



*Royal London  
and  
St Bartholomew's  
Hospitals*



## **Invasive Fungal Diseases and Improved Diagnostic Testing**

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# Conflicts of interest



**Research grants – advisory boards – speaker**

# Diagnosing Invasive Fungal Diseases

## *Topics I will address:*

- *IFD – is it important ?*
- Clinical diagnosis - Laboratory Diagnosis
- Can YOU do better in the lab?

# Diagnosing Invasive Fungal Diseases

## Setting the scene. True or False :

1. Globally, deaths due to IFD are commoner than TB ?
2. Mortality rates for IFD are typically 40% or more ?
3. Biomarker assays for IFD are available in 15% of labs ?
4. 85% of patients treated for IFD have *no evidence of IFD* ?

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# Diagnosing Invasive Fungal Diseases

## Global burden of fungal diseases<sup>1</sup>

- Superficial - 1 billion
- Mucosal candidiasis - 150 million
- Fungal deaths - > 1.5 million

## Global Burden of Fungal Disease – Annual Incidence<sup>1</sup>

### Acute invasive

Invasive candidiasis

~750,000

Haem - Onc

Includes 60,000–100,000 cases of  
intra-abdominal candidiasis  
From about 10 million at risk annually

Invasive aspergillosis

>300,000

*Pneumocystis jirovecii* pneumonia  
in AIDS and non-AIDS

~500,000

Cryptococcosis in AIDS

~223,000

HIV-related, up to another 10%  
non-HIV

Mucormycosis

>10,000

Based on French data = 4200.  
Based on Indian data = 910,000

Disseminated histoplasmosis

~100,000

No reliable estimates

Talaromycosis \*

~8000

SE Asia only;

# Diagnosing Invasive Fungal Diseases

## IFD management – is it important ?

- **Mortality:** ranges from **40–90%** in high-risk patients<sup>1-5</sup>
  - Invasive candidiasis , aspergillosis , mucormycosis
- **Delayed treatment** = increased mortality
- **Diagnosis** is challenging = **Empirical** treatment
- **Antifungal prophylaxis:** common in haematological malignancy and HSCT<sup>6</sup>
- **Impact?**
  - **Exposure to unnecessary drugs<sup>7</sup> , increased costs<sup>7</sup> , missed infections (?)<sup>8</sup>**
  - Increased risk of **antifungal resistance** (an emerging issue)<sup>7,8</sup>

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HSCT, haematopoietic stem cell transplant. 1. Dagenais TR, Keller NP. Clin Microbiol Rev 2009;22:447–65; 2. Wingard J. Adv Stud Med 2006;6:S526–30; 3. Skiada A, et al. Clin Microbiol Infect 2011;17:1859–67; 4. Rüping MJ, et al. J Antimicrob Chemother 2010;65:296–302; 5. Lanternier E, et al. Clin Infect Dis 2012;54(Suppl 1):S35–43; 6. Arvanitis M, et al. J Clin Microbiol 2014;52:3731–42; 7. Muñoz P, et al. J Antimicrob Chemother 2016;71(Suppl 2):ii5–12; 8. Maertens J, et al. Clin Infect Dis. 2005;41(9):1242–50; 9. Fisher MC, et al. Science 2018;360:739–42.

# Diagnosing Invasive Fungal Diseases

## IFD management – is it important ?

- Empirical treatment - **82%** (150/183) **no evidence of IFD**<sup>1</sup>
- “Optimal” management: £0.13M reduction per month<sup>2</sup>
- **NHS England budget ~ £150M per annum**
- In haemato-oncology, **80-85% of**
  - antifungal drug budget spent in patients with **no evidence of IFD**
  - patients treated for IFD have **no evidence of IFD**<sup>3</sup>

1, Whitney L, et al. *J Antimicrob Chemother.* 2019;74: 234–41;

2, Nwankwo L, et al. *Antimicrob Agents Chemother.* 2018;62:e00402–18.

3, Nannini F et al. *Haematologica.* 2014; 99: 749-749



# Diagnosing Invasive Fungal Diseases

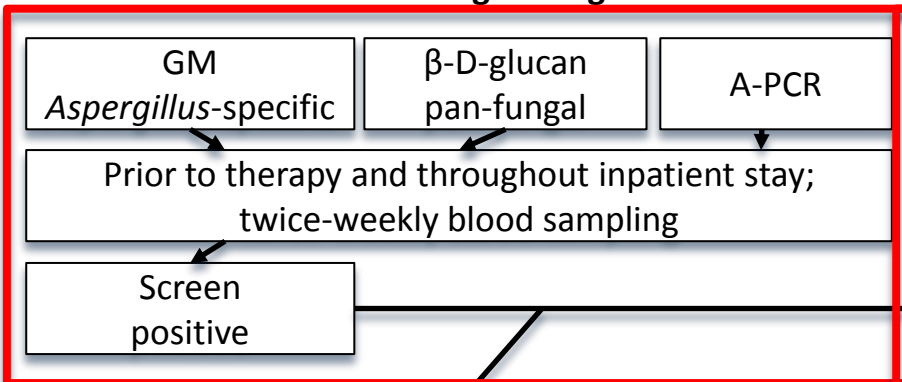
## *Topics I will address:*

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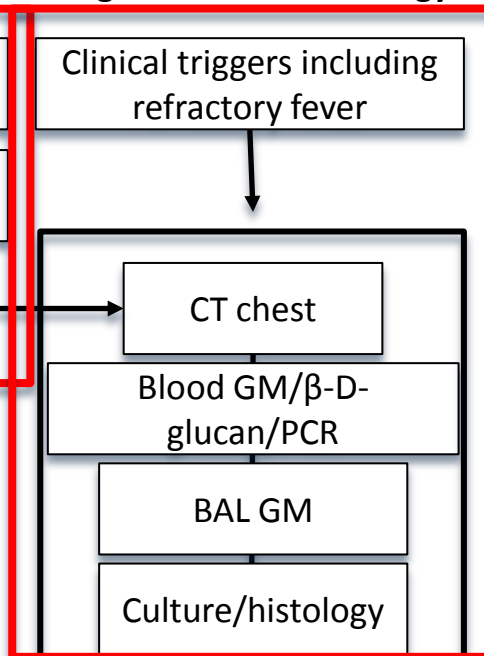
# Diagnosing Invasive Fungal Diseases

## Strategies for IFD management

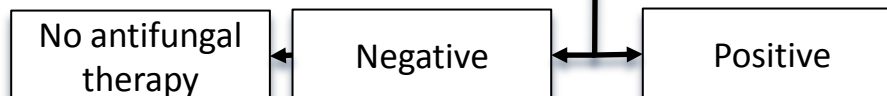
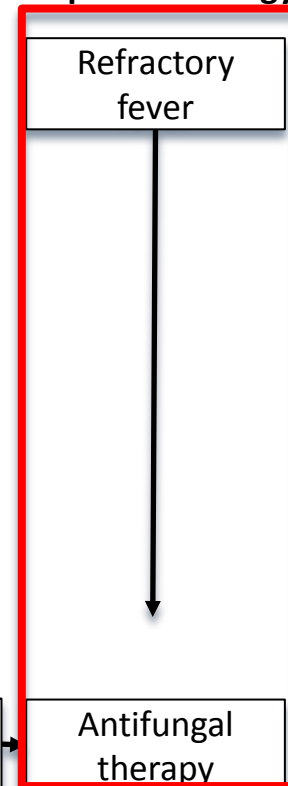
### Screening strategies



### Diagnostic-driven strategy



### Empirical strategy



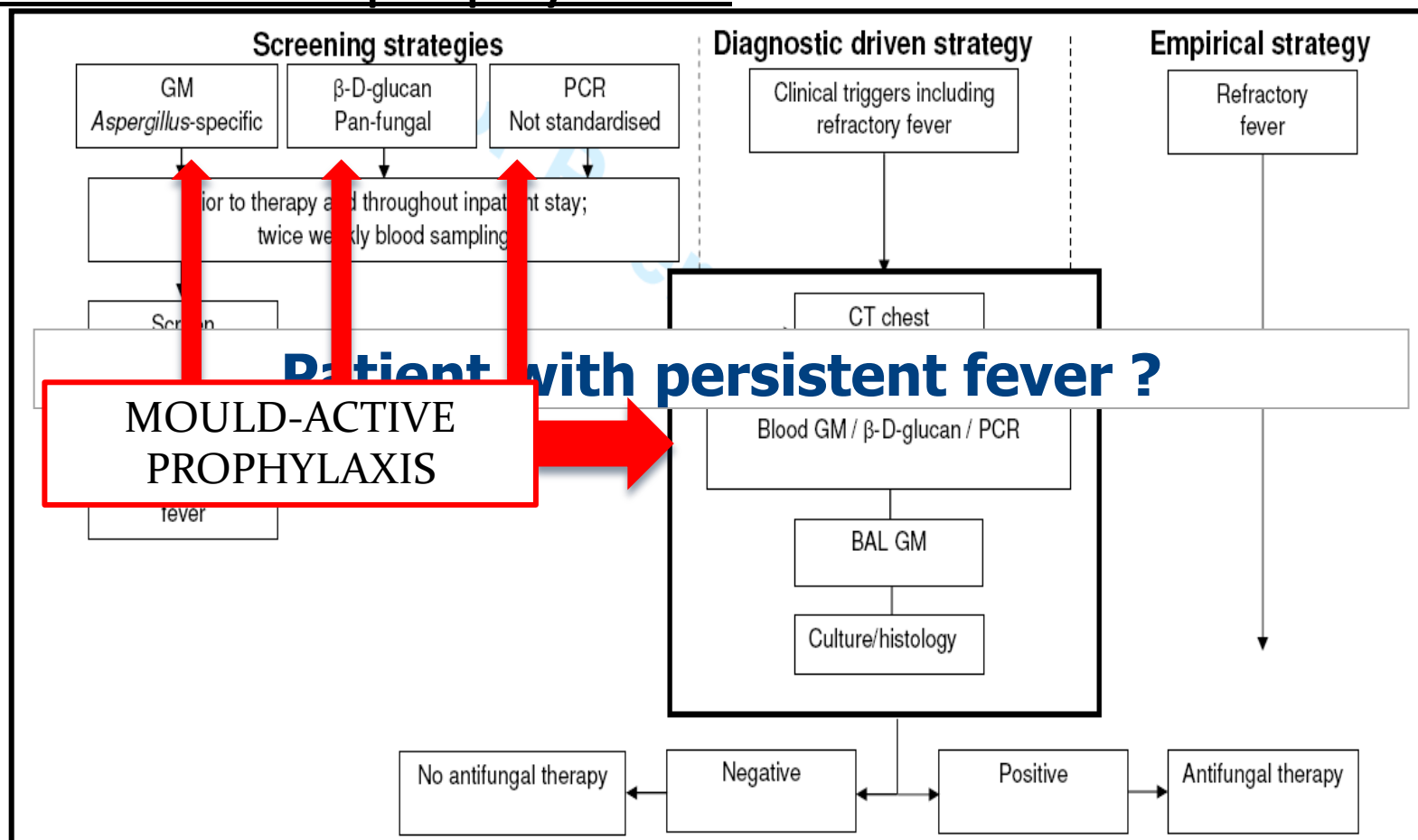
# Diagnosing Invasive Fungal Diseases

## Strategies for IFD management

- **What is usual in your centre?**
  1. Empirical
  2. Screening
  3. Diagnostic
  4. Not a clue / Don't care
- **PROPHYLAXIS (mould-active) ?**

# Diagnosing Invasive Fungal Diseases

## Mould-active prophylaxis?

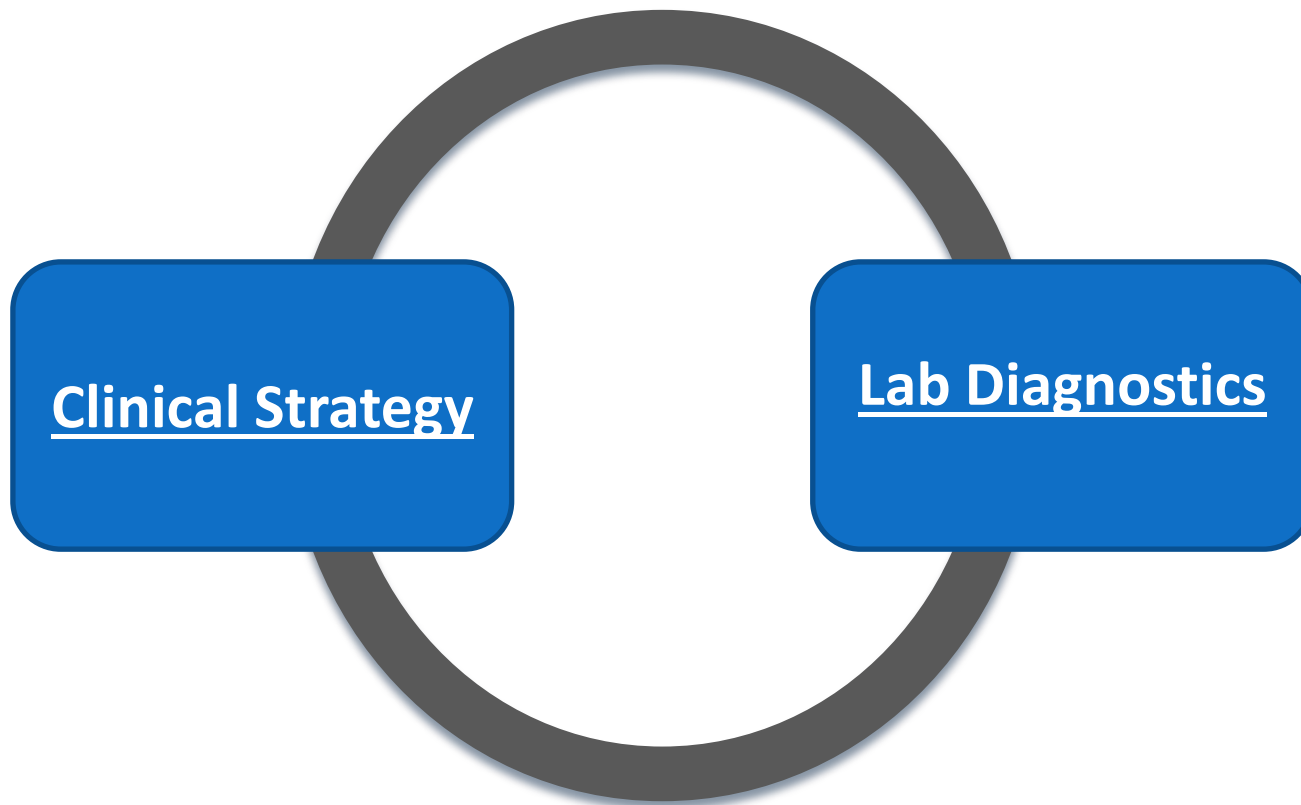


1. Mennink-Kersten MA, et al. *Lancet Infect Dis.* 2004;4(6):349–57;

2. Eigl S, et al. *Int J Antimicrob Agents.* 2015;46(4):401–5;

3. Barnes RA. *J Antimicrob Chemother.* 2008;61(Suppl. 1):i3–i6.

# Diagnosing Invasive Fungal Diseases



# Diagnosing Invasive Fungal Diseases

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# Diagnosing Invasive Fungal Diseases

## Commercially available assays

- Galactomannan – *Aspergillus* spp. (not mucor)
- $\beta$ -D-glucan – pan-fungal (not mucor, but useful for PJP)
- PCR – *Aspergillus* spp. (and resistance genes)
- **Rapid antigen tests** – lateral flow devices

# Diagnosing Invasive Fungal Diseases

## Studies in haem-onc using GM/A-PCR<sup>1-3</sup>

- 2013 empirical 'plus' vs GM + A-PCR
  - 50% mould prophylaxis
  - Decreased AF 32% vs 15% ( $p=0.002$ ); Mortality same
- 2015 GM vs GM + A-PCR
  - No mould prophylaxis
  - Decreased empirical AF 29% vs 17% ( $p=0.038$ ); Mortality same
- 2005 prospective feasibility study using GM, CT, BAL
  - Fluconazole prophylaxis
  - Decreased AF 35% vs 8%
  - **10 pts (7%) started AF based on biomarker (no fever)**

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AF, antifungal drugs; A-PCR, *Aspergillus* PCR; BAL, broncho-alveolar lavage;  
GM, galactomannan; IMD, invasive mould disease; PCR, polymerase chain reaction

1. Morrissey CO, *et al. Lancet Infect Dis.* 2013;13(6):519–28;

2. Aguado JM, *et al. Clin Infect Dis.* 2015;60(3):405–14;

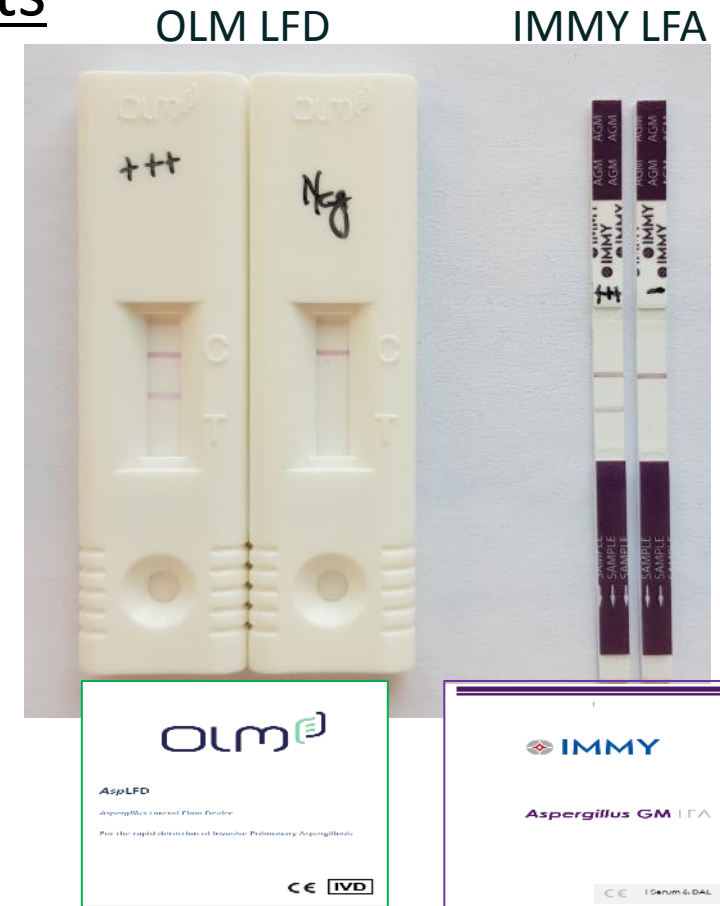
3. Maertens J, *et al. Clin Infect Dis.* 2005;41(9):1242–50.



# Diagnosing Invasive Fungal Diseases

## Studies in haem-onc using rapid tests

- Current biomarkers
  - Not available in all centres
  - Turn-around times?
- **Lateral flow tests**
  - Aspergillus-specific antigens
  - Single-sample tests
  - Fast – 15 min to 1 hour
  - Point-of-care for BAL



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BAL, broncho-alveolar lavage; IMD, invasive mould disease;  
LFA, lateral flow assay; LFD, lateral flow device

1. Heldt S, et al. *J Infect.* 2018;77(3):235–41;
2. Mercier T, et al. *J Clin Microbiol.* 2019. [Epub ahead of print];
3. Jenks JD, et al. *J Infect.* 2019;78(3):249–59;
4. Jenks JD, et al. *Mycoses.* 2019;62(3):230–6.

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# Diagnosing Invasive Fungal Diseases

## *Can YOU do better in the lab?*

- **YES !**
  - 'Rapid' assays
    - GM, BDG, A-PCR
    - Lateral flow tests ( BAL fluid )
  - Daily
  - Turn-around-time < 48 hours

# Diagnosing Invasive Fungal Diseases

## Infection Management in Haem-Onc

### Prophylaxis?

- Fluoroquinolone
- Antifungal
- Antivirals

**0 Hours  
1<sup>st</sup> Fever**

**48 Hours  
Fever**

**72 / 96 hours  
Ongoing fever**

Antibiotics

Anti-fungal ?

*Escalating empirical therapy – no diagnosis!*

Pip-Tazo / Amik

Meropenem  
Vancomycin

**L-AMB** , Echinocandin ,

**Voriconazole** , Isavuconazole

B/C : blood culture ; L-AMB, liposomal amphotericin B

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# Diagnosing Invasive Fungal Diseases

- Empirical reality of clinical practice



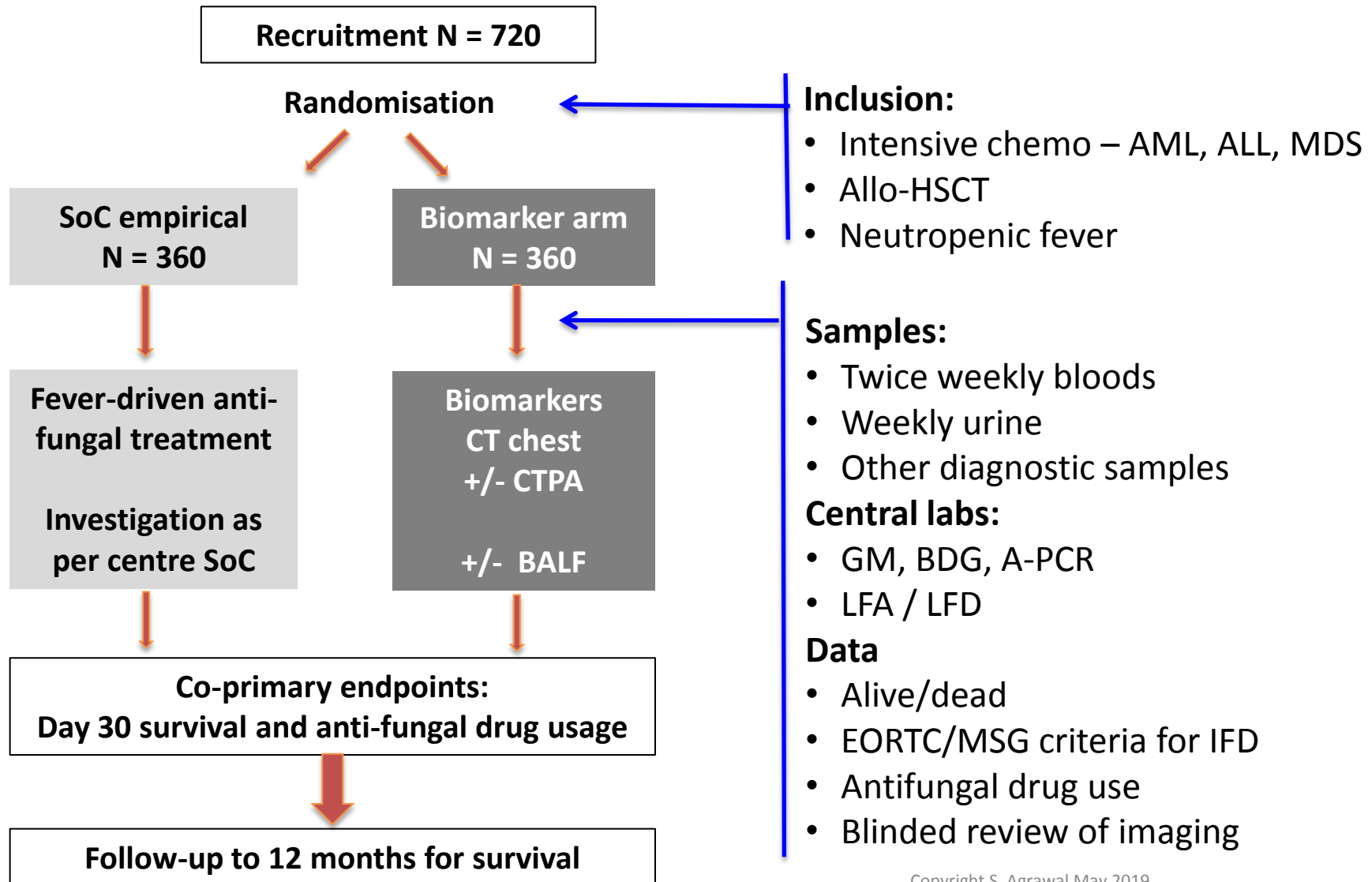
**No Diagnostics**

**No Diagnosis**

**No Organism**

## Study Flowchart: DEFEAT-IFD

*RanDomisEd controlled trial of the safety of FEmpirical versus biomarker-guided Anti-fungal Treatment in Haemato-Oncology patients at high-risk of Invasive Fungal Disease*



# Diagnosing Invasive Fungal Diseases

## *YOU really can help :*

- *IFD is globally important – morbidity / mortality*
- *Economic impact of antifungal drugs*
- *Lack of diagnostics – empiricism ( high mortality rates )*
- *Antifungal resistance – antibiotic resistance*
- *Trial data, including RCTs, showing diagnostics work*
- *UK – “could do better”*

*Your country needs you !*

# Thank you