

Article title: Application of transthoracic echocardiography for cardiac safety evaluation in the clinical development process of vaccines against Group A *Streptococcus*

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Online Resource 1 Investigator questionnaire (Investigator’s guide for collection of signs and symptoms of pharyngitis and major manifestations of acute rheumatic fever [ARF]: rheumatic carditis and other manifestations)

Pharyngitis – ask participants if they had documented pharyngitis or were treated for one since last clinic visit	
<p>Symptoms</p> <p>Throat pain / sore throat</p> <p>Difficulty swallowing</p> <p>Not eating as much</p> <p>Not drinking as much</p> <p>Croaky voice</p> <p>Feeling hot</p>	<p>Signs</p> <p>Fever (>38°C)</p> <p>Swollen, enlarged tonsils</p> <p>Erythematous tonsils with exudate</p> <p>Enlarged, tender cervical lymph nodes</p> <p>Absence of cough</p>
Major manifestations of ARF	
<p>A) Rheumatic carditis (mostly valvulitis)</p> <p>B) Other manifestations of ARF</p> <ul style="list-style-type: none"> ○ Arthritis (usually migratory polyarthritis) ○ Sydenham chorea ○ Erythema marginatum ○ Subcutaneous nodules 	
Rheumatic carditis	
<p>Symptoms</p> <ul style="list-style-type: none"> ○ Fatigue ○ Weakness ○ Shortness of breath (dyspnea) on exertion ○ Shortness of breath when lying flat (orthopnea) ○ Sudden awakening at night with breathlessness (paroxysmal nocturnal dyspnea) ○ Chest pain ○ Bilateral feet swelling <p>Physical examination findings</p> <p>a) <u>Mitral regurgitation (MR): assessed by Doppler auscultation</u></p> <ul style="list-style-type: none"> ○ Mid/pan-systolic murmur at apex, radiating laterally (occasionally medially/ posteriorly) ○ Apical mid-diastolic murmur (Carey Coombs) ○ Displaced apex beat in severe MR 	

b) Aortic regurgitation: assessed by Doppler auscultation

- Decrescendo early diastolic murmur at the base of the heart (aortic area) or left sternal edge, accentuated by the patient sitting forward in held expiration
- Mid-to-late diastolic murmur heard best at the cardiac apex (Austin Flint)
- Systolic murmur due to increased flow
- Wide pulse pressure

c) Heart block assessed by electrocardiography

- Prolonged P-R interval

d) Cardiac failure

- Displaced apex beat
- Pulmonary edema
- Raised jugular venous pressure
- Bilateral pedal edema
- Tachycardia
- Tachypnea

Signs and symptoms of other manifestations of ARF

Arthritis

Painful, tender joints, most commonly in the knees, ankles, elbows and wrists (migratory, asymmetrical)

Sydenham chorea

Jerky, uncoordinated movements, especially affecting the hands, feet, tongue and face, disappears during sleep

Subcutaneous nodules

Crops of small, round, painless nodules over the elbows, wrists, knees, ankles, Achilles' tendon, occiput and posterior spinal processes of the vertebrae

Erythema marginatum

Circular patterns of bright pink macules or papules on the trunk and proximal extremities

Online Resource 2 Participant leaflet/questionnaire (participant's guide for reporting symptoms of rheumatic carditis and arthritis as most prevalent manifestations of acute rheumatic fever in adults)

Symptoms of rheumatic carditis
Fatigue Weakness Shortness of breath (dyspnea) when you are physically active Shortness of breath when lying on your back (orthopnea) Sudden awakening at night with breathlessness (paroxysmal nocturnal dyspnea) Chest pain Swelling in both feet
Symptoms of arthritis as a manifestation of acute rheumatic fever
Arthritis Painful joints. This is most common in the knees, ankles, elbows and wrists. The pain can affect any joint and move from one joint to another.