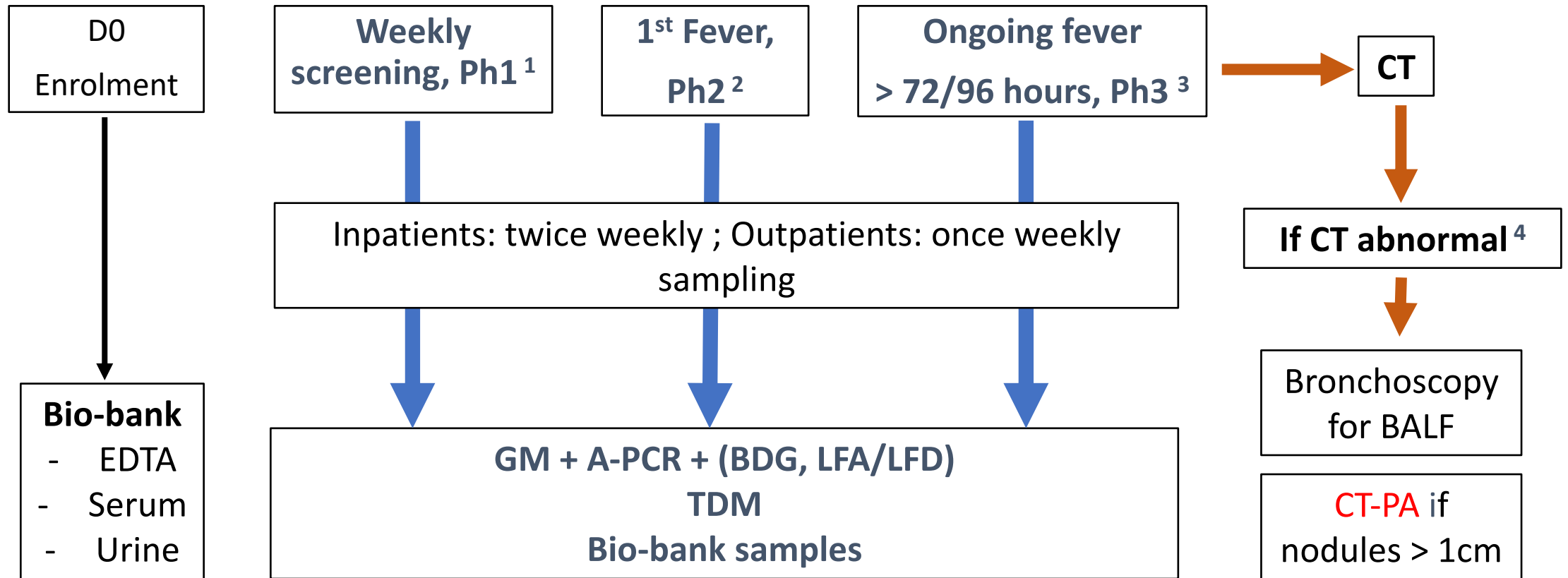
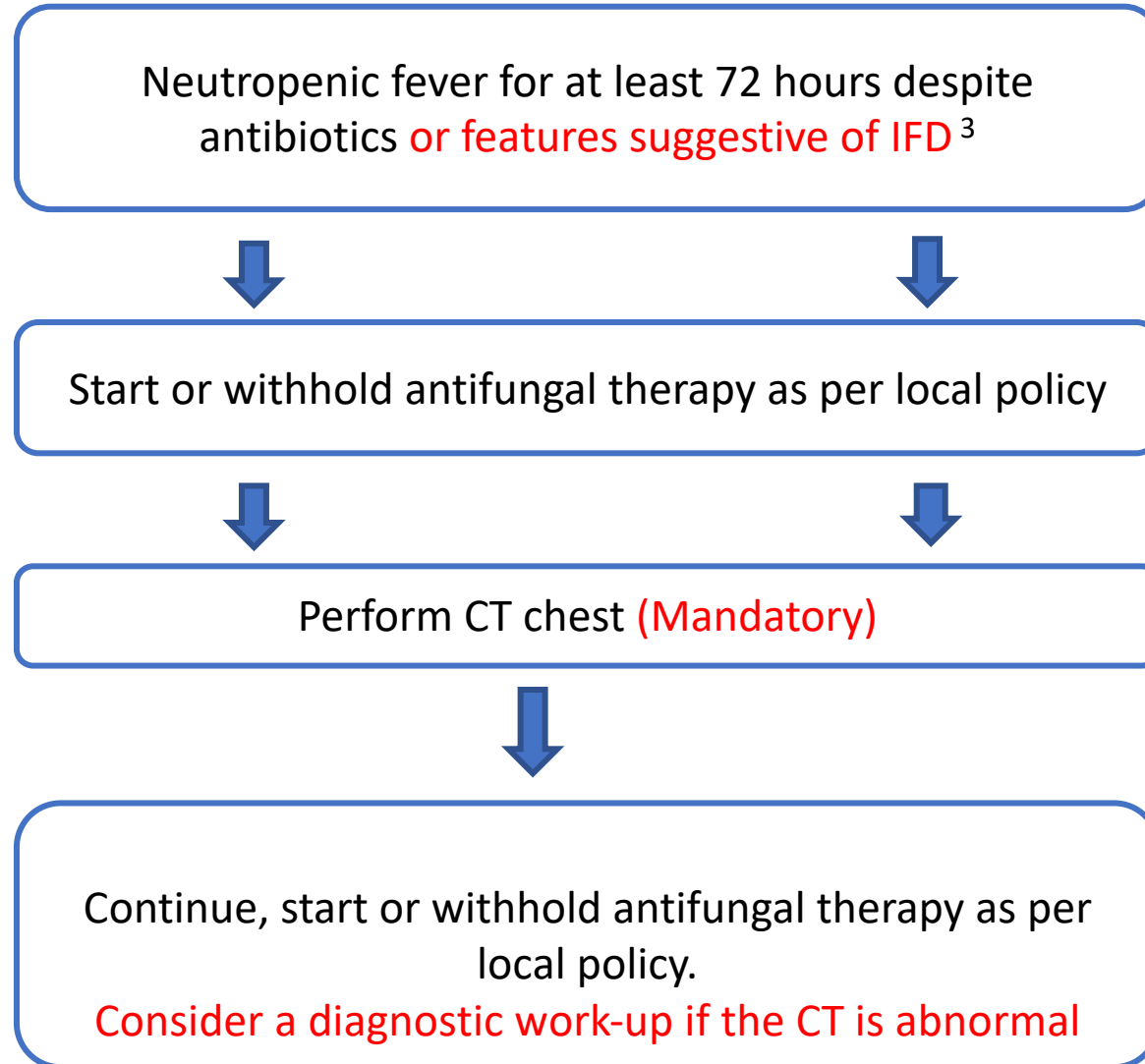


# Sampling in study - see Explanatory Notes

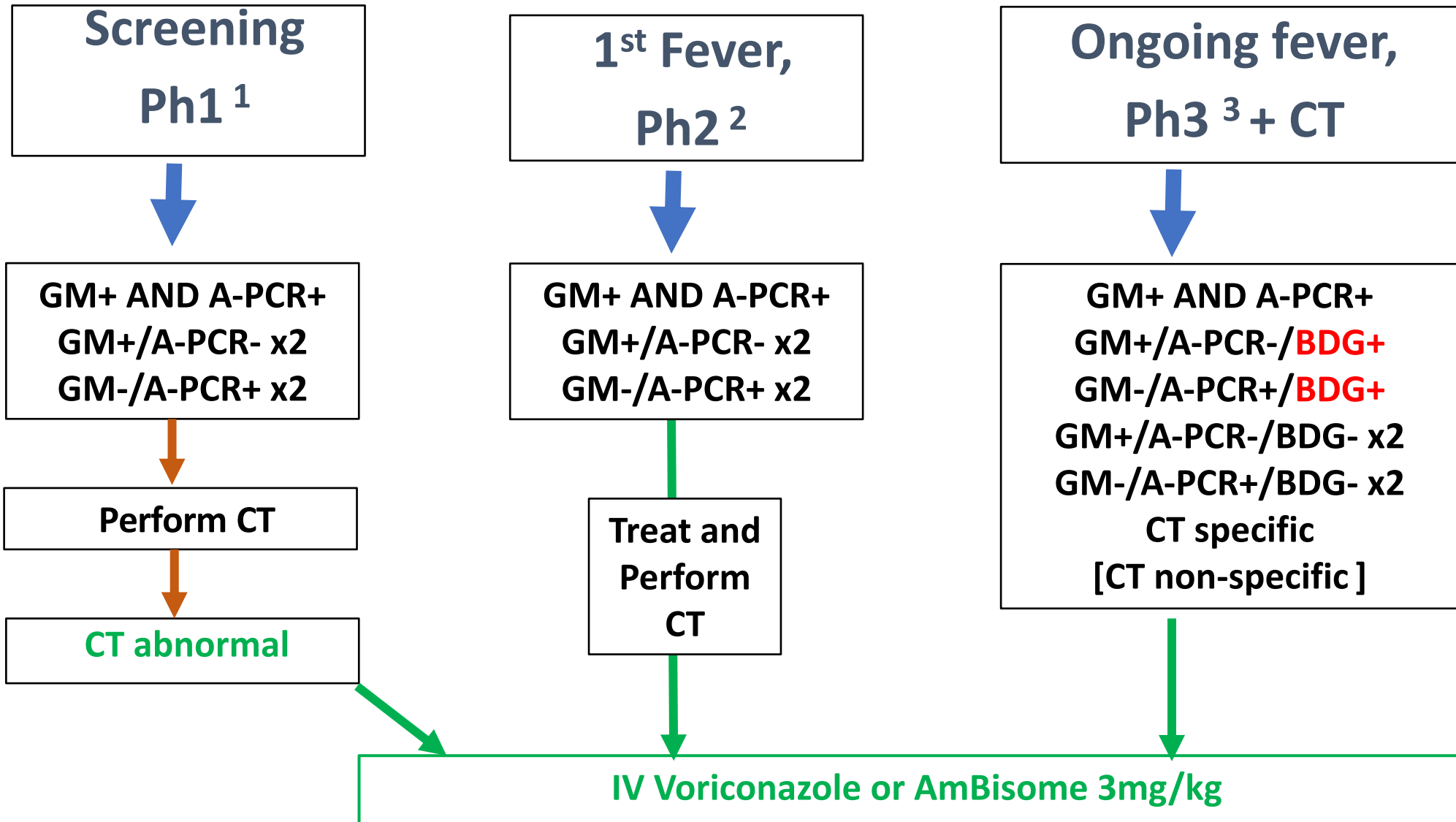


A-PCR: *Aspergillus* PCR ; BALF: broncho-alveolar fluid ; BDG: b-D-glucan ; CT-PA: CT pulmonary angiogram ; D0: day 'zero', study randomisation ; GM: galactomannan ; LFA/LFD: lateral flow assay/device on BALF; TDM : therapeutic drug monitoring for mold active azole prophylaxis ; Ph: phase of study samples – Ph1, screening; Ph2, first fever; Ph3, persistent fever

# Standard Of Care, Empirical Arm - Algorithm



# Biomarker Arm - Algorithm



### Explanatory Notes for Study Schematic

1. Screening, Ph1. Inpatients - twice weekly EDTA and serum samples – Mondays and Thursdays - and weekly urine. Only the Monday blood samples will be tested. Outpatients – once weekly EDTA, serum and urine samples.  
Continue until Ph2, neutrophil recovery ( $N > 0.5$  for 3 consecutive days), discharge or death.
2. Fever or other clinical indicator of infection. With the first fever, (Ph2), send EDTA and serum samples. If any assay is *positive* ( $GM > 0.5$ , A-PCR positive), then a confirmatory sample must be sent immediately. If all assays are negative continue weekly screening.
3. With persistent/relapsing fever or other clinical feature suggestive of invasive fungal disease (IFD), (Ph3), send EDTA and serum samples. For adult patients: If **only 1 of 3** assays is positive ( $GM > 0.5$ , A-PCR or  $BDG > 80$  mg/L), then a confirmatory sample must be sent immediately. If all assays are negative, continue weekly screening. If 2 of 3 assays are positive, Ph3 is regarded as positive and start antifungal treatment.  
For paediatric patients (aged 2 – 16 yrs of age): If both assays are positive in the first sample, start antifungal treatment. If 1 of 2 assays is positive ( $GM > 0.5$  or A-PCR), then a confirmatory sample must be sent immediately. If all assays are negative, continue weekly screening, if 1 of 2 assays is positive in the confirmatory sample, start antifungal treatment.  
Features suggestive of IFD:
  - a. Any new fever during prolonged, severe neutropenia or immunosuppression
  - b. Fever resistant to broad spectrum antibacterial therapy while neutropenic for at least 72 hours
  - c. Symptoms and signs of new, resistant or progressive lower respiratory tract infection, e.g. pleuritic pain, pleural rub
  - d. Prolonged, severe lymphopenia and fever in chronic graft versus host disease (GVHD)and immunosuppression
  - e. Symptoms and signs of progressive upper respiratory tract infection
  - f. Periorbital swelling
  - g. Maxillary swelling and tenderness
  - h. Palatal necrosis or perforation
  - i. Focal neurological or meningeal irritation symptoms and signs with fever
  - j. Unexplained mental changes with fever
  - k. Papular or nodular skin lesions
  - l. Intra-ocular signs of systemic fungal infection
4. For a CT chest to be classified as abnormal (e.g. suggestive of infection) the specific EORTC/MSG CT criteria do NOT need to be met; all imaging suggestive of infection is classified as abnormal and requires bronchoscopy and lavage