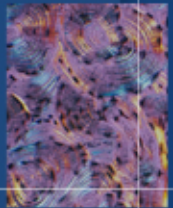




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7th Annual Phase I Clinical Trials

- Breaking Free from the Mold - Examining Challenges and Innovation in Early Phase I Study Designs
- Stephen Freestone MD FRCPE FFPM
Medical Director

Phase I Studies

- Principal aims:
 - Assess safety and tolerability
 - Determine pharmacokinetics
 - Assess pharmacodynamic effects (when possible)

Pharmacodynamic Measurements

Analgesia

- Pain models (SETT)

CNS

- EEGs
- Computerized pupilometry
- Computerized cognitive function

Gastrointestinal

- Gastric pH
- Gastric emptying
- Endoscopic assessments including GI mucosal changes

Cardiovascular

- Holter monitoring
- 24hr blood pressure monitoring
- Impedance cardiography
- Electrocardiography including digital ECG databases
- QT interval analysis

Hematology

- Platelet function & coagulation factors
- FACS analysis
- Bleeding time
- Hematology sampling including differential white blood cell counts

Respiratory

- Respiratory function tests (spirometry)
- Bronchial provocation tests
- Bronchoalveolar lavage

Dermatology

- Skin biopsies

Other

- Clinical chemistry assessment
- Immunology parameters
- Urine electrolytes and osmolality
- Creatinine clearance

Protocol Amendments

- Substantial amendments must be notified to MHRA (UK) and Ethics Committee
- Substantial amendments are changes that:
 - Impact on safety of trial subjects
 - May change interpretation of study data
- Recommend flexible protocols

Flexible Protocols

- State starting and maximum dose levels
- Wording to allow variations to dose escalation based on interim safety and / or PK evaluation
- Statements to allow variations to PK sampling schedules

“Umbrella” Protocols

- Trend to increased complexity of Phase I protocol designs.
- Now common to have ascending dose, multiple dose, food effect, age and gender comparisons in one protocol.
- Advantages - potential time and cost savings.
- Disadvantages – thorough planning required but unforeseen problems may still emerge.



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