Development and validation of a risk model for identification of non-neutropenic, critically-ill, adult patients at high risk of invasive *Candida* infection

STUDY PROTOCOL

Version 1.4

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PROJECT SUMMARY

Invasive fungal infections (IFIs) are associated with increased morbidity and mortality. Up to half occur in critically-ill patients, and the majority of IFIs in the critical care setting are due to *Candida* species. A number of randomised controlled trials have evaluated antifungal prophylaxis in non-neutropenic, critically-ill patients. The patient groups for these trials were very heterogeneous, but all represented groups at high risk of IFI. Despite this heterogeneity in patient groups, the trials demonstrated a remarkably homogeneous effect of antifungal prophylaxis on the risk of proven IFI and suggested a reduction in mortality. However, as widespread use of antifungal drugs may promote resistance, it is necessary to establish a method to identify those patients at greatest risk of IFI, who stand to benefit most from antifungal prophylaxis.

The project consists of six phases, commencing 1 November 2008:

Phase 1. A systematic literature review to identify risk factors for invasive fungal infections

(Months 1 to 3)

Phase 2. A prospective audit of risk factors for and outcomes of invasive *Candida* infection

(Months 3 to 18)

Phase 3. Development and internal validation of risk models for invasive *Candida* infection

(Months 19 to 24)

Phase 4. External validation of the risk models for invasive *Candida* infection

(Months 18 to 27)

Phase 5. Economic modelling to assess the cost-effectiveness of prophylaxis based on the risk model for invasive *Candida* infection

(Months 19 to 29)

Phase 6. Recommendations for future research based on value of information analysis

(Months 22 to 30)

RESEARCH OBJECTIVES

The primary aim of this project is to develop a risk model that can be used, with confidence, to identify non-neutropenic, critically-ill, adult patients at high risk of invasive *Candida* infection as a basis for treatment decisions regarding antifungal prophylaxis.

Specific, sequential objectives are:

- To identify potential factors associated with increased risk of invasive fungal infection.
- To collect data on risk factors/IFIs in critical care units.
- To develop and validate a risk model to identify non-neutropenic, critically-ill, adult patients at high risk of invasive *Candida* infection.
- Using estimates both from previous randomised controlled trials (RCTs) and from the risk model, to model the clinical and cost-effectiveness of using antifungal prophylaxis in non-neutropenic, critically-ill, adult patients identified as being at high risk of invasive *Candida* infection.
- To make recommendations for further research to establish the optimum strategy for the use of antifungal prophylaxis in non-neutropenic, critically-ill, adult patients.

BACKGROUND

Invasive fungal infections in critically-ill patients

In the past, fungal infections were most likely to be found in patients that were either neutropenic, had received a solid organ transplant, or had been treated with corticosteroids or cytotoxic agents. Increasingly, serious invasive fungal infections (IFIs) are now more likely to be seen in non-neutropenic patients in critical care units.[1] The majority of IFIs in the critical care setting are due to *Candida* species. Surveillance of IFIs by the Communicable Disease Surveillance Centre identified that over three quarters of hospital-wide IFIs within England and Wales were invasive *Candida* infections;[2] this proportion is likely to be higher if restricted to the critical care unit setting, for which no accurate surveillance data exist. The Health Protection Agency (HPA) estimates that over 5,000 cases of invasive *Candida* infection occur in the UK each year, and around 40% of these occur in critical care units.[3] An epidemiological survey in six UK sentinel hospitals reported that 45% of *Candida* bloodstream infections, the most invasive, occurred in critical care.[4] IFIs in critically-ill patients are associated with increased morbidity and mortality at a cost to both the individual and the NHS.[5;6]

Antifungal prophylaxis

A number of RCTs have evaluated antifungal prophylaxis in non-neutropenic, critically-ill patients, predominantly with either fluconazole[7-11] or ketoconazole.[12-15] Several systematic reviews and meta-analyses of these RCTs have been performed,[16-21] including a Cochrane systematic review.[16] The reviews reveal that patient groups selected for the individual RCTs were very heterogeneous, ranging from high-risk surgical patients[10;11;15] to those with septic shock[7] or with acute respiratory distress syndrome.[12;14] All seemed to represent groups that were at high risk of IFI, with rates of IFI in the control arms of these studies typically over 10%. Despite this heterogeneity in patient groups, the RCTs demonstrated a remarkably homogeneous effect of antifungal prophylaxis on the risk of proven IFI (relative risk 0.46, 95% confidence interval 0.31 to 0.68) and suggested a reduction in mortality (relative risk 0.76, 95% confidence interval 0.59 to 0.97).[16] The question, therefore, is not whether antifungal prophylaxis is effective, but rather, how to select an appropriate group of patients at high risk of IFI in which to use it, as more widespread use of antifungal drugs is likely to promote increased resistance.

A recent systematic review of the risk of resistance associated with fluconazole prophylaxis concluded that the evidence from RCTs indicated an increased risk of colonisation with either fluconazole-susceptible, dose-dependent or fluconazole-resistant fungi.[22] There was also some suggestion of increased breakthrough infections with non-*albicans Candida* including *Candida krusei*, which has innate resistance to fluconazole, and strains of *Candida glabrata* with acquired resistance to fluconazole.

Identifying patients at high risk of invasive fungal infections

Given the effectiveness of antifungal prophylaxis has only been demonstrated in groups at high risk of IFI, and that more widespread use of antifungal drugs may promote resistance, it is necessary to establish a method to identify and target antifungal prophylaxis at those patients at highest risk of IFI, therefore targeting use to those who stand to benefit most from any antifungal prophylaxis strategy.[23]

Several models for identifying patients at high risk of IFI have been proposed.[24-27] These models, however, are limited. The populations included have typically been selected based on the length of stay in the critical care unit, for example, to those staying two,[24] four,[25;26] or seven[27] days in the unit, and are therefore not appropriate for making treatment decisions earlier in the stay. The populations have been restricted in other ways, for example, by including either only post-surgical patients[24;26] or only those with *Candida* colonisation.[27] These again limit the generalisability of the resultant model to a mixed UK critical care population. Finally, no models have been developed or validated in UK NHS patients.

Clinical decision rules

A clinical decision rule is a tool that quantifies the contributions that past medical history, physical examination and laboratory results make towards the diagnosis, prognosis or likely response to treatment for a patient. McGinn *et al* [28] define four levels of evidence for clinical decision rules:

- Level 1: Rules that can be used in a wide variety of settings with confidence that they can change clinical behaviour and improve patient outcomes. This requires at least one prospective validation in a different population and one impact analysis demonstrating change in clinical behaviour with beneficial consequences.

- Level 2: Rules that can be used in various settings with confidence in their accuracy. This requires demonstrated accuracy in either one large prospective study including a broad range of patients and clinicians or validation in several smaller and varied settings.

- Level 3: Rules that clinicians may consider using with caution and only if patients in the study are similar to the clinician's setting. This requires validation on only one narrow prospective sample.

- Level 4: Rules that need further evaluation before they can be applied clinically. These are rules that have been derived but not validated or validated only in split samples, large retrospective databases or by statistical techniques.

No existing clinical decision rule for antifungal prophylaxis in non-neutropenic, critically-ill, adult patients could be considered to achieve higher than Level 4. The aim of this study is to develop a Level 2 rule, and to scope and assess the value of further research to establish a Level 1 rule.

STUDY DESIGN

The project will consist of six phases, detailed below.

Phase 1: Systematic literature review of risk factors for invasive fungal infections

The objectives of the systematic literature review are:

- to identify potential risk factors for IFI;
- to describe and assess the relationship between these factors and the risk of IFI;
- to classify the risk factors according to the strength of association with the incidence of IFI; and, following consultation with the panel of experts both in fungal infection and in critical care,
- to identify a final list of potential risk factors for invasive *Candida* infection, with definitions, for prospective data collection.

A set of highly sensitive search criteria will be developed to identify all published studies that either: (a) investigate the predictive value of risk factors for IFI in non-neutropenic, critically-ill, adult patients; (b) develop or evaluate a risk score or risk model for IFI in non-neutropenic, critically-ill, adult patients; or (c) develop or evaluate a clinical decision rule or patient algorithm for use of antifungal prophylaxis in non-neutropenic, critically-ill, adult patients. See Appendix 1 for the draft search strategy.

Electronic searches using these search criteria will be conducted in MEDLINE, EMBASE and CINAHL. Abstracts of all studies matching the search terms will be reviewed to identify those potentially meeting the inclusion criteria, for which the full text will be obtained. The full text of these studies will then be compared against the inclusion criteria to establish the included studies. Reference lists of any review articles identified by the search will be checked to identify additional studies. No publication time limit will be imposed.

From each study meeting the inclusion criteria, the following will be recorded: study design; method of data collection; setting; population characteristics; method of analysis; risk factors reported; outcome (types/definitions of IFI); and strength of association demonstrated.

A panel of experts in fungal infection and critical care will then assess the list of potential risk factors and add any additional factors that have not been identified by the literature review. The panel will also be asked to identify whether any variables are not feasible to collect in routine practice; agreement of the panel on such variables will result in their exclusion. The experts will also be asked to identify any potential interactions between variables, and to identify potential reasons for missing data for each variable. The panel will identify and define a final list of risk factors for invasive *Candida* infection. We have chosen to restrict this study to invasive *Candida* infection rather than all IFIs because it represents the overwhelming majority of IFIs occurring in UK critical care units. Although invasive aspergillosis may be an emerging problem in steroid treated patients with chronic airways disease, it remains infrequent in UK critical care units. Other fungal pathogens which may be endemic in many parts of the world, are not encountered in the UK.

Phase 2: Prospective audit of risk factors for and outcomes of invasive Candida infection

A data collection form, data collection manual (with rules/definitions), field specification and flows will be produced.

Data collection for risk factors for invasive *Candida* infection will be piggy-backed onto routine data collection for the Case Mix Programme (CMP), the national, comparative audit of patient outcomes from adult, general critical care units in England, Wales and Northern Ireland. Units will be invited to take part in the audit of invasive *Candida* infection. Projected recruitment rates are based on the assumption that 80 units will participate in, and complete, data collection and validation.

The amount of additional data required for each patient, over and above those routinely collected for the CMP, will be relatively small. Additional data will include risk factors for invasive *Candida* infection, identified and confirmed by expert panel from Phase 1, plus data required to exclude neutropenic patients (See: Planned inclusion/exclusion criteria) and the outcome of proven invasive *Candida* infection.

Depending on local infrastructure for CMP data collection, one of three possible modes for data collection will be identified:

- Modification of existing Version 3.0 CMP-compatible software applications to include the additional fields,
- Web-based data entry of additional fields and CMP Admission Number for linkage to CMP data,
- Simple, one-page, paper form to include the additional fields.

As for CMP data, all the additional data will undergo extensive validation, both locally and centrally, for completeness, illogicalities and inconsistencies.

Data collection for Phase 2 is anticipated to be completed in twelve months, assuming 80 participating critical care units admitting an average of 500 admissions per year (average admissions per year derived from CMP Database).

Phase 3: Development and internal validation of risk models for invasive Candida infection

Using the data collected in Phase 2, two alternative models for the risk of invasive *Candida* infection will be developed in parallel using two different approaches. The performance of the two modelling approaches will then be compared.

Random-effects Poisson regression

First, using a classical statistical approach, the rate of invasive *Candida* infection will be modelled using a hierarchical (multilevel), random-effects, Poisson regression model. The Poisson regression model is preferred to the more commonly used logistic regression model as it makes allowance for the exposure of the individual to the risk of infection – in this instance, the duration of stay in the critical care unit – whereas the logistic regression model assumes a fixed exposure for all individuals. Using a hierarchical model, with patients nested within critical care units, will enable us to include both fixed and random effects at the unit level, taking appropriate account of the covariance structure. Alternative approaches to modelling each individual risk factor, identified in Phase 1, will be compared and evaluated in univariable analyses. All risk factors, modelled using the best approach identified in the univariable analyses, will be entered into a full multivariable model. The full model will be progressively simplified by removing the least significant variable in turn (backwards stepwise selection) until no variables remain. At each step, the model will be

fitted in 100 repeated development samples (randomly selected two thirds of patients) and the performance evaluated in the corresponding 100 validation samples (remaining one third of patients). The best model will be selected to balance model performance against ease of use. Coefficients for the final model will be estimated in the full dataset.

Artificial neural networks – multilayer perceptron model

Second, using a computational, artificial intelligence-based approach, models will be fitted using artificial neural networks. Artificial neural networks are computational models inspired by networks of biological neurons.[29] The models contain layers of nodes (neurons) that are richly interconnected by weighted connections (synapses). These weights are adjusted to development data through a "training" process. We will use a multilayer perceptron model, which consists of input nodes, hidden intermediate layers of nodes, and an output node. Artificial neural networks have potential advantages over classical statistical models as the underlying model structure is less rigidly defined, allowing unforeseen interactions between risk factors to be taken into account; the multilayer perceptron can model any piecewise continuous function of its inputs. However, the complexity of the potential models produces a significant risk of overfitting the model to the data.[30] Artificial neural networks have previously been applied to predict outcomes in a critical care unit setting.[31;32]

Handling of missing data

Extensive data validation will be employed to ensure the data are as complete as possible. Patients missing large amounts of routine data (for example, patients dying very shortly after admission to the unit with no physiological observations recorded) will be excluded from the modelling. Other missing data will be handled with multiple imputation techniques.[33]

Internal validation of the risk models

The performance of the risk models within the development dataset will be evaluated using statistical methods to adjust for overfitting – the tendency for models to perform better in the data from which they were derived than in future datasets.[34] This form of internal validation meets the requirements for a Level 4 clinical decision rule.[28]

The primary requirement of a risk model for identification of patients to receive antifungal prophylaxis is the ability to discriminate between those that will, and will not, go on to develop invasive *Candida* infection. Discrimination will be measured by the concordance (or *c* index)[35] which, for binary outcomes, is equivalent to the area under the receiver operating characteristic curve.[36]

In addition, the accuracy of the models for predicting the risk of invasive *Candida* infection will be assessed by Brier's score (the mean square error between the outcome and the prediction),[37] the Hosmer-Lemeshow calibration statistic,[38] and by graphical plots of observed against predicted *Candida* infection rates.

Estimates of these performance measures will be adjusted for overfitting using Efron's .632 bootstrap method.[39] Whereby, repeated samples are taken with replacement from the development dataset (bootstrap samples). The model is refitted in each bootstrap sample and the performance measure (θ) based on this model is calculated in both the original dataset and the bootstrap sample. The degree of optimism in θ due to overfitting is estimated by comparing the values of θ from the original dataset and the bootstrap sample, and the estimate of θ for the original model is adjusted for the average optimism observed across the bootstrap samples.

Phase 4: External validation of the risk models for invasive Candida infection

Once data collection for Phase 2 is complete, data collection will continue in the same critical care units for a further six months and also in additional, new, critical care units recruited during, but not involved in data collection for, Phase 2. The risk models, developed in Phase 3, will be evaluated in the full external validation dataset, collected from all units, and also solely in those units that were not involved in Phase 2, providing an independent validation data set.

External validation of risk models

The discrimination and accuracy of the risk models developed in Phase 3 will be assessed in the validation datasets using the same performance measures as for the internal validation. External validation in a large, multicentre prospective cohort meets the requirements for a Level 2 clinical decision rule.[28]

Comparison with existing models

The discrimination and accuracy of the risk models developed in Phase 3, and the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) at specific risk thresholds, will be compared with that of the existing models identified in Phase 1.

Phase 5: Economic modelling

The economic evaluation will assess the cost-effectiveness of prophylaxis based on the risk model for invasive *Candida* infection. The economic modelling will run in parallel with the development of the risk model to enable feedback in both directions. The focus will be on comparing a treatment protocol of giving antifungal prophylaxis to patients identified as high risk ('the intervention') with using no prophylaxis ('current practice'). The economic evaluation will use a decision-analytical approach to project the lifetime cost-effectiveness of the intervention.[40]

Model structure

The economic model will include a hypothetical cohort of 1000 cases with characteristics defined by the non-neutropenic, critically-ill, adult patients meeting the study inclusion/exclusion criteria. For the group receiving current practice, the model will estimate the probability of invasive *Candida* infection during the critical care unit stay based on the optimal risk model from Phase 4.

For the intervention group, the initial probability of invasive *Candida* infection will be reported using the risk model (Phase 4) and based on the characteristics of the cohort (see Appendix 2). A proportion of cases will then be assigned to prophylaxis or no prophylaxis according to whether they are defined as having high (P) or low (1–P) baseline risk. This proportion (P) will depend on the risk threshold (P_T). For cases assigned to low baseline risk, the probability of *not* having an invasive *Candida* infection will be taken as the NPV from the risk model (Phase 4). For high baseline risk, the probability of having an invasive *Candida* infection will be the baseline PPV from the risk model multiplied by the relative risk (RR) associated with antifungal prophylaxis. This relative risk will be taken from systematic reviews of published RCTs,[16] adjusted to reflect the baseline risk in the study context. For each health state, cases will be assigned an appropriate probability of

mortality for this patient group; these probabilities will vary according to age, acute severity of illness, underlying condition, and prior hospital stay.[41]

Estimating costs and health-related quality of life (HRQOL)

A hospital perspective will be taken to costing. The costs of routine care for non-neutropenic, critically-ill, adult patients not receiving antifungal prophylaxis will be assigned by combining information on activity from the study dataset with cost data from Payment by Results. Costs of critical care will be assessed based on Healthcare Resource Groups (HRGs) derived from organ support data in the Critical Care Minimum Data Set (CCMDS), which forms part of the routine CMP data collection. Additional costs of the hospital stay will be estimated based on appropriate HRGs for ward care plus the costs of antifungal therapy. Baseline hospitalisation costs with and without invasive *Candida* infections, will be reported. For the intervention, the proportion of cases predicted to receive prophylaxis will be combined with treatment costs from the British National Formulary. The cost associated with infection will include antifungal treatment and ensuing morbidity costs. Information on the mean HRQOL for non-neutropenic, critically-ill, adult patients, with and without invasive *Candida* infections, will be estimated from collaborative studies following up long-term outcomes of patients in the CMP.

Analysis

The economic model will estimate, over a lifetime time horizon, the life-years, quality-adjusted life-years (QALYs) and costs associated with the intervention versus current practice. To reflect the uncertainty surrounding key parameters, they will be incorporated as probability distributions. The model will be analysed using probabilistic sensitivity analysis which will report the expected value of the intervention (incremental cost per QALY) and appropriate measures of uncertainty (cost-effectiveness acceptability curves). The model will also be run under different scenarios, in particular looking at the impact of: (i) changing the risk of infection threshold (P_T) on the cost-effectiveness of prophylaxis; and (ii) making different assumptions about the likely impact of the intervention on resistance.

The analysis will also consider the potential impact antifungal prophylaxis may have on preventing onward transmission. Literature on nosocomial fungal outbreaks will be reviewed and implications about transmission will be evaluated using standard dynamic

transmission approaches.[42] If preliminary modelling suggests that allowing for the impact of antifungal prophylaxis on onward transmission is likely to be important, then the cost-effectiveness analysis will be extended. The model will then estimate the incremental cost-effectiveness of antifungal prophylaxis for a range of plausible values for transmission probabilities and hospital population characteristics.

Phase 6: Recommendations for future research

The uncertainties surrounding whether or not prophylaxis based on a risk model is cost-effective will be fully considered using value of information methods.[43;44] To assess whether further research would be worthwhile, we will assess the expected value of perfect information (EVPI) for this decision problem.[43] We will also examine where further research may be most valuable, by using expected value of information about parameters[45] to identify where improving the precision of particular parameter estimates may be most worthwhile, and whether subsequent RCTs will be justified.

Important outputs from the economic modelling (Phase 5) will therefore be a projection of the likely cost-effectiveness of using a risk model for identifying patients at high risk of invasive *Candida* infection, based on the best evidence currently available, and an assessment of the value of further research.

To establish a Level 1 clinical decision rule for the use of antifungal prophylaxis will also require at least one impact analysis, assessing the impact of applying the rule on clinician behaviour.[28] The scope for potential future research in this area will also be considered.

Inclusion/exclusion criteria

Data will be collected on all patients admitted to the participating critical care units with the following exclusion criteria applied to the data retrospectively:

- Neutropenia (neutrophil count less than $1 \times 10^9\ l^{-1}$)
- Age less than 18 years
- Second and subsequent admissions of the same patient
- Patient groups for whom established algorithms for the use of antifungal agents exist (solid organ transplant recipients, patients with haematological malignancies)

identified from the reasons for admission to the critical care unit and conditions recorded in the past medical history

Interventions

None.

Outcome measures

The outcome for the risk model will be proven invasive *Candida* infection, defined according to a modification of the latest European Organisation for Research and Treatment of Cancer/Mycosis Study Group (EORTC/MSG) consensus definitions (See: Appendix 3). The estimation of clinical and cost-effectiveness will be based on reduction in proven invasive *Candida* infections, hospital mortality and IFI-associated mortality, fungal-free survival, antifungal susceptibility, type and duration of organ support (including mechanical ventilation), and length of stay in critical care and in hospital. The primary outcome of the cost-effectiveness model will be the cost per QALY with a lifetime horizon.

Sample size

Assuming a 1% incidence of invasive *Candida* infection among non-neutropenic, adult patients admitted to UK critical care units,[3;4] and based on a requirement of 20 events per variable with an anticipated 20 candidate variables in the risk model, we would require a sample size of 40,000 patients in the development sample. This sample size will be sufficient to give 80% power to detect as statistically significant ($P<0.05$) a risk factor present in 10% of the population associated with a 50% increase in the risk of invasive *Candida* infection.

With an average of 500 admissions per unit per year, to achieve this sample size would require 80 units collecting data for 1 year (Phase 2). To obtain a ratio of development to validation samples of 2:1, we will recruit 20,000 additional patients over a 6-month period to form the validation sample (Phase 4).

ORGANISATION

Study Steering Group

The Study Steering Group (SSG) responsibilities are to approve the study protocol and any amendments, to monitor and supervise the study towards its research objectives, to review relevant information from external sources, and to resolve problems identified by the Study Management Group. Face-to-face meetings will be held at regular intervals determined by need and not less than once a year, with routine business conducted by telephone, email and post. The SSG membership is shown below and terms of reference are given in Appendix 4.

Membership

Dr Bernard Riley (Independent Chair)	Consultant in Adult Critical Care, Nottingham University Hospital NHS Trust
Dr David Harrison (Chief Investigator)	Statistician, Intensive Care National Audit & Research Centre (ICNARC)
Dr Rosemary Barnes (Co-investigator)	Reader and Honorary Consultant, Department of Medical Microbiology, Cardiff University
Dr Jonathan Edgeworth (Co-investigator)	Consultant Microbiologist, Guy's and St Thomas' Hospital NHS Foundation Trust
Dr Richard Grieve (Co-investigator)	Lecturer in Health Economics, London School of Hygiene and Tropical Medicine
Dr Mark Jit (Co-investigator)	Health Economist/Mathematical Modeller, Centre for Infections, Health Protection Agency
Prof Christopher Kibbler (Co-investigator)	Lead Consultant, Medical Microbiology, Royal Free Hampstead NHS Trust
Prof Kathryn Rowan (Co-investigator)	Director, ICNARC

Dr Neil Soni (Co-investigator)	Consultant in Anaesthesia and Intensive Care, Chelsea and Westminster Hospital NHS Foundation Trust
Dr Thomas Stambach (Independent)	Consultant Anaesthetist, West Hertfordshire Hospitals NHS Trust
Dr Ronan McMullan (Independent)	Consultant Microbiologist, Belfast Health and Social Care Trust
HTA observer	
Dr Gavin Eyres (Study Co-ordinator)	FIRE Study Co-ordinator, ICNARC
(Research Fellow)	To be appointed

Study Management Group

The day-to-day running of the trial will be overseen by a Study Management Group consisting of the Chief Investigator and Co-investigators, the Study Co-ordinator and the Research Fellow.

Data monitoring

As the study does not involve any change to usual care for patients, an independent Data Monitoring Committee (DMC) will not be required. The SSG will oversee those responsibilities usually delegated to a DMC and these have been incorporated into the terms of reference (Appendix 4)

External advisors

The following external advisors have been identified to provide expert advice on specific aspects of the study:

Dr James Carpenter (missing data)	Senior Lecturer in Medical Statistics, London School of Hygiene and Tropical Medicine
Dr Richard Dybowski (neural networks)	CEO, InferSpace
Prof Mark Sculpher (value of information)	Professor of Health Economics, York University

Service user involvement

While undertaking the value of information analysis (Phase 6), we will promote and support active public involvement in this research with a view to ensuring any recommendations regarding future research and policy are relevant to future patients' needs and concerns. We will circulate recommendations for future research and policy, arising from this work, to a wide range of users for comment, feedback, and where appropriate, direct inclusion.

All involvement of service users in this study will follow the guidelines and recommendations for good practice from INVOLVE (http://www.invo.org.uk).

Research Governance

This study will be managed according to the Department of Health Research Governance Framework (http://www.dh.gov.uk/en/Researchanddevelopment/A-Z/Researchgovernance/index.htm) and the Medical Research Council Guidelines for Good Research Practice (http://www.mrc.ac.uk/pdf-good_research_practice.pdf), Guidelines for Good Clinical Practice in Clinical Trials (http://www.mrc.ac.uk/pdf-ctg.pdf) and Procedure for Inquiring into Allegations of Scientific Misconduct (http://www.mrc.ac.uk/pdf-mis_con.pdf). The study will be co-ordinated at the Intensive Care National Audit & Research Centre (ICNARC). ICNARC has developed its own policies and procedures based on these guidelines, which are adhered to for all research activities at ICNARC. In addition, ICNARC has contractual confidentiality agreements with all members of staff. Policies regarding alleged scientific misconduct and breach of confidentiality are reinforced by disciplinary procedures.

Ethical arrangements

The Case Mix Programme has approval under Section 251 of the NHS Act 2006 (originally enacted as Section 60 of the Health and Social Care Act 2001) to hold limited patient identifiable data (date of birth, sex, postcode, NHS number) without consent (approval number: PIAG 2-10(f)/2005). No additional patient identifiable data will be required for this study and individual patient consent will not be sought. The Patient Information Advisory Group has approved the extension of the Section 251 approval of the Case Mix Programme to cover the FIRE study.

The study has received a favourable ethical opinion from the Bolton Research Ethics Committee (REC reference number: 08/H1009/85).

Funding

Research costs for this study have been met by a grant from the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme (project reference 07/29/01). There are no NHS support costs or excess treatment costs associated with this research as there is no deviation from usual care.

Indemnity

ICNARC holds professional liability insurance (certificate number A05305/0808, Markel International Insurance Co Ltd) to meet the potential legal liability of the sponsor for harm to participants arising from the management of the research. Indemnity to meet the potential legal liability of the sponsor and employers for harm to participants arising from the design of the research is provided by the NHS indemnity scheme. Indemnity to meet the potential legal liability of investigators/collaborators for harm to participants arising from the conduct of the research is provided by the NHS indemnity scheme or through professional indemnity.

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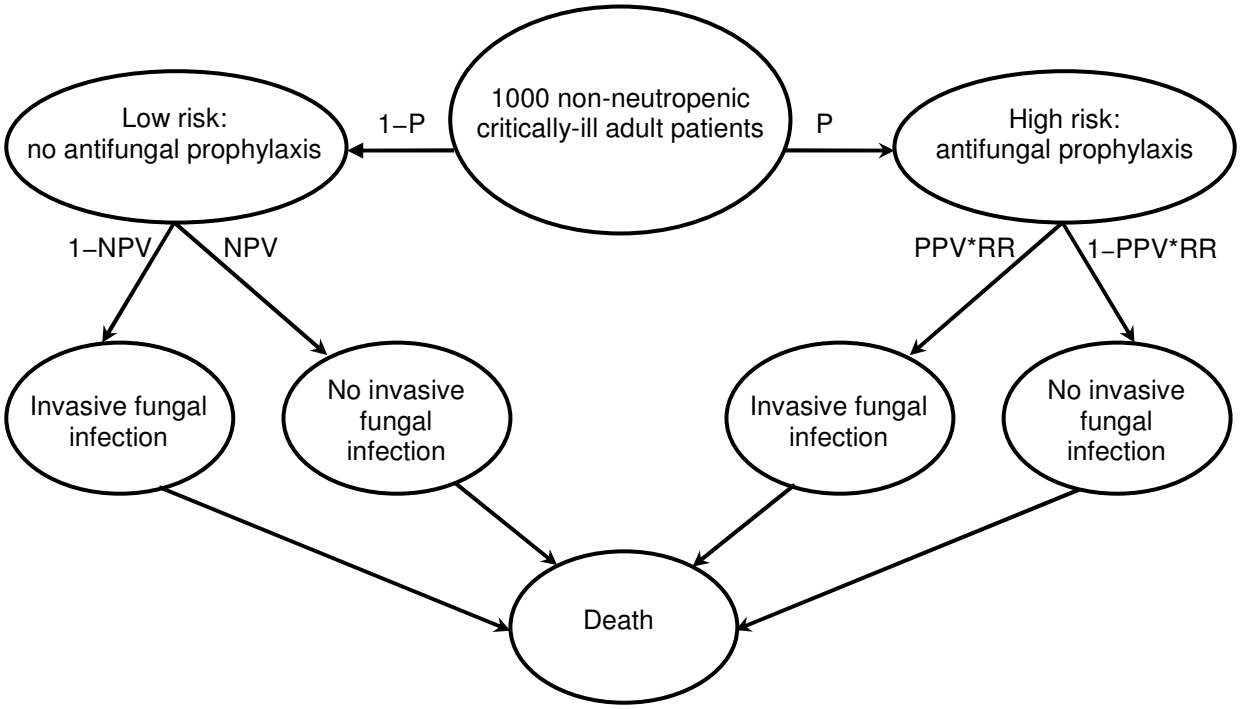
Appendix 1. Draft search strategy for systematic review (Ovid MEDLINE format)

1. exp Mycoses/
2. exp Antifungal Agents/
3. fung$.tw.
4. candid$.tw.
5. fluconazole.tw.
6. diflucan.tw.
7. itraconazole.tw.
8. sporanox.tw.
9. ketoconazole.tw.
10. nizoral.tw.
11. voriconazole.tw.
12. amphotericin.tw.
13. ambisome.tw.
14. amphotec.tw.
15. abelcet.tw.
16. flucytosine.tw.
17. nystatin.tw.
18. miconazole.tw.
19. echinocandin$.tw.
20. caspofungin.tw.
21. (select$ adj5 decontam$).tw.
22. or/1-21
23. exp Intensive Care Units/
24. exp Critical Care/
25. intensive care.tw.
26. critical$.tw.
27. or/23-26
28. 22 and 27
29. exp Risk/
30. exp Models, Statistical/
31. exp Regression Analysis/
32. exp Sensitivity and Specificity/
33. exp Survival Analysis/
34. exp Operations Research/
35. exp Decision Support Techniques/
36. Clinical Protocols/
37. Practice Guidelines/
38. Patient Selection/
39. risk$.tw.
40. predict$.tw.
41. model$.tw.
42. rule$.tw.
43. ((decision or algorithm) adj5 (clinical or treatment or prophyla$)).tw.
44. or/29-43
45. 28 and 44

Appendix 2. Cost-effectiveness model for providing antifungal prophylaxis to cases predicted by the risk model to be at high risk of invasive *Candida* infection



P = proportion of patients with predicted risk exceeding risk threshold P_T

PPV = positive predictive value (from validation of risk score)

NPV = negative predictive value (from validation of risk score)

RR = relative risk of invasive *Candida* infection associated with antifungal prophylaxis (from systematic reviews of published RCTs, adjusted to reflect the baseline risk in the study context)

Appendix 3. EORTC/MSG Consensus Revised definitions for proven invasive *Candida* infection (http://www.doctorfungus.org)

Deep tissue disease

Histopathologic or cytopathologic examination[a] of a needle aspiration or biopsy specimen from a normally sterile site excluding mucous membranes showing *Candida* species yeast cells (may also show pseudohyphae or true hyphae).

OR

Recovery of a *Candida* species by culture from a sample obtained by a sterile procedure (including a freshly (<24h) placed drain) from a normally sterile and clinically or radiologically abnormal site consistent with an infectious disease process.

Fungemia

Blood culture that yields *Candida* species.

[a] Tissue and cells submitted for histopathology or cytopathology should be stained by Grocott-Gomorri methenamine silver stain or by periodic acid Schiff stains to facilitate inspection of fungal structures. Where possible, wet mounts of specimens from foci related to invasive fungal infectious disease should be stained with a fluorescent marker (e.g. calcofluor or Blancophor).

Appendix 4. Terms of Reference for the Study Steering Group

The role of the Study Steering Group (SSG) is to provide overall supervision for FIRE on behalf of the funder (HTA) and sponsor (ICNARC) and to ensure that the study is conducted to the rigorous standards set out in the MRC Guidelines for Good Clinical Practice. The day-to-day management of the study is the responsibility of the Investigators, and the Chief Investigator will set up a separate Study Management Group (SMG) to assist with this function.

- The SSG should approve the protocol and study documentation in a timely manner.
- In particular, the SSG should concentrate on progress of the study, adherence to the protocol, patient safety and consideration of new information of relevance to the research question.
- In the absence of a Data Monitoring Committee, the SSG should monitor the study data, and data emerging from other related studies, and consider whether there are any ethical or safety reasons why the study should not continue.
- The safety, rights and well being of the study participants are the most important consideration and should prevail over the interests of science and society.
- The SSG should provide advice, through its chair, to the Chief Investigator, the sponsor, and the funder, on all appropriate aspects of the study. Specifically, the SSG will:
    - Monitor recruitment rates and encourage the SMG to develop strategies to deal with any recruitment problems.
    - Monitor data completeness and comment on strategies from SMG to encourage satisfactory completion in the future.
    - Monitor follow-up rates and review strategies from SMG to deal with problems including sites that deviate from the protocol.
    - Approve any amendments to the protocol, where appropriate.

- Approve any proposals by the SMG concerning any change to the design of the study.
- Oversee the timely reporting of study results.
- Approve and comment on the statistical analysis plan.
- Approve and comment on the publication policy.
- Approve and comment on the main study manuscript.
- Approve and comment on any abstracts and presentations of results during the running of the study
- Approve external or early internal requests for release of data or subsets of data.

- Membership of the SSG should be limited and include an independent Chair and at least two other independent members. The Investigators and the study staff are ex-officio.
- Representatives of the sponsor and the HTA should be invited to all SSG meetings.
- Responsibility for calling and organising the SSG meetings lies with the Chief Investigator. The SSG should meet at least annually, although there may be periods when more frequent meetings are necessary.
- There may be occasions when the sponsor or the HTA will wish to organise and administer these meetings in exceptional circumstances.
- The SSG will provide evidence to support any requests for extensions, including that all practicable steps have been taken to achieve targets.
- The SSG will maintain confidentiality of all study information that is not already in the public domain.