The A-Stop Study

Antifungal stewardship opportunities with rapid tests for fungal infection in critically ill patients

Protocol Number:	B17/23
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Chief Investigator:	Dr Ronan McMullan Senior Lecturer/Consultant Medical Microbiologist Queen's University Belfast & Belfast HSC Trust Kelvin Laboratory Building, The Royal Hospitals Grosvenor Road, Belfast, BT12 6BA

PROTOCOL AUTHORISATION

Protocol Title	Antifungal stewardship opportunities with rapid tests for fungal infection in critically ill patients.
Protocol Acronym (if applicable)	A-Stop
Protocol Number	B17/23
Protocol Version Number/Date	v8.0_27/05/2021
Protocol Amendments	**v1-v2 key changes** 9.2.1 Blood sampling -research blood sample increased from approximately 12mL to approximately 14mL in adult participants.
	v2-v3 key changes 8.0 Informed consent -removal of reference to Scottish sites/processes 9.1 Schedule of assessments -timing of standard care blood culture changed to within 24 hours of starting antifungal treatment -additional risk factors added for assessment of probable Candida infection 14.9 Patient confidentiality -an exception to unique trial identifier pseudonymisation is noted as NICTU determining participant mortality via the participant's GP
	v3-v4 key changes Inclusion criterion changed- Prescribed systemic antifungal therapy, for suspected or confirmed Candida infection, during the preceding 24 hours. Exclusion criterion added- Treatment with antifungal therapy for superficial Candida infection (e.g. thrush) 7.1 – Confirmation of eligibility by a person suitably qualified by education, training or experience. 9.2.1 – Blood sampling: For children, the preferred research sample volume is 4mL, however, this may be either increased or decreased as deemed appropriate by the clinical team up to a maximum of 14mL 9.2.1- Blood sampling: research blood should be obtained as soon as possible within 24 hours of the standard care blood culture.
	v4-v5 key changes Exclusion criterion removed- Treatment with antifungal therapy for superficial Candida infection (e.g. thrush) 9.1 Glucocorticosteroid treatment paediatric prednisolone equivalent dose added
	v6 withdrawn
	v5 – v7 key changes 1_Study Summary: Exclusion criteria: added Proven or suspected active infection with COVID-19 Target Sample Size: reduced to 1250

	Study Duration: extended to 63 months Co-investigators: Evie Gardner replaced by Cliona McDowell as Co-investigator. Trial Statistician: replaced as Christina Campbell. 6 Study design 6.3 Study Schematic Diagram Figure 1: Revised study infection numbers inserted 6.4 Study Timeline Table 1: Updated Study Timeline Gantt Chart 7 Patient eligibility, screening and recruitment 7.1.2 Exclusion criteria: Proven or suspected active infection with COVID-19 7.4 Recruitment Adjusted numbers of patients to be recruited from 1750 to 1250 as per study extension. Added that recruitment is estimated at one patient per site per month. 8 Informed consent Reference made to the Mental Capacity Act 2016 for patients without capacity in Northern Ireland. 8.1 & 8.2 Added 'If possible, this Telephone Agreement can be followed up by written consent' to allow the verbal consent. 8.5 To clarify what data will be retained in the event of patient withdrawal. 9 Schedule of assessments and study procedures 9.1 To redefine the timeline for EQ5D5L questionnaire. 9.2.1 Blood Sampling Wording has been added to explain that research blood samples are 'paired' with standard care blood cultures taken and, if these are not taken at the same time as 'paired' blood cultures, then should be obtained as soon as possible within 24 hours of the 'paired' standard care blood culture using the same sampling technique *when possible*. 9.2.3 To redefine the timeline for EQ5D5L questionnaire. 11 Statistical considerations 11.1 Sample Size Sample size figures adjusted from 1750 to 1250. Prevalence of disease reduced from 5% to 4%. Method for revision of sample size calculation updated
	v7 – v8 key changes **6.6** Reference to Appendix 1 and updated wording **Appendix 1.** Inclusion of protocol for A-STOP & Newcastle MIC Qualitative Study. Added as Appendix 1

A review of the protocol has been completed and is understood and approved by the following:

Ronan McMullan		____ / ____ / 2021
Chief Investigator Name	Signature	Date
Christina Campbell		____ / ____ / 2021
Statistician	Signature	Date

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LIST OF ABBREVIATIONS

Abbreviation / Acronym	Full Wording
AIK	Akaike's Information Criteria
APACHE	Acute Physiology and Chronic Health Evaluation
BDG	Beta-D-glucan
BHSCT	Belfast Health and Social Care Trust
CI	Chief Investigator
CRF	Case Report Form
CTU	Clinical Trials Unit
DIC	Deviance Information Criteria
EQ-5D-5L	EuroQol-5 Dimension Questionnaire (5 level version)
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
HRQoL	Health Related Quality of Life
ICH	International Conference on Harmonisation
ICNARC	Intensive Care National Audit & Research Centre
ICU	Intensive Care Unit
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
LCM	Latent Class Models
MDT	Multi-disciplinary Team
MHRA	Medicine and Healthcare Products Regulatory Agency
Newcastle MIC	Newcastle In Vitro Diagnostics Co-operative
NHS	National Health Service
NIHR HTA	National Institute for Health Research Health Technology Assessment
NICE	National Institute for Health and Care Excellence
NICTU	Northern Ireland Clinical Trials Unit
NPV	Negative Predictive Value
PI	Principal Investigator
PCR	Polymerase Chain Reaction
PELOD-2	Paediatric Logistic Organ Dysfunction (2)
POC	Point of Care
PSSRU	Personal Social Services Research Unit
QALY	Quality Adjusted Life Year
QUB	Queen's University Belfast
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RMP	Registered Medical Practitioner
ROC	Receiver Operator Characteristic
SOFA	Sequential Organ Failure Assessment
SOP	Standard Operating Procedure
SSC	Surviving Sepsis Campaign
STARD	Standards for Reporting of Diagnostic Accuracy
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UK	United Kingdom

STUDY SUMMARY

Protocol Title	Antifungal stewardship opportunities with rapid tests for fungal infection in critically ill patients.
Health condition(s) or problem(s) studied	Rapid test for fungal infection
Study Design	A multi-centre, prospective, diagnostic test accuracy study.
Study Aim and Objectives	**Aim** The purpose of this project is to assess the performance of three rapid tests for fungal infection. The accuracy of these tests will be compared and the optimal test (or combination) identified. The emphasis will be on their ability to rule-out infection. **Main Objectives**: The main objectives of this study are: (i) To assess the diagnostic accuracy of three commercially available rapid tests for Candida infection (beta-D-glucan and two PCR-based tests) in the UK critical care setting. (ii) To develop a test-based protocol, that could be used to guide antifungal drug prescribing in this setting. **Secondary Objectives**: The secondary objectives of this study are: (i) To model the clinical effectiveness of implementing the resultant protocol in UK intensive care units (ICUs) as a tool for more appropriately targeting antifungal therapy. (ii) To estimate the proportion of patients currently receiving empirical antifungal therapy in UK ICUs for whom treatment is not clearly indicated. (iii) To model the cost effectiveness of implementing a protocol in UK ICUs, taking account of both beneficial and adverse consequences. (iv) To assess patient and physician risk preferences, for using the tests to discontinue presumptive antifungal therapy.

	(v) To use these data, along with value of information analysis, to estimate the potential utility of, and propose the design for, a future randomised trial.
Primary Outcome	The primary outcome measure is negative predictive value for each index test. Other diagnostic test accuracy measures will also be reported to support this. The analysis for this primary outcome will be based on an international consensus reference standard for <u>proven</u> invasive fungal disease, applied for Candida infection.
Secondary Outcomes	Secondary outcome measures of the study are based on: (i) Measures of diagnostic test accuracy, for each test alone and in combination, based on an international consensus reference standard for <u>proven</u> invasive fungal disease, applied for Candida infection. These will comprise sensitivity, specificity, positive/negative predictive values and positive/negative likelihood ratios. (ii) Measures of diagnostic test accuracy, for each test alone and in combination, based on an international consensus reference standard for <u>proven and probable</u> invasive fungal disease, applied for Candida infection. (iii) Estimated proportion of patients receiving systemic antifungal therapy in this cohort for whom treatment is unnecessary, derived from the reference standards used. Estimated number of days' avoidable antifungal treatment if negative index test results were used to stop treatment. (iv) Development of a test-based protocol using the index tests (alone or in combination), as a strategy for early cessation of empirical antifungal treatment, with assessment of its expected cost-effectiveness modelled on test accuracy, disease prevalence and clinical/economic outcomes in this patient group. (v) Risk preferences of clinicians and patients supporting an evaluation of barriers to test adoption.

Inclusion and Exclusion Criteria	**Inclusion criteria**: 1. Adults and children >4 weeks old. 2. Admitted to a UK ICU (level 2 or 3). 3. Prescribed systemic antifungal therapy, for suspected or confirmed Candida infection, during the preceding 24 hours. **Exclusion criteria**: 1. More than 24 hours systemic antifungal therapy in the preceding 7-days. 2. Treatment with antifungal therapy for proven or suspected mould infection (e.g. aspergillosis). 3. Neutropenia (absolute neutrophil count $<0.5x10^9$/L) during preceding 28 days. 4. Acute leukaemia or within 12 months of bone-marrow transplantation. 5. Hospitalised prisoners 6. Previously enrolled in this study. 7. Proven or suspected active infection with COVID-19
Countries of Recruitment	United Kingdom
Study Setting	Adult and paediatric Intensive Care Units (ICU)
Target Sample Size	1250
Study Duration	63 months

STUDY TEAM

Chief Investigator	**Dr Ronan McMullan** Senior Lecturer/Consultant Medical Microbiologist Queen's University Belfast & Belfast HSC Trust Kelvin Laboratory Building, The Royal Hospitals Grosvenor Road, Belfast, BT12 6BA
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	Dr Joy Allen Newcastle University
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	Dr David Harrison Intensive Care National Audit and Research Centre
	Dr Laura Loughlin Belfast Health and Social Care Trust
	Dr Kevin Morris Birmingham Children's Hospital NHS Foundation Trust
	Clíona McDowell, Head of Statistics Northern Ireland Clinical Trials Unit (NICTU)
Trial Statistician	**Christina Campbell,** Senior Biostatistician, NICTU
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3. BACKGROUND AND RATIONALE

3.1 Background Information

3.1.1 Invasive Candida infection is an uncommon but important disease among patients in UK ICUs

Data from the FIRE Study, which included over 60,000 admissions to 96 UK ICUs, indicate that only 0.6% of patients in UK ICUs are either admitted with invasive fungal infection or develop this during their ICU episode [1]. Around half of these (0.32%) acquired their fungal infection while in the ICU. Candida was the type of fungus implicated in almost all of these cases and bloodstream infection was the most common primary site of infection. ICU remains an important target population, with almost half of candidaemias in UK hospitals arising among ICU patients [2]; invasive candidiasis has been reported to occur up to 10 times more frequently in ICUs than other healthcare settings [3].

Overall ICU and hospital mortality in patients with invasive Candida infection in the FIRE study were 29.9% and 39.6%, respectively – significantly higher than was observed among patients without this infection (16.6% & 24.5%, respectively) [1]. This is, broadly, consistent with candidaemia mortality of 40-50% reported in other datasets [4, 5]. Therefore, while invasive Candida infection is uncommon in the UK ICU setting, its high mortality understandably heightens physician-alertness to the possibility of its occurrence and lowers the threshold for starting antifungal therapy on a presumptive basis. This assertion is supported by the FIRE study data, in which 7% of ICU admissions had treatment started while in the ICU [1]. No intervention has yet been established to adjust this risk-based therapy after it has been started, in the setting of diagnostic uncertainty.

3.2 Rationale for the Study

3.2.1 A small minority of patients in UK ICUs who are treated with a systemic antifungal drug are found to have a definite fungal infection

The FIRE Study revealed that only 5% of patients who had systemic antifungal treatment started during their ICU episode were subsequently found to meet criteria for proven Candida infection [5]. Even if this is an underestimate, it is clear that the vast majority of patients are overtreated. A recent survey in UK ICUs examined indications for starting antifungal treatment; this highlighted that it is common for treatment to be started on the basis of little, or no, evidence of infection [6]. Candida colonisation is common in ICU patients and, since this is one of the recognised risk factors for development of invasive infection, it drives initiation of empirical treatment [6].

Efforts have been aimed towards the development of risk models to predict the occurrence of infection with a view to avoiding delayed treatment in high risk patients. However, in order to develop a model with sufficient sensitivity the positive predictive values of putative clinical risk models are inevitably low [7, 8].

3.2.2 New rapid tests offer an opportunity for timely treatment decisions to avoid unnecessary treatment

Tests recently introduced to market, such as the new PCR-based tests, as well as BDG tests, can be completed within one working day and offer the opportunity to influence prescribing decisions at an early time-point. Prior to commercialisation of these Candida PCR tests, the performance of a variety of in-house assays has been described in small series. Collectively,

in meta-analyses, these have shown promising accuracy and it is assumed that commercial tests of a similar nature will perform similarly [9]. BDG is a biomarker that has demonstrable potential for improving the diagnosis of a number of fungal infections, in various populations, including candidaemia and deep-seated candidiasis [10-13].

The most obvious advantage these new tests bring over current culture-based techniques is their speed. Although blood cultures tend to become positive after 2-3 days at least 5-days must lapse before they can be declared negative. After 5-days of presumptive antifungal treatment, even though the patient may have improved for a variety of reasons, doctors are usually unwilling to stop treatment since it is uncertain whether the patient's response is due to antifungal treatment or other factors. By comparison, a negative result obtained within 24hrs of starting presumptive treatment is much more likely to guide antifungal treatment, before the patient is seen to have improved. Hence tests that bring timely results are better able to influence decision-making and redirect conventional practices. The new tests may also bring improved sensitivity, hence higher negative predictive values, than conventional culture methods.

Diagnostic accuracy data currently available for these tests consists of small studies in heterogeneous patient groups. While their performance has been assessed in meta-analyses, it is impossible to be certain that the findings from assimilating low-to-moderate quality data in this way are correct. The diagnostic test accuracy study we propose here will meet this need and offer a pathway to practice change and better targeted antifungal prescribing.

4. STUDY AIMS AND OBJECTIVES

4.1 Research Hypothesis

The rapid tests under study have high diagnostic accuracy for ruling out Candida infection in critically ill adults and children.

4.2 Study Aim

The purpose of this project is to assess the performance of three rapid tests for fungal infection. The accuracy of these tests will be compared and the optimal test (or combination) identified. The emphasis will be on their ability to rule-out infection so that a test-based protocol for early discontinuation of antifungal therapy can be developed.

This test-based protocol will be modelled for clinical and cost effectiveness, accounting for expected beneficial and adverse outcomes. This modelling, together with a value of information analysis, will inform the design of a future clinical & cost effectiveness RCT.

4.3 Study Objectives

4.3.1 Main Objectives:

The main objectives of this study are:

(i) To assess the diagnostic accuracy of three commercially-available rapid tests for Candida infection (beta-D-glucan and two PCR-based tests) in the UK critical care setting.

(ii) To develop a test-based protocol that could be used to guide antifungal drug prescribing in this setting.

4.3.2 Secondary Objectives:

The secondary objectives of this study are:

(i) To model the clinical effectiveness of implementing the resultant protocol in UK ICUs as a tool for more appropriately targeting antifungal therapy.

(ii) To estimate the proportion of patients currently receiving empirical antifungal therapy in UK ICUs for whom treatment is not clearly indicated.

(iii) To develop a test-based protocol using the index tests (alone or in combination), as a strategy for early cessation of empirical antifungal treatment, with assessment of its expected cost-effectiveness modelled on test accuracy, disease prevalence and clinical/economic outcomes in this patient group.

(iv) To assess patient and physician risk preferences, for using the tests to discontinue presumptive antifungal therapy.

(v) To use these data, along with value of information analysis, to estimate the potential utility of, and propose the design for, a future randomised trial.

5. OUTCOME MEASURES

5.1 Primary Outcome Measure

The primary outcome measure is negative predictive value for each index test. Other diagnostic test accuracy measures will also be reported to support this (comprising sensitivity, specificity, positive predictive value and positive/negative likelihood ratios). The analysis for this primary outcome will be based on an international consensus reference standard for proven invasive fungal disease, applied for Candida infection.

5.2 Secondary Outcome Measures

Secondary outcome measures of the study are based on:

(i) Measures of diagnostic test accuracy, for each test alone and in combination, based on an international consensus reference standard for proven invasive fungal disease, applied for Candida infection. These will comprise sensitivity, specificity, positive/negative predictive values and positive/negative likelihood ratios.

(ii) Measures of diagnostic test accuracy, for each test alone and in combination, based on an international consensus reference standard for proven and probable invasive fungal disease, applied for Candida infection.

(iii) Estimated proportion of patients receiving systemic antifungal therapy in this cohort for whom treatment is unnecessary, derived from the reference standards used. Estimated number of days' avoidable antifungal treatment if negative index test results were used to stop treatment.

(iv) Development of a test-based protocol using the index tests (alone or in combination), as a strategy for early cessation of empirical antifungal treatment. Assessment of its expected cost-effectiveness modelled on test accuracy, disease prevalence and clinical/economic outcomes in this patient group.

(v) Risk preferences of clinicians and patients supporting an evaluation of barriers to test adoption.

6. STUDY DESIGN

6.1 Study Design

This is a multi-centre, prospective, diagnostic test accuracy study.

6.2 Study Setting

At least 35 adult and paediatric intensive care units (ICU) across the UK will participate. They will range in size and scope from smaller general ICUs to larger specialist units.

6.3 Study Schematic Diagram

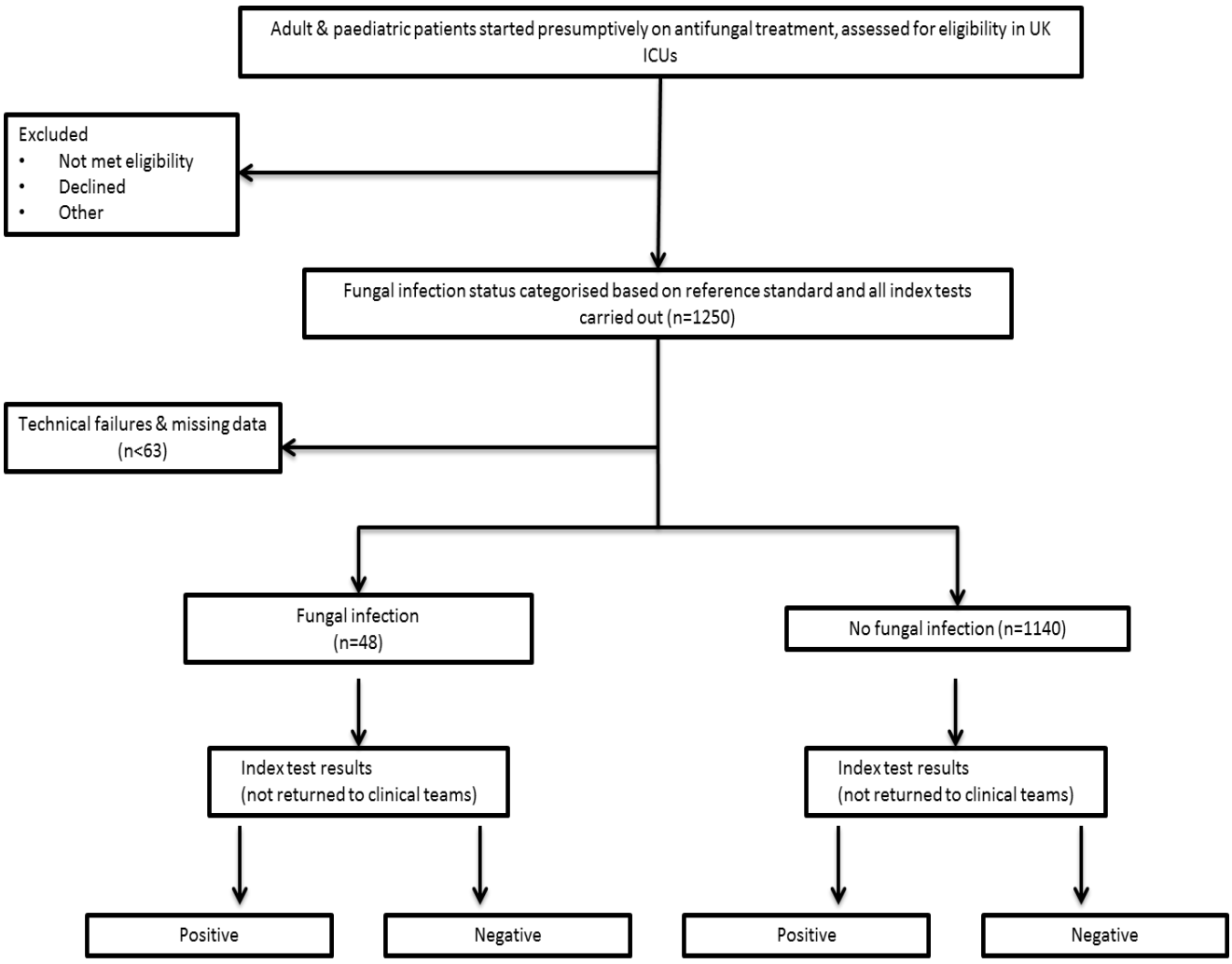


Figure 1: Study Schematic for the A-Stop study

6.4 Study Timeline

Table 1: Study Timeline Gantt Chart

Year		1						2								3								4								5						6	
Quarter		Q1		Q2		Q3		Q4		Q5		Q6		Q7		Q8		Q9		Q10		Q11		Q12		Q13		Q14		Q15		Q16		Q17		Q18		Q19		Q20	Q21
Trial stage	Pre-award	Set-up				Internal Pilot								Main Trial																								Close-down	
Assay validation	X	X	X	X	X	X																																	
Recruit staff	X	X	X	X																																			
Ethics approval	X	X	X	X	X	X																																	
Sponsorship	X	X	X	X	X																																		
Local R&D approvals	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X																						
Site initiation		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X														X	X	X				
Recruitment								X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
No of sites open							0		8		21		27		33		34		35		38		39		41		0		32		40		40		44		44			
Accrual projection							0		0		48		120		220		338		459		574		670		745		745		781*		833*		903*		1008*		1128*		1250		
Study assessments						X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Data entry						X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TMG meetings	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TSC meetings					X								X								X								X								X			
Site close-down																																						X	X	X		
Data analysis													X	X																									X	X	X	X
Economic modelling																																			X	X	X	X	X	X	X	X	X
Report-writing																																								X	X	X
Dissemination																																									X	X

6.5 Internal Pilot Study

An internal 12 month pilot study in at least 24 sites will precede the main trial and will follow the processes described in the main study below. The pilot will be used to confirm screening, consent procedures, recruitment rates, data collection, protocol compliance and ensure follow-up processes run smoothly. Patients enrolled in the pilot will be included in the analysis of the main study. Progression to the main trial will be dependent on recruitment and at the discretion of the funder.

6.6 Qualitative risk preferences

A qualitative evaluation of the risk preferences of a sample of patients and clinicians regarding the use of rapid diagnostic tests to discontinue presumptive antifungal therapy is detailed in Appendix 1.

6.7 End of Study

For the purposes of submitting the end of trial notification to the Sponsor and Research Ethics Committee (REC) the end of trial will be considered to be when database lock occurs for the final analysis. The trial will be stopped prematurely if:

- Mandated by the Research Ethics Committee (REC)
- Mandated by the Sponsor (e.g. following recommendations from the Trial Steering Committee (TSC)
- Funding for the trial ceases

The REC originally providing a favourable opinion of the trial will be notified in writing once the trial has been concluded or if terminated early

7. PATIENT ELIGIBILITY, SCREENING AND RECRUITMENT

7.1 Eligibility Criteria

Patients will be screened for eligibility based on the inclusion/ exclusion criteria outlined below. Eligibility to participate in the trial will be confirmed by a person suitably qualified by education, training or experience and named on the delegation log.

7.1.1 Inclusion criteria:

1. Adults and children >4 weeks old.
2. Admitted to a UK ICU (level 2 or 3).
3. Prescribed systemic antifungal therapy, for suspected or confirmed Candida infection, during the preceding 24 hours.

7.1.2 Exclusion criteria:

1. More than 24 hours systemic antifungal therapy in the preceding 7-days.
2. Treatment with antifungal therapy for proven or suspected mould infection (e.g. aspergillosis).
3. Neutropenia (absolute neutrophil count $<0.5x10^9$/L) during preceding 28 days.
4. Acute leukaemia or within 12 months of bone-marrow transplantation.
5. Hospitalised prisoners.
6. Previously enrolled in this study.
7. Proven or suspected active infection with COVID- 19.

7.2 Co-enrolment Guidelines

Patients enrolled in any other studies are potential candidates for this study. This is at the Principal Investigator's (PI) discretion and should be considered when the burden on participants is not expected to be onerous. Co-enrolment with any studies should be documented in the Case Report Form (CRF).

7.3 Screening Procedure

Adult and paediatric patients admitted to ICU who are started presumptively on systemic antifungal therapy for Candida infection, are potentially eligible for this study and will be screened regularly, on the basis of the inclusion/ exclusion criteria as specified in the protocol. Only those meeting the inclusion criteria should be recorded on the screening log.

All screening data must be recorded via electronic data capture (EDC) which must be completed by the PI or designee to document all patients screened for the study and all patients recruited. Patients screened and not recruited on to the study will be documented via EDC, including the reason(s) for not being enrolled on the study. The PI or designee will be required to submit screening data to the CTU approximately every month.

7.4 Recruitment

In order to robustly assess the diagnostic accuracy of the tests 1250 patients are required. Recruitment is estimated to be 1 patient per site per month.

8. INFORMED CONSENT

The consultation and recruitment of patients lacking capacity is regulated by different legal jurisdictions across the sites of this study. Practice will adhere to local regulations as outlined below.

It is the responsibility of the Principal Investigator (PI) (or designee) to ensure that informed consent is obtained for each participant. Consent may be obtained by: the PI; an appropriately trained Research Nurse; or medically trained investigator. The PI (or designee) taking informed consent must be suitably qualified and experienced and have been delegated this duty by the Principal Investigator on the delegation log.

A Covering Statement, Patient Information Sheet and Consent/ Declaration Form approved by the Research Ethics Committee (REC) will be provided to study sites. Wherever possible, consent will be taken directly from the patient or from the child's Parent/ Legal Representative.

However, the incapacitated nature of patients in intensive care units will usually preclude obtaining prospective informed consent from participants.

For patients who lack capacity to give informed consent due to, for example, the effects of sedation, infection, delirium and mechanical ventilation; consent or personal / nominated consultee opinion will be obtained as outlined below and in line with the legal requirements for patients without capacity in England and Wales (Mental Capacity Act 2005), and in Northern Ireland (Mental Capacity Act 2016).

At all sites, a deferred consent process will be applied. Samples will be taken as outlined in section 9 of this protocol and will be held at site for up to 7 days pending consent being obtained for inclusion in the study. Once approached for consent, patients or their Parent/ Legal Representative or their Personal/ Nominated Consultee will be allowed up to 2 days to decide whether or not to take part in the study. No samples will be transferred to the Belfast laboratory for testing, or stored at site beyond 7 days, without consent having first been obtained.

8.1 Parent/ Legal Representative (Paediatric) – England, Wales and Northern Ireland

The researcher will seek consent from the Parent or Legal Representative of the child. This should normally take place during a face-to-face meeting. An authorised staff member/researcher will describe the trial to the Parent/ Legal Representative, and provide them with a Covering Statement, Information Sheet and Consent Form for the Parent/ Legal Representative (England, Wales and Northern Ireland).

After the researcher has checked that the information sheet is understood, the researcher will invite the Parent/ Legal Representative to sign the consent form and will then countersign it. The original signed form should be provided to the Parent/ Legal Representative. A copy of the form should be placed in the patient's medical notes and a copy filed in the Investigator Site File (ISF).

If the Parent/ Legal Representative is not available at site, the researcher may contact them by telephone and seek verbal agreement. This verbal agreement will be recorded in the Telephone Agreement Form. The Telephone Agreement Form will be signed by a second member of staff who has witnessed the telephone consent. This witness may be a member of the site study team or site medical staff. The original signed form should be provided to the Parent/ Legal Representative. A copy of the Telephone Agreement Form should be placed in the patient's medical notes and a copy filed in the ISF.
If possible, this Telephone Agreement can be followed up by written consent and the original signed consent form provided to the Parent/ Legal Representative. A copy of the form should be placed in the patient's medical notes and a copy filed in the Investigator Site File (ISF).

8.2 Personal Consultee (Adults) – England, Wales and Northern Ireland

The researcher will seek advice from a Personal Consultee (who may be a relative, partner or friend of the participant). This should normally take place during a face-to-face meeting. An authorised staff member/researcher will describe the trial to the individual, and provide them with a Covering Statement, Information Sheet and Declaration Form for Personal Consultee (England, Wales and Northern Ireland). The researcher will seek their views about whether the patient should take part in the study. They will be asked about their opinion of the wishes and feelings of the patient if they had capacity.

After the researcher has checked that the information sheet is understood, the researcher will invite the Personal Consultee to sign the declaration form and will then countersign it. The original signed form should be provided to the Personal Consultee. A copy of the form should be placed in the patient's medical notes and a copy filed in the Investigator Site File (ISF).

If the Personal Consultee is not available at site, the researcher may contact the Personal Consultee by telephone and seek verbal agreement. This verbal agreement will be recorded in the Telephone Agreement Form. The Telephone Agreement Form will be signed by a second member of staff who has witnessed the telephone consent. This witness may be a member of the site study team or site medical staff. The original signed form should be provided to the Personal Consultee. A copy of the Telephone Agreement Form should be placed in the patient's medical notes and a copy filed in the ISF.
If possible, this Telephone Agreement can be followed up by written consent and the original signed declaration form should be provided to the Personal Consultee. A copy of the form should be placed in the patient's medical notes and a copy filed in the Investigator Site File (ISF).

8.3 Nominated Consultee (Adults) - Approval by a Registered Medical Practitioner (RMP) – England, Wales and Northern Ireland

In the event that there is no Personal Consultee for sites in England, Wales and Northern Ireland, authorisation to recruit the patient will be sought from a RMP (a doctor unrelated to the study conduct). The RMP will be informed about the trial by a member of the research team and given a copy of the Registered Medical Practitioner Form (England, Wales and Northern Ireland) and a copy of the Information Sheet. If the RMP decides that the patient is suitable for entry into the study they will be asked to complete the relevant authorisation form. The original signed form should be provided to the RMP. A copy of the authorisation form should be placed in the patient's medical notes and a copy filed in the ISF. In the event that a Personal Consultee is identified after the RMP has provided their opinion, the above process for Personal Consultee will be followed and all forms will be filed as instructed above.

In the event that a patient dies subsequent to clinical samples being obtained but prior to consent having been obtained, authorisation to recruit the patient may be sought from a RMP. The RMP will be informed about the trial by a member of the research team and given a copy of the Registered Medical Practitioner Form (England, Wales and Northern Ireland) and a copy of the Information Sheet. If the RMP decides that the patient is suitable for entry into the study they will be asked to complete the relevant authorisation form. The original signed form should be provided to the RMP. A copy of the authorisation form should be placed in the patient's medical notes and a copy filed in the ISF.

8.4 Patient Consent to Continue (Adults) –England, Wales and Northern Ireland

Site research staff as delegated by the PI will assess whether the patient has regained capacity to give informed consent. Patients may be approached to obtain permission to continue in the study either whilst still in ICU or within 96hrs after their discharge from ICU. In

the event that the patient does not regain capacity, or staff have been unable to obtain consent to continue, the opinion provided by the Personal/Nominated Consultee will continue.

The consent to continue process will include providing the Covering Statement, Patient Information Sheet and Consent Form and allowing sufficient time for the patient to understand the material and ask questions. If the patient agrees to continue in the study they will be asked to sign the Consent Form which will then be counter signed by a member of the research team. The original signed form should be provided to the patient. A copy of the Consent Form should be placed in the patient's medical notes and a copy filed in the ISF.

If the participant declines on-going participation in the study this will be noted in the CRF and no further follow-up will take place. Blood samples and data collected up until that point will be pseudonymised before returning to Queen's University Belfast and the co-ordinating centre respectively.

8.5 Withdrawal of Consent

Participants, their Parent/ Legal Representative, Personal/ Nominated Consultee or Registered Medical Practitioner may withdraw the patient from the study at any time without prejudice. In the event of a request to withdraw, participants will be given the option to withdraw consent from part or all of the study, including long term storage of blood samples. In the event of a request to withdraw from the study anonymised data recorded up to the point of withdrawal will be included in the study analysis unless requested otherwise. We will seek permission to continue to collect patient data during the patient's hospital admission and to follow up to ascertain their long term health status using NHS/HSC hospital information systems, NHS Digital or via their GP (if they have been discharged).

9. SCHEDULE OF ASSESSMENTS AND STUDY PROCEDURES

9.1 Schedule of Assessments

All patients will be evaluated during the study and data collected at each of the following time-points. For routinely collected clinical data the NHS record will be the source document and for study specific clinical measurements the CRF will be the source document, with the exception of the EQ-5D-5L which may be originally completed on a paper worksheet.

Baseline

- Age and gender
- Inclusion and exclusion criteria
- Hospital admission date and location of patient prior to admission
- ICU admission date and main diagnosis
- Date research blood sample obtained for index tests and reference standard test
- Candida colonisation status at non-sterile anatomic sites, as determined by local laboratory testing in the course of normal clinical care
- Drug, dose and start date of systemic antifungal therapy
- Indication for starting antifungal therapy (e.g. for suspected or proven Candida infection)
- Patient characteristics triggering suspicion of Candida infection (e.g. fever, leucocytosis, increasing inotrope requirement, new or worsening organ failure, signs of intra-abdominal sepsis, failure to demonstrate improvement with broad-spectrum antibacterial treatment)
- Severity of illness indicators: APACHE II on admission to ICU (ICNARC case mix programme number) and SOFA score (adults) & PELOD-2 score (children- when available) on the day of recruitment.

Index and Reference Test Data

Assessed by central laboratory research staff (blinded to reference test results):

- Outcome of each index test in all participants sampled. Because the classification of index test results requires no subjective assessment, staff completing a given index test will not be blinded to the results of other index tests. However, staff completing index tests will be blinded to the results of reference tests.
- Laboratory tests to support classification of participants using a constructed reference standard for probable Candida infection.
    - Mannan antigen
    - Anti-mannan antibody

Assessed by site staff:

- Outcome of reference standard for proven fungal disease, as applied to Candida infection (based on data collected/laboratory results from day of enrolment). This will comprise:
    - Blood culture, yielding Candida species, drawn within 24 hours of starting antifungal treatment; AND/OR
    - Culture showing Candida species in specimen obtained by a sterile procedure from a normally sterile site (excluding urine). This includes a drain placed within 24 hours before sampling.

    A blood culture will be drawn from each participant within 24 hours of starting antifungal treatment, usually in the course of standard clinical care, in accordance with usual practice for patients started on antifungal treatment. Specimens from

other normally sterile sites will be obtained as considered appropriate by the attending physician in the course of normal clinical care.

- Outcome of any blood cultures yielding Candida species taken +/-7 days from obtaining the research blood sample.

- Host factors and clinical findings pertinent to classification using a recently constructed consensus definition for probable Candida infection. Data collection for this classification will comprise:

    - HOST FACTORS:
        - Glucocorticosteroid treatment (prednisolone equivalent of ≥ 20 mg/day or >1mg/kg prednisolone for children under 20kg)
        - Treatment with other systemic immunosuppressant drugs
        - History of diabetes
        - Major surgery during current ICU episode
        - Renal replacement therapy
        - Neutrophil abnormality (e.g. inherited neutrophil deficiency)
        - Impaired gut wall integrity (Recent abdominal surgery, biliary tree abnormality, recurrent intestinal perforations, ascites, mucositis, severe pancreatitis, parenteral nutrition)
        - Impaired cutaneous barriers to bloodstream infection (Presence of central vascular access device, hemodialysis)
        - Colonization with *Candida* species in ≥ 2 sites (Respiratory tract secretions, stool/rectal swab, skin, wound sites, urine and drains that have been in place for ≥24 hours)
        - Solid organ transplant

    - CLINICAL FINDINGS
        - Presence of clinical findings consistent with an infectious disease process that are otherwise unexplained (e.g. fever, leucocytosis, increasing inotrope requirement, new or worsening organ failure, signs of intra-abdominal sepsis, failure to demonstrate improvement with broad-spectrum antibacterial treatment)

Day 1 - Day 28

- Duration and dose of treatment with each systemic antifungal drug prescribed
- Occurrence of side effects (specifically liver/kidney failure) related to antifungal therapy

Day 28

- Mortality
  EQ-5D-5L questionnaire for adults only, measured on preferably at day 28 but can be completed at a later date.

Day 90

- Mortality
- Discharge data including;
    - Date of critical care discharge
    - Date of hospital discharge
    - Location on hospital discharge

9.2 Study Procedures

9.2.1 Blood Sampling

Blood cultures will be taken in the usual manner, for the participating study site, in the course of routine care. The standard care blood culture must be obtained **within 24 hours of starting antifungal treatment**. A 'research' blood sample for testing should be taken at the same time as the standard care sample from an eligible patient,, that is 'paired' with one of the standard care blood cultures. For adults, this will be approximately 14mL. For children, the preferred research sample volume is 4mL, however, this may be either increased or decreased as deemed appropriate by the clinical team up to a maximum of 14mL. If it is not possible to obtain the research blood from the same sampling event as the blood culture then research blood should be obtained as soon as possible **within 24 hours of the standard care blood culture** being taken, using the same sampling technique as the standard care blood culture it is paired with (i.e. venepuncture or accessing the same vascular device), when possible.

Specimens from other normally sterile sites will be obtained as considered appropriate by the attending physician in the course of normal clinical care.

9.2.2 Sample Processing and Storage

Arrangements for sample processing and storage are described in the sample handling guideline.

9.2.3 EQ-5D-5L Questionnaire

Health related quality of life (HRQoL) will be measured in adult participants using the EQ-5D-5L administered preferably at day 28 but can be completed at a later date. Where the patient has been discharged from hospital, the questionnaires may be administered by telephone.

9.2.4 Participant Follow Up

Data will be censored at 90 days should patients still be in ICU and/or hospital. Patient survival after discharge from hospital will be determined either from hospital information systems (e.g. electronic care record) or by using the NHS Digital if available in that region or by contacting the GP (which will be undertaken centrally by NICTU staff).

9.2.5 Clinical Management of Patients in the Study

There will be no change to standard care treatment. Results of index tests will not be made available to clinical care teams.

10. DATA COLLECTION & MANAGEMENT

10.1 Data Quality

Data integrity and study credibility depend on factors such as ensuring adherence to the protocol and using quality control measures to establish and maintain high standards for data quality.

The Chief Investigator (CI) and CTU will provide training to site staff on trial processes and procedures including the case report form (CRF) and data collection.

Quality control is implemented by the CTU in the form of Standard Operating Procedures (SOPs), which are defined to encompass aspects of the clinical data management process, and to ensure standardisation and adherence to International Conference of Harmonisation Good Clinical Practice (ICH-GCP) guidelines and regulatory requirements.

Data validation will be implemented and discrepancy reports will be generated following data entry to identify discrepancies such as out of range, inconsistencies or protocol deviations based on data validation checks programmed in the clinical trial database.

10.2 Data Collection

All data for an individual patient will be collected by the PI or designee and recorded in source documents/ electronic CRF for the study. Patient identification on the CRF will be through their unique trial identifier, allocated at the time of recruitment.

Data should be entered onto the online electronic study database as per the CRF entry guidelines.

10.3 Data Management

Following the entry of patient data into the study database, the data will be processed as per the CTU Standard Operating Procedures (SOPs). Data queries will be generated for site staff as required to clarify data or request missing information. The designated site staff will be required to respond to these queries within approximately 2 weeks. All queries will be responded to and resolved within the study database. Any amended information will then be entered in the study database.

11. STATISTICAL CONSIDERATIONS

11.1 Sample Size

The sample size of 1250 gives 90% power to test the negative predictive value (NPV) > 99% and 93% power of point estimates for sensitivity > 90%.

Assumptions:

(i) In a survey of clinicians, the “minimum acceptable threshold for sensitivity” of a test that would be used to stop empirical antifungals, 90% emerged as an important sensitivity cut-off to influence practice.

(ii) Based on the above survey, clinicians were asked to select a minimum threshold of NPV to allow discontinuation of antifungals and a value of greater than 98% would satisfy the test performance requirements of all respondents. As the disease prevalence is anticipated to be low, we have set a more stringent criterion of 99% NPV for the sample size calculation.

(iii) 4% true disease prevalence

(iv) 92% true test specificity, and 95% true test sensitivity.

(v) 5% dropout

Among the 1250 participants at least 1188 will provide evaluable data (95%), of whom 48 are expected to have true infection (4%). With up to 4 false negative results with the best index test (or combination), the 95% CI around a point sensitivity estimate of 91.7% would be 80%-97.7%. This indicates the approximate size of the confidence interval envisaged and reflects a degree of precision that is likely to be acceptable to clinicians if the point sensitivity estimate is above 90%.

11.2 Statistical Methods

The main analysis will be undertaken to estimate the diagnostic test accuracy of each index test, expressed as sensitivity, specificity, positive/negative predictive values (at specified prevalence) and positive/negative likelihood ratios. They will be calculated with their respective 95% confidence intervals, to express precision of these measures. The PCR-based index tests will produce a categorical result whereas the BDG test will produce a quantitative result. The BDG results will be classified as positive or negative before data analysis begins and the cut-off value used for this will be based on established manufacturer recommendations and expert opinion (currently 80pg/mL).

Analysis of test combinations will also be undertaken as a secondary analysis and will include assessment of these accuracy metrics for all possible permutations of index test results. Taking account of FDA guidance, use of a constructed reference standard will be used for the main analysis because of the difficulties inherent in other approaches when there is no perfect reference test available. The main analysis will, firstly, be undertaken using the international consensus definition of proven fungal disease, as applied for Candida infection, as the reference standard to classify participants. This is acknowledged as an imperfect standard; while its specificity for fungal disease is accepted to be high, its sensitivity is the main source of imperfection. Therefore, it is foreseeable that use of this reference standard alone in the analysis may lead to underestimation of the specificity of the index tests; this may arise if the reference standard fails to detect participants with true disease in instances where the index tests correctly detect this. This concern will be mitigated by also using the forthcoming availability of an internationally-accepted expert consensus standard for probable Candida infection which has been specifically developed for application to ICU patients.

Therefore, as well as being completed using the definition of proven infection, the analysis will also be undertaken using this definition of probable infection; hence, in a secondary analysis,

the reference standard will be proven + probable Candida infection. This helps to overcome the imperfection in sensitivity implicit in using only the definition for proven infection – although this may trade-off some specificity in the reference standard.

Using this approach, we will produce a range for the diagnostic accuracy metrics based on these two reference standards; this reflects uncertainty in the classification of patients resulting from the absence of a perfect reference standard. In the present study, the reference standard comprising proven + probable infection will be particularly useful since certainty in maximising disease detection is a priority when a test may be used to rule-out infection & stop treatment. When future test users consider adopting the index tests, they will be able to consider both the 'optimistic' and pessimistic' accuracy scenarios depending on whether their intended use of the tests is to rule-in or rule-out infection.

11.3 Missing Data

Where data is incomplete despite the efforts to ensure continuous high quality data collection and reporting, information relating to the corresponding participant will be excluded from relevant analyses. A dropout rate of 5% has been accounted for in the sample size calculation.

11.4 Health Economic Analysis

11.4.1 Clinical Effectiveness Modelling

The clinical effectiveness of a test-based protocol used to stop empirical antifungal therapy will be modelled for each index test & test combination. This will take account of their diagnostic accuracy as well as the expected benefits and disadvantages of using such protocols to stop treatment. Benefit will be based on unnecessary antifungal treatment avoided (expressed as number of treatment-days) and disadvantage based on necessary antifungal treatment inappropriately stopped. This analysis will include estimation of the proportion of patients receiving unnecessary antifungal treatment, which will be derived from the two reference standards used in the main analysis and expressed as a range with 95% CI. We will take account of various degrees of implementation of the proposed protocol to reflect reduced compliance due to factors such as severity of illness and Candida colonisation rates, which may influence clinical practice (even though this may not always be appropriate influence).

11.4.2 Economic Modelling

Given that this is a diagnostic test accuracy study, with participants treated in accordance with standard NHS practice, it is not possible to conduct a cost-effective analysis solely from the results of the trial. As such, all evidence produced on the relative cost-effectiveness of the three tests will need to be modelled. All analyses will be conducted in accordance with the NICE reference case. The most important data required for the analysis is the relative sensitivity and specificity of each strategy (consisting of a single or multiple tests). These data would allow proportions from a hypothetical cohort of patients to be divided into patients who had antifungal treatment appropriately discontinued earlier than occurs with standard care (due to a protocol incorporating an index test), and those patients who had antifungal treatment inappropriately discontinued earlier than occurs with standard care (due to a protocol incorporating an index test). These two groups represent patients who would benefit from the introduction of a protocol incorporating the index tests and those who would be harmed.

The cost and quality adjusted life year (QALY) implications associated with each group would be estimated from modelling. An outline of the anticipated model is provided. A key concept will be the division of the population into four for each index test under study. It is envisaged

that the distribution of patients across the four categories can be estimated from the A-Stop study. The categories are:

1) A patient has fungal infection and the index test shows a positive result (true positive)
2) A patient has fungal infection and the index test shows a negative result (false negative)
3) A patient does not have a fungal infection and the index test shows a positive result (false positive)
4) A patient does not have a fungal infection and the index test shows a negative result (true negative)

For all four populations there will be an increase in the costs associated with the use of a new, rapid, test in addition to standard practice. This will be estimated from data collected in the A-Stop study.

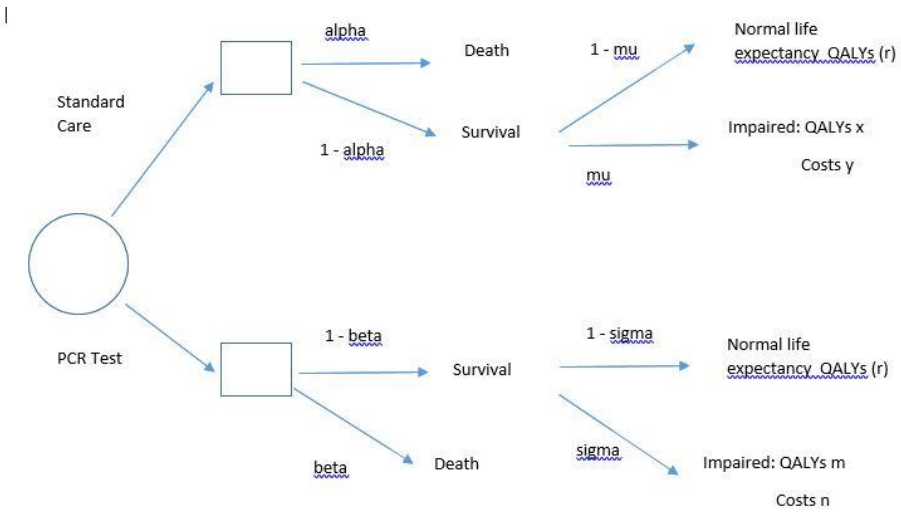
Initial clinical advice suggest that where the rapid (index) test is positive (populations 1 and 3) there would be no change in the clinical management of the patient.

There would, however, potentially be different clinical management for population 2 (where antifungals may be inappropriately stopped) and for population 4 (where antifungals may be appropriately stopped).

Patients in Population 2 are at increased risk of adverse outcomes (mortality and morbidity) and there may be cost implications, both of reduced drug costs and potentially for longer duration of hospitalisation (both in the ICU and total duration of stay). Patients in Population 4 are not at risk of fungal infection and there may be a reduction in drug costs, and potential reductions in adverse events associated with antifungal treatment and duration of hospitalisation.

A schematic of the anticipated model for patients with a false negative result is provided in Figure 2. Key information denoted in the figure are described below. It is anticipated that these values would be populated from a mixture of literature review, the A-Stop study and elicitation where necessary.

1) Alpha and Beta provide the relative survival between those who receive standard care and those who have antifungals withdrawn inappropriately following a rapid test.
2) Mu and Sigma provide the relative proportion of survivors who have impaired quality of life dependent on whether they received standard care or had antifungals withdrawn inappropriately following a rapid test. It is possible that there will be multiple impairment states based on the data identified.
3) R. This will be dependent on the age of the patient. It is possible that there may be a reduction in utility, but not that associated with impaired states.
4) X and M would be calculated taking into account any data on life expectancy and utility (which could differ between treatments).Y and N would be calculated based on life expectancy and cost per year (we may need to elicit this) Separate values have been used for standard of care and the rapid test arms to allow for any difference in the costs and disutility of impairment between the arms.



In addition there will be costs associated with increased drug costs in the standard care arm, and potential differential in utility within the patient treatment phase, and potentially longer duration of hospitalisation.

Figure 2: Anticipated model structure for patients with false-negative index test result.

The model will allow an estimate of the cost per QALY gained to be produced which would allow the cost-effectiveness of the strategies evaluated to be viewed within the context of published NICE cost-effectiveness thresholds (£20,000 and £30,000 per QALY gained). A full exploration of the uncertainty in the conclusions from the modelling will be undertaken. Value of information analyses will also be undertaken to determine those parameters with the greatest influence on the conclusions and to estimate whether future research is likely to represent value for money.

11.5 Additional Analysis

Baseline characteristics and follow-up data will be presented using descriptive statistics. A number of exploratory analyses will also be undertaken to support the main analysis:

11.5.1 Comparison of the Diagnostic Accuracy of Index Tests Singly and in Combination

The diagnostic accuracy of the index tests (alone and in combination) will be compared initially using Cochran's Q test at the 5% significance level. If significant, then McNemar's test will be used to explore further which test (or combination) is the most accurate compared to the reference standard. Corresponding 95% confidence intervals for the paired differences will also be generated.

11.5.2 Subgroup Analysis

An exploratory sub-analysis of the main diagnostic accuracy analysis will be undertaken to evaluate variation in accuracy measures in the following subgroups: children; patients with end-organ dysfunction, assessed using SOFA & PELOD-2 (when available) score (for adults and children, respectively); whether antifungal treatment had been administered prior to the research blood sample being obtained; patients with infection due to different Candida species; and patients with candidaemia (vs other types of invasive candidiasis, such as peritonitis). This analysis will be expressed using 99% CI.

11.5.3 Latent Class Analysis

This exploratory analysis will be carried out to support the main analysis. Assuming that both of the reference standards explored are imperfect, Bayesian latent class models (LCMs) can be used to estimate prevalence of true disease and sensitivity and specificity of the two reference standards and three index tests from the observed frequencies of each possible combination of test results. This analysis will initially assume conditional independence between the test results, however since there are obvious correlations between the reference standards and also between the two PCR based tests, this analysis will be repeated with plausible assumptions surrounding the correlations between the test results. Estimates for these correlations will be extracted from trial data where possible and cross checked with published knowledge; both fixed and random effects models will also be used to explore all possible correlations. All parameters will be estimated using 95% CIs and sensitivity analysis will be performed around any assumptions made. The results of these models will be compared using Bayesian p-values, deviance information criteria (DIC) and Akaike's information criterion (AIC).

12 DATA MONITORING

12.1 Data Access

Prior to commencement of the study, the PI will give permission for trial related monitoring, audits, ethics committee review and inspections, by providing direct access to source data and trial related documentation. Consent from patients for direct access to data will also be obtained. The patients' confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

12.2 Monitoring Arrangements

The CTU will be responsible for trial monitoring. The frequency and type of monitoring will be detailed in the monitoring plan and agreed by the trial Sponsor. Remote and central monitoring activities will be conducted in accordance with the trial monitoring plan and will comply with the principles of Good Clinical Practice (GCP).

The PI or designee should ensure that access to all trial related documents including source documents (to confirm their consistency with CRF entries) are available during any on-site monitoring visits which may take place.

13. TRIAL COMMITTEES

13.1 Trial Management Arrangements

The CI will have overall responsibility for the conduct of the study. The CTU will undertake trial management including all clinical trial applications (Ethics and Research Governance), site initiation/training, monitoring, analysis and reporting. The Trial Co-ordinator will be responsible on a day to day basis for overseeing and co-ordinating the work of the multi-disciplinary trial team, and will be the main contact between the trial team (and other parties involved. Before the trial starts site training will take place to ensure that all relevant essential documents and trial supplies are in place and that site staff are fully aware of the trial protocol and procedures. The CTU will assist and facilitate in the setting up and co-ordination of the trial committees including the Trial Management Group (TMG) and Trial Steering Committee (TSC).

13.2 Trial Management Group (TMG)

A Trial Management Group (TMG) will be established and Chaired by the CI. The TMG will have representation on it from the CTU and other investigators/collaborators who are involved in the study and provide trial specific expertise (e.g. trial statistician, health economist). This group will have responsibility for the day to day operational management of the trial, and regular meetings of the TMG will be held to discuss and monitor progress. The discussions of the TMG will be formally minuted and a record kept in the TMF.

A TMG Charter will be drawn up to detail the terms of reference of the TMG including roles and responsibilities.

13.3 Trial Steering Committee (TSC)

The conduct of the trial will be overseen by a TSC. The TSC is a group that act as the oversight body for the trial on behalf of the Sponsor/ Funder. Throughout the trial the TSC will take responsibility for monitoring and guiding overall progress, scientific standards, operational delivery and protecting the rights and safety of trial patients.

The TSC will include an independent Chair, not fewer than two independent clinicians/ trialists, a statistician, a patient representative and the CI. Representatives of the Sponsor/Funder and CTU may attend TSC meetings as observers at the discretion of the Chair. The TSC Charter will document the membership of the committee and outline the terms of reference of the TSC including roles/responsibilities, organisation of meetings, reporting, decision making and the relationship with the other trial committees. An inaugural meeting will be held prior to recruitment commencing. Subsequent meetings will be scheduled approaching the end of the internal pilot study and approximately annually thereafter.

14. REGULATIONS, ETHICS AND GOVERNANCE

The trial will comply with the principles of GCP, the requirements and standards set out by the applicable regulatory requirements in the UK and the Research Governance Framework.

14.1 Sponsorship

Queen's University Belfast (QUB) will act as Sponsor for the study and the CI will take overall responsibility for the conduct of the trial. Separate agreements will be put in place between the Sponsor and each organisation who will undertake Sponsor delegated duties in relation to the management of the study.

14.2 Funding

This study is funded by the National Institute of Health Research (NIHR) Health Technology Assessment Programme, project reference 15/116/03.

14.3 Indemnity

Queen's University Belfast (QUB) as Sponsor will provide indemnity for the management and design of the study. QUB will provide indemnity for negligent and non-negligent harms caused to patients by the design of the research protocol. The NHS indemnity scheme will apply with respect to clinical conduct and clinical negligence.

14.4 Competing Interests

The CI and members of the TMG have no financial or non-financial competing interests. The study is funded by NIHR HTA.

14.5 Ethical Approvals

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The protocol will be approved by a Research Ethics Committee.

14.6 Good Clinical Practice

The trial will be carried out in accordance with the principles of the International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines (www.ich.org).

14.7 Protocol Compliance

A protocol deviation is defined as an incident which deviates from the normal expectation of a particular part of the trial process. Any deviations from the protocol will be fully documented on the protocol deviation form in the CRF.

A serious breach is defined as a deviation from the trial protocol or GCP which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the subjects of the trial; or
(b) the scientific value of the trial

The PI or designee is responsible for ensuring that serious breaches are reported directly to the CTU within one working day of becoming aware of the breach.

Protocol compliance will be monitored by the CTU to ensure that the trial protocol is adhered to and that necessary paperwork (e.g. CRF's, patient consent) is being completed appropriately.

14.8 Protocol Amendments

The investigators will conduct the study in compliance with the protocol given approval/favourable opinion by the Ethics Committee. Changes to the protocol may require ethics committee approval/favourable opinion prior to implementation. The CTU in collaboration with the sponsor will submit all protocol modifications to the research ethics committees for review in accordance with the governing regulations.

14.9 Patient Confidentiality

In order to maintain confidentiality, all study reports and communication regarding the study will identify the patients by the assigned unique trial identifier only. The only exception to this may occur to facilitate the NICTU determining participant mortality by contacting the participant's GP. Computers where information will be stored will be password protected. Patient confidentiality will be maintained at every stage and will not be made publicly available to the extent permitted by the applicable laws and regulations.

14.10 Record Retention

The PI will be provided with an Investigator Site File (ISF) by the CTU and will maintain all trial records according to GCP and the applicable regulatory requirements. The Trial Master File (TMF) will be held by the CTU. On completion of the trial, the TMF and study data will be archived by the CTU according to the applicable regulatory requirements and as required by the Sponsor. Following confirmation from the Sponsor the CTU will notify the PI when they are no longer required to maintain the files. If the PI withdraws from the responsibility of keeping the trial records, custody must be transferred to a person willing to accept responsibility and this must be documented in writing to the CTU and Sponsor.

15. DISSEMINATION/ PUBLICATIONS

15.1 Trial Publications

The final statistical report will be provided by the Trial Statistician; it is anticipated that the study findings will be published in national and international peer reviewed journals and that the preparation of the report will be led by the CI. This will secure a searchable compendium of these publications and make the results readily accessible to the public and health care professionals. In addition study findings may be presented at both national and international meetings and also to appropriate patient groups.

15.2 Authorship Policy

Authorship will be determined according to the internationally agreed criteria for authorship www.icmje.org.

15.3 Trial Registration

The trial will be registered with the International Standard Randomised Controlled Trial Number (ISRCTN) register.

15.4 Data Sharing Statement

Requests for data sharing will be reviewed on an individual basis by the CI and TMG.

15.5 Data Access

Following the publication of the primary and secondary outcomes there may be scope to conduct additional analyses on the data collected. In such instances formal requests for data will need to be made in writing to the CI who will discuss this with the TMG and Sponsor. In the event of publications arising from such analyses, those responsible will need to provide the CI with a copy of any intended manuscript for approval prior to submission. Authorship will need to take the format of “[name] on behalf of the A-Stop Clinical Trial Group” or something similar which will be agreed by the TMG.

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Appendix 1

A-STOP & Newcastle MIC Qualitative Study: Protocol

Care pathway analysis of fungal infections in the Intensive Care Unit (ICU)

A qualitative evaluation of the risk preferences regarding the use of rapid diagnostic tests to inform antifungal therapy decision-making for critically ill patients in the ICU: Semi-structured interviews with NHS staff, patients, and legal representatives of patients.

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2 Newcastle MIC Work Package

2.1 Study design

The Newcastle MIC team will perform a set of semi-structured interviews with NHS staff, patients and legal representatives of patients. We will perform interviews with a maximum 30 NHS staff (adult intensivists, paediatric intensivists, microbiologists, laboratory managers, assistant directors from the business/development directorate or equivalent) and a maximum of 10 interviews with patients and legal representatives of patients. The aim of the interviews with NHS staff is to understand the care pathway for fungal infection diagnosis and treatment in the ICU. The aim of the interviews with patients and legal representatives is to understand their, or their dependent's, experience in the ICU and as a participant in the A-STOP trial. The interviews will last between 30-45 minutes for the NHS staff and approximately 30 minutes for the patients and legal representatives of patients. The interviewers will be conducted via video call or phone, whichever is the most convenient for the participant. The data from the interviews will be subjected to qualitative, thematic analysis, and the results will be presented in a report.

2.1.1 Participant Eligibility

Table 1: Inclusion/exclusion criteria for MIC work packages.

	NHS staff	Patients	Legal representatives
Inclusion criteria	1) Relevant expertise and experience of the management and/or diagnosis of invasive fungal infection in the ICU, 2) or, insight into possible route to adoption for diagnostic devices.	1) Discharged adult ICU patients with suspected or confirmed fungal infection as part of the A-STOP trial.	1) Legal representative of child ICU patient (>4 weeks old) with suspected or confirmed fungal infection as part of the A-STOP trial.
Exclusion criteria	None	1) Patients too unwell to participate in interview.	1) Legal representatives that lost their child.

2.1.2 Participant Recruitment

1. NHS staff

The A-STOP clinical coordinator will introduce the Newcastle MIC to the principal investigators (PIs) and lead research nurses (LRNs) at each A-STOP hospital site via email. The Newcastle MIC will liaise with the A-STOP PIs and/or LRNs to arrange the recruitment of NHS staff at their sites who are willing to participate, and who satisfy the inclusion criteria, as specified in Table 1. The Newcastle MIC will contact potential participants via email and will provide them with the participant information sheet (PIS)[1]. If the individual is willing to participate, the Newcastle MIC will organise a time and date for the interview that best suits the individual. Additional NHS staff from outside the A-STOP study may be recruited, if appropriate and necessary. These will be identified by the PIs at each A-STOP hospital site.

2. Patients and legal representatives of patients

The A-STOP clinical coordinator will introduce the Newcastle MIC to the PIs and LRNs at each A-STOP hospital site via email. The Newcastle MIC will liaise with the A-STOP PIs and/or LRNs to coordinate recruitment of patients and legal representatives of patients into this study. The PIs and/or LRNs at each A-STOP hospital site will identify and first contact patients and legal representatives of patients who satisfy the inclusion criteria, as specified in Table 1. For

[1] 'A-STOP_NewcastleMICQualitativeStudy_PIS_NHSstaff_v01.docx'

only the potential patients and legal representatives of patients who indicate to the PI/ LRN and have agreed that they are willing to be contacted about further research, will the PIs or LRNs at each A-STOP hospital site provide the Newcastle MIC team with the minimal contact information necessary on the potential participants, in a password protected spreadsheet. This information will be solely managed by a Senior NHS Healthcare Scientist in the Newcastle MIC, Dr Will Jones. When the Newcastle MIC has received contact information, they will send the potential participants (via post or email) the PIS[2], so that they can learn about what the study involves and decide whether they would like to participate. The Newcastle MIC team will give each individual a minimum of 48 hours to consider the information in the PIS, at which point they will call the individual to discuss their potential participation. At this point, the Newcastle MIC team will give them an opportunity to answer any questions they may have about the study. If they are happy to participate, the Newcastle MIC team will organise a time and date for this interview that best suits the individual.

2.1.3 Participant consent

The Newcastle MIC will take verbal consent from the participants to perform in this study. Verbal consent will be taken immediately prior to commencing the interview. To enable consent, two researchers from the Newcastle MIC team must (and will) be present on the phone or video call. One of the Newcastle MIC team will talk the participant through the aspects of the consent form[3], whilst the other serves as a witness to this consent process. After the interview a signed copy of the consent form will sent to the participant, by email or post.

The Newcastle MIC will ask for permission to audio-record the interviews. These are not mandatory for participation, but would help to ensure that the Newcastle MIC team accurately captures the perspectives of the participants. If recording is not consented to, the Newcastle MIC team will make hand-written notes (only).

2.1.4 Data management and protection

Queen's University of Belfast organisation is the sponsor for this study, based in the UK. The Newcastle MIC team are based in Newcastle upon Tyne, UK. The Newcastle MIC organisation bridges the Newcastle upon Tyne Hospitals (NuTH) NHS Foundation Trust and Newcastle University. The NuTH organisation is a named trust on the main A-STOP trial. The NuTH organisation will keep identifiable information for 5 years after the study has finished. All personal data collected from participants will be kept confidential, conforming with the rules of the Data Protection Act (2018), stored securely on a Newcastle MIC password protected computer, in an encrypted folder. Personal data will only by accessed by the team of researchers named in this protocol. No personal information will be shared at any point of this study and any data used in formal reports and publications will be anonymised. Data collected from each interview will consist of an audio or video recording or handwritten notes. Immediately after the interview, a Newcastle MIC researcher will transfer the audio data to a Newcastle MIC, password-protected computer. Also, any handwritten notes will be typed-up and stored on a Newcastle MIC, password-protected computer, and the handwritten notes will be destroyed. All other outputs arising from the interview will be stored, and processed, in the same secure manner. The web-based transcription service Otter.ai will be used to transcribe, edit and prepare transcripts based on the recorded interviews. Data is synchronised over a secure network and encrypted. No other parties have access to the data and all data is deleted from remote servers following the conclusion of the study.

[2] 'A-STOP_NewcastleMICQualitativeStudy_PIS_PatientsAndLegalRepresentatives_v01.docx'

[3] 'A-STOP_ NewcastleMICQualitativeStudy_VerbalConsentForm_PatientAndLegalRepresentatives_v01.docx' *and*:

'A-STOP_ NewcastleMICQualitativeStudy_VerbalConsentForm_NHSstaff_v01.docx'