-enrolment in invasive candidiasis trials

Considering all three trials together, only 2 of 256 patients (0.8%) pre-screened for eligibility were enrolled in the respective trial at our centre, whereas 254 of 256 patients (99.2%) were ineligible for participation.

Nine eligibility criteria could be identified that were present in all three studies, accounting for approximately half of the eligibility criteria in each study. This included an age limitation, the ability or willingness to participate, use of birth control measures during the study period, and a diagnosis of candidaemia within the last 96 h as shared inclusion criteria. Exclusion criteria that were present in all three analysed studies were pregnancy or lactation, certain candidiasis organ manifestations, hepatic impairment with variable cut-off values, prior treatment with the investigational drug, and treatment with another investigational drug within a given time frame.

Several other criteria were similar in two of the three studies, including prohibition of concomitant medication with known CYP interactions, renal impairment or dialysis, and life expectancy below a given threshold (ACTIVE and APX), required presence of clinical signs and symptoms of infection, known hypersensitivity to the investigational or comparator drugs (ACTIVE and ReSTORE) and systemic antifungal treatment for more than 42 h and inappropriate source control (APX and ReSTORE). Other eligibility criteria addressed drug-specific matters of special interest such as neurotoxicity or QTc changes.

### Table 1. Continued

| Eligibility criteria for APX001-201 (NCT03604705) | Non-enrolled patients |
|-----------------------------------------------|----------------------|
| Moderate or severe renal dysfunction (serum creatinine >3x ULN or an estimated creatinine clearance <50 mL/min calculated by Cockcroft–Gault or Modification of Diet in Renal Disease equation). | 28/89 (31.5%) |
| Inappropriate fungal infection source control (e.g. persistent indwelling catheters or intravascular devices). | 1/89 (1.1%) |

| Eligibility criteria for ReSTORE (NCT03667690) | Non-enrolled patients |
|-----------------------------------------------|----------------------|
| Inclusion criteria                            |                      |
| Willing and able to provide written informed consent. If the subject is unable to consent for himself/herself, a legally acceptable representative [i.e. acceptable to International Council on Harmonisation (ICH) and local law, as applicable] must provide informed consent on his/her behalf. | 7/13 (53.8%) |
| Males or females ≥18 years of age.            | 1/13 (7.7%) |
| Established mycological diagnosis of candidaemia and/or invasive candidiasis from a sample taken ≤4 days (96 h) before randomization defined as: | 5/13 (38.5%) |
| ≥1 blood culture positive for yeast or Candida |                      |
| Positive test for Candida from a sponsor-approved rapid in vitro device |                      |
| Positive Gram stain (or other method of direct microscopy) for yeast or positive culture for Candida spp. from a specimen obtained from a normally sterile site. |                      |
| Presence of one or more systemic signs attributable to candidaemia or invasive candidiasis (e.g. fever, hypothermia, hypotension, tachycardia, tachypnoea, local signs of inflammation) appearing from ≤12 h prior to the qualifying positive culture through time of randomization. | 1/13 (7.7%) |
| Exclusion criteria                            |                      |
| Received systemic treatment with an antifungal agent at approved doses for treatment of candidaemia for >48 h (e.g. >2 doses of a once-daily antifungal agent or >4 doses of a twice-daily antifungal agent) and ≤4 days (96 h) before randomization. | 5/13 (38.5%) |
| Exception: receipt of antifungal therapy to which any Candida spp. isolated in culture is not susceptible |                      |
| Presence of an indwelling vascular catheter or device that cannot be removed or an abscess that cannot be drained and is likely to be the source of candidaemia or invasive candidiasis. | 2/13 (15.4%) |
| History of severe ataxia, tremor or neuropathy, or a diagnosis of multiple sclerosis or a movement disorder (including Parkinson's disease or Huntington's disease). | 1/13 (7.7%) |
| Planned or ongoing therapy at screening with a known neurotoxic medication. | 1/13 (7.7%) |

HIPAA, Health Insurance Portability and Accountability Act. Overall, 154 patients were pre-screened for ACTIVE (WSA-CA-008; NCT00413218) study enrolment, but only 2/154 patients (1.3%) were enrolled. For the APX001-201 trial (NCT03604705) and the ReSTORE trial (NCT03667690), 89 and 13 patients were pre-screened for study enrolment, respectively, but no patients were enrolled.

source control by removal of indwelling devices or abscess drain could not be attained. The study was completed without patient enrolment at our site.

Considering all three trials together, only 2 of 256 patients (0.8%) pre-screened for eligibility were enrolled in the respective trial at our centre, whereas 254 of 256 patients (99.2%) were ineligible for participation.

Nine eligibility criteria could be identified that were present in all three studies, accounting for approximately half of the eligibility criteria in each study. This included an age limitation, the ability or willingness to participate, use of birth control measures during the study period, and a diagnosis of candidaemia within the last 96 h as shared inclusion criteria. Exclusion criteria that were present in all three analysed studies were pregnancy or lactation, certain candidiasis organ manifestations, hepatic impairment with variable cut-off values, prior treatment with the investigational drug, and treatment with another investigational drug within a given time frame.

Several other criteria were similar in two of the three studies, including prohibition of concomitant medication with known CYP interactions, renal impairment or dialysis, and life expectancy below a given threshold (ACTIVE and APX), required presence of clinical signs and symptoms of infection, known hypersensitivity to the investigational or comparator drugs (ACTIVE and ReSTORE) and systemic antifungal treatment for more than 42 h and inappropriate source control (APX and ReSTORE). Other eligibility criteria addressed drug-specific matters of special interest such as neurotoxicity or QTc changes.
Discussion

There are several important knowledge gaps on the prevention and treatment of candidaemia and invasive candidiasis. Advances in diagnostics and antifungal therapy have not led to improved survival in recent years, underscoring the importance of novel antifungal drugs in the pipeline. Clinical trials offer unparalleled insights into the efficacy of anti-infectives in development. Reaching appropriate enrolment rates is essential to accelerate the pace for new therapies and to timely provide patients with more convenient and potent treatment options.

Immense collaborative efforts of the medical mycology community allow for studies with multiple participating centres. However, rates of patient enrolment for trials testing new antifungal agents are notoriously low. Low enrolment rates result in long study durations, directly impacting the licensing and availability of new drugs. As a consequence, it takes years from discovery of a new antifungal drug to its clinical use. A leading cause for slow enrolment rates is the rarity of diseases. However, we found a significant number of patients ineligible due to the study designs, making recruitment efforts in this rare patient population even more challenging.

Strict inclusion and exclusion criteria ensure safety of the participants and promote homogeneity of the study population on the one hand. The availability of studies with similar design and entry criteria leads to comparability between studies and makes combined analysis of clinical trials possible. On the other hand, strict eligibility criteria deny access for many patients and create an artificial population of patients. Both the EMA and the FDA have published guidance documents for the clinical evaluation of antifungal agents. These documents provide patient selection criteria that focus on adequate diagnostics but do not impose strict constraints on patient characteristics. Candidaemia is a condition of a critically ill population at the extremes of age, with immunosuppression, intensive care treatment and invasive procedures as major risk factors. In a case-control analysis from our centre, Day 30 crude mortality of candidaemia patients was significantly higher compared with mortality rates in recent clinical trials, leading to the conclusion that the highly selected population in clinical trials is not representative. In the present analysis, more than 99% of patients pre-screened for study enrolment were excluded as they did not meet the entry criteria. It is arguable if these patients should be barred from clinical trials and if licensing of novel drugs should be based on these artificial patient cohorts.

Poor enrolment in clinical trials continues to be challenging not only in anti-infective research. A meta-analysis of 280 randomized controlled trials for prevalent chronic diseases had a mean non-enrolment rate of 40%, including several studies with a non-enrolment rate higher than 90%, comparable to our results. In addition, only a minority of studies provide sufficient information to allow calculation of non-enrolment rates. Therefore, analyses from the literature may underestimate the number of non-enrolled subjects in current clinical trials.

We identified inability or unwillingness to give informed consent as a major barrier to patient enrolment. Active patient refusal has also been reported as a significant barrier to enrolment in interventional therapeutic trials for solid tumours, such as breast and lung cancer. In these analyses, patient refusal was a substantial reason for non-enrolment and points to the need for continued efforts to educate physicians and the public in the safety and value of clinical trials. In our dataset, no distinction was made between active patient refusal and non-enrolment due to inability to consent, such as in mechanically ventilated patients. As per German law, patients cannot be enrolled in clinical trials with the consent of a legal representative in our centre. In candidaemia, this precludes a large number of potential participants.

Comparing eligibility criteria of recent trials investigating invasive candidiasis, a considerable overlap of criteria is obvious. In our opinion, several of the common entry criteria can be dismissed as they either bias the study population towards a more artificial cohort or they are negligible in quantity.

The presence of disease-specific symptoms should not be obligatory as diagnostic steps such as blood cultures have been initiated by clinical suspicion. As per current guidance documents, targeted treatment is indicated for any positive blood culture. Therefore, candidiasis-related signs and symptoms such as fever do not add value to the selection process.

Various forms of invasive candidiasis have been excluded in APX and ReSTORE. Examples include endocarditis, endophthalmitis, hepatosplenic candidiasis and osteomyelitis. We do not consider this approach useful for several reasons. Organ manifestations are not systematically screened for study participation and therefore cannot be systematically excluded. In addition, these rare manifestations do not qualify for a separate prospective clinical trial. Treatment recommendations therefore depend on subgroup data from clinical trials to overcome extrapolations from small retrospective cohorts or anecdotal case reports.

Another recurring exclusion criterion addresses source control measures. Removal of catheters is recommended in current guidelines and is independently associated with decreased mortality. However, in certain clinical situations source control is not feasible to perform. When the anticipated benefit outweighs the potential harm for the patient, this should not lead to an exclusion from clinical trials.

The exclusion of patients with a short life expectancy in the ACTIVE and the APX trial is conflicting as life expectancy cannot be objectified. We propose to instead exclude patients with a treatment goal of palliative care symptom management, a wording that is also used in the ReSTORE trial.

Limitations

This study is a retrospective chart review conducted at a single institution and is therefore limited in its conclusions. Results must be interpreted with caution as the used source data were not initially captured for this analysis. Not all entry criteria were systematically screened and documented in the logs, resulting in incomplete or overlapping documentation. For the same reason, factors that led to inability or unwillingness to participate were not differentiated. Phase II and Phase III trials were evaluated together. Nonetheless, this study strives to provide a decent overview of the enrolment landscape in a single centre and is therefore considered a preliminary analysis and outlook for future studies that prospectively evaluate overly restrictive entry criteria and identify biases between trial-eligible and -ineligible populations.
Conclusions

Repetitive and strict inclusion and exclusion criteria of patients with Candida bloodstream infections and other forms of invasive candidiasis hamper a straightforward conduct of clinical trials and foster the selection of an unrepresentative patient population. The design of invasive candidiasis trials has been nearly consistent over time. The reality is more nuanced and it is reasonable to question the use of strict entry criteria. Interpretation of results from randomized controlled trials as the highest-quality evidence should always happen with the knowledge of applied inclusion and exclusion criteria.

This work paves the way for a prospective evaluation with detailed analysis of reasons for non-enrolment in candidaemia and invasive candidiasis treatment trials.

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Author contributions

R.S. analysed and interpreted data, drafted the manuscript and tables, and revised and approved the final manuscript. J.H.G. and S.H. contributed to manuscript writing and revised and approved the final manuscript. O.A.C. conceived the study idea, interpreted data, contributed to manuscript writing and revised and approved the final manuscript.

Supplementary data

Table S1(a–c) is available as Supplementary data at JAC Online.

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