An overview on how clinical trials are conducted: An insight into Infectious disease drugs and vaccine development.

Dr Suzanne Elliott
Q-Pharm Pty Limited

AACB-AIMS 2016
All views of this presentation made today are my personal views and not reflective of the company I work for.
An overview on how clinical trials are conducted: An insight into Infectious disease drugs and vaccine development.

- Study Design
- Use of Pathology testing
- Factors impacting on test selection
- Unusual Cases
- Updates on new therapeutic approaches for infectious diseases

AACB-AIMS 2016
Therapeutic Products Development

- Discovery Science
  - New technology
  - Intellectual Property

- Pre-clinical
  - Formulation
  - Toxicology
  - Process scale up

- Clinical
  - Clinical trials
  - Safety
  - Efficacy

- Market Entry
  - Regulatory approval
  - Reimbursement
  - Clinical uptake

- Early Phase
  - First In Human
  - Safety & Tolerability
  - PK, PD and POC

- Phase 2/3
  - Proof of Concept
  - Efficacy
  - Dose Ranging

- Phase 4
  - Post Marketing
  - Pharmacovigilance

Complex early phase studies often with Safety and POC aim
Absorption, Distribution, Metabolism and Elimination of Drugs (ADME)
Comparative PK: New Formulation Delivery

- IV – Drug 100% bioavailable
- Oral capsule – via Liver metabolism
- Transdermal – Topical – directly systematic
Vaccine Trial Design

Screening → Vaccine 1 → Follow-up → Vaccine 2 → Follow-up → Vaccine 3 → Follow-up → Follow-up → Follow-up → EOS

Screen and Vaccine 1 → Follow-up → Vaccine 2 → Follow-up → Follow-up → Follow-up → EOS
Clinical Trial: Phase 1 - Standard

- Healthy volunteers (HV) (* patients)
- Small cohorts (n = 6-10)

**Single Ascending Dose (SAD)**
- Active ± placebo (blinded)
- Sentinels (dosed 1-2 days ahead)
- Day -1 Baseline & Fasting
- Dose & confine 1-3 days (**protocol**)
- PK intense Day 1

**Multiple Ascending Dose (MAD)**
- Dose (Daily/Bidaily) & confine 3-10 days (**protocol**)
- PK intense Day 1 & D7 (± urine PK)

- Dose Escalation & Stopping rules
- Safety Review/Monitoring Committees
Clinical Trial: Phase 1 – Dose Escalation

CHB1
D-1 * D2 * D3 * D4 * D5

CHB2
D-1 * D2 * D3 * D4 * D5

CHA1
D-1 * D1 * D2 * D3 * DE * D5

CHA2
D7 * D9

CHA3

MAD

CHB2
D-1 * D1 * D2 * D3 * D4 * D5

D10

D10
Sample Collection

Clinical Trial Safety
Eligibility & Monitoring
(Blood & Urine)

- **Safety samples**
  - FBC
  - Biochemistry
  - Viral Serology
  - Urinalysis

- **Optional/Protocol Dependent**
  - Urine Drug Screen
  - Blood/Urine β-HCG
  - Urine cotinine
  - Urine/Breath Alcohol

**Blood Volume**
- Varies (mL)/Trial
- *Max over 4 months ~ 500 mL*
- Collection issues - Anticoagulants
Vaccine Studies-Immune Response

- **Antibody**
  - ELISA – Pre screening/seroprevalence
  - Virus neutralisation (eg HAI)
  - ADCC

- **Cell Mediated (PBMC)**
  - Immunophenotype (FACS) – CD3/4/8, CD20, CD25, other
  - Cytokines
  - Elispot

- **Immune Biomarkers**
Sample Collection: Considerations

- Blood Volume
- Processing instructions
- Location of where testing **Note O/S
- Shipping timing & Instructions

FUTURE USE OF STORED SPECIMENS ** HREC review – Separate Optional PISCF
- Where Samples stored?
- Period of Storage
- Identification (identifiable, re-identifiable (coded) or non-identifiable)
- Confidentiality - Who has access?
- If genetic testing – specific PISCF
- a statement that genetic testing will or will not be performed.
Suitability = Eligibility criteria

**FBC:**
- Haemoglobin (*HGB*)
- Haematocrit (*HCT*)
- Mean Cell Volume (*MCV*)
- Red blood cell count (*RBC*)
- White blood cell count (*WBC*)
  - incl differential
  
  *(NEUT, LYM, MONO, EOS, BASO)*
- Platelet count (*PLAT*)
- ± Coagulation (*PT, APTT*)

**Viral Serology**
- Hepatitis B surface antigen (*HBSAG*)
- Hepatitis C antibodies (*HCAB*)
- HIV antibodies (*HIV1AB, HIV2AB*)

**Females**
- WOCBP – β-HCG (serum/urine) (*HCG*)
- WNOCBP – *(FSH*)

**Urinalysis:** *dipstick urinalysis*
- Protein, Hemoglobin & Glucose;
- IF abnormal, complete urinalysis with microscopic evaluation is required.

Clinical Data Interchange Standards Consortium (CDISC) – datasets/nomenclature
## Biochemistry Panel
- Albumin
- Alkaline phosphatase
- Total bilirubin (conjugated & unconjugated)
- Bicarbonate/CO2 (*Bicarbonate*)
- Calcium
- Cholesterol
- Chloride
- Creatinine
- Gamma glutamyltranspeptidase (GGT)

## Biochemistry Panel
- Glucose (*Fasting**)
- LDH
- Inorganic phosphorus (*Phosphate*)
- Potassium
- Total protein
- AST
- ALT
- Sodium
- Triglycerides
- Urea (BUN)
- Uric acid

Suitability = Eligibility criteria
### Variable/non-Standard tests

#### Haematology Panel
- MCH
- MCHC
- Reticulocytes
- RDW/ PDW
- Fibrinogen, D-Dimers

#### Biochemistry Panel
- Amylase
- Lipase
- Alkaline Phosphatase
- Creatinine Kinase
- Lipid studies – HDL, LDL (VLDL)
- Thyroid – TSH, T3, T4
- Sex hormones – testosterone, oestradiol, prolactin, C-telopeptide
- Cardiac Markers – Troponin
- Reactive Markers – AFP, CRP
- Diabetes – HBA1C
- Hepatitis C – HCV virus load, genotype
95% Confidence intervals

There are some healthy people who test positive for a disease (false positive) and some people with a disease who test negative (false negative).

Extracted:-
Pathology: The Facts

https://www.rcpa.edu.au/Library/Fact-Sheets/Pathology-The-Facts/docs/Path-Fcts-Booklt
Case - Suitability = Eligibility criteria

**FBC:**
- Haemoglobin (HGB)
- Haematocrit
- Red blood cell count
- MCV
- Reticulocytes
- White blood cell count - incl differential
- Platelet count

**Haemolytic Panel:** ***variation timepoints***
- Serum haptoglobin
- Indirect (unconjugated) bilirubin
- Direct antiglobulin test (direct Coombs test) (DAT)
- Serum lactate dehydrogenase (LDH) with isoenzymes (LDH1 and LDH2) if total LDH > ULN
<table>
<thead>
<tr>
<th>Biochemistry Panel</th>
<th>Biochemistry Panel</th>
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</thead>
<tbody>
<tr>
<td>• Albumin</td>
<td>• Glucose <em>(Fasting)</em></td>
</tr>
<tr>
<td>• Alkaline phosphatase</td>
<td>• LDH</td>
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<tr>
<td>• Total bilirubin (conjugated and unconjugated)</td>
<td>• Inorganic phosphorus</td>
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<td>• Bicarbonate/CO2</td>
<td>• Potassium</td>
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<td>• Total protein</td>
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<td>• Magnesium</td>
<td>• AST</td>
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<td>• Chloride</td>
<td>• Sodium</td>
</tr>
<tr>
<td>• Creatinine</td>
<td>• Triglycerides</td>
</tr>
<tr>
<td>• Gamma glutamyltranspeptidase (GGT)</td>
<td>• Urea</td>
</tr>
<tr>
<td></td>
<td>• Uric acid</td>
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### Single Ascending Dose Schedule

<table>
<thead>
<tr>
<th>Wed</th>
<th>Thur</th>
<th>Fri</th>
<th>Sat</th>
<th>Sun</th>
<th>Mon</th>
<th>Tue</th>
<th>Wed</th>
<th>Thur</th>
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<td>28-Aug</td>
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<td>30-Aug</td>
<td>31-Aug</td>
<td>1-Sep</td>
<td>2-Sep</td>
<td>3-Sep</td>
<td>4-Sep</td>
<td>5-Sep</td>
<td>6-Sep</td>
<td>7-Sep</td>
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<td>9-Sep</td>
<td>10-Sep</td>
<td>11-Sep</td>
<td>18-Sep</td>
</tr>
<tr>
<td>D-1</td>
<td>D1/0</td>
<td>D2/24</td>
<td>D3/48</td>
<td>D5/96</td>
<td>D7/144</td>
<td>D10/216</td>
<td>D14/312</td>
<td>D21/480</td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Screened ( -D-28 to D-2) - Eligible ✓**  
D -1/Baseline – required per protocol to **re-continue to meet eligibility criteria**  
D1/ Dose – Blood PK – process to Plasma ( Pre dose + 6 samples to 12 h)  
D2 to D21 – FBC, Biochemistry, haemolysis panel (** variable days)**
Suitability = Eligibility criteria

Incl 5. Must have haematology, clinical chemistry and urinalysis results at screening that are within the reference range or, if outside the range, not clinically significant as judged by the investigator and confirmed and agreed by the medical monitor; aspartate aminotransferase (AST), ALT and bilirubin must be within the reference range at screening.

Excl 16. Haemoglobin levels below 13.0 g/dL (males) or 11.5 g/dL (females) at screening as determined by Full Blood Cell (FBC) counts.

Excl 19: ALT and/or AST and/or lactase dehydrogenase (LDH) should be ≤ ULN.

Excl 24: Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs, or which may jeopardize the subject in case of participation in the study. The Investigator should make this determination in consideration of the subject’s medical history and/or clinical or laboratory evidence of any of the following: The Investigator should be guided by the following criteria:

a. Any single parameter may not exceed 1.5 x upper limit of normal (ULN). A single parameter elevated up to and including 1.5 x ULN should be re-checked once more as soon as possible, and in all cases, at least prior to enrolment/randomisation, to rule out lab error.

b. Any elevation of more than one parameter excludes a subject from participation in the study unless otherwise agreed by the medical monitor. Testing may be repeated once more as soon as possible, but in all cases, at least prior to enrolment/randomisation, to rule out lab error.

Re-check results must not be clinically significant in order for subject to qualify and confirmed and agreed by the medical monitor.
## Post Dose: Safety Monitoring

<table>
<thead>
<tr>
<th></th>
<th>D4</th>
<th>D7</th>
<th>D10</th>
<th>D14</th>
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</thead>
<tbody>
<tr>
<td>Date/Time</td>
<td>02/09/13 08:37</td>
<td>04/09/13 08:34</td>
<td>07/09/13 07:22</td>
<td>11/09/13 08:30</td>
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<td>Sodium</td>
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<td>140</td>
<td>139</td>
<td>140</td>
</tr>
<tr>
<td>Potassium</td>
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<td>4.0</td>
<td>4.3</td>
<td>4.3</td>
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<tr>
<td>Chloride</td>
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<td>104</td>
<td>104</td>
<td>103</td>
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<tr>
<td>Bicarbonate</td>
<td>27</td>
<td>25</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td>Ca (corr)</td>
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<td>2.28</td>
<td>2.35</td>
<td>2.33</td>
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<tr>
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<td>1.0</td>
<td>1.3</td>
<td>0.9</td>
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<td>0.38</td>
<td>0.34</td>
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<td>102</td>
<td>89</td>
<td>103</td>
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<tr>
<td>eGFR</td>
<td>90</td>
<td>82</td>
<td>&gt;90</td>
<td>81</td>
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<tr>
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<tr>
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<td>68</td>
<td>66</td>
<td>65 L</td>
<td>69</td>
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<tr>
<td>Albumin</td>
<td>44</td>
<td>43</td>
<td>43</td>
<td>45</td>
</tr>
<tr>
<td>T Bilirubin</td>
<td>15</td>
<td>17</td>
<td>9</td>
<td>21 H</td>
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<tr>
<td>C Bilirubin</td>
<td>5</td>
<td>6</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>ALP</td>
<td>43</td>
<td>44</td>
<td>48</td>
<td>44</td>
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<tr>
<td>AST</td>
<td>15</td>
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<td>15</td>
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<tr>
<td>ALT</td>
<td>12</td>
<td>11</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>GGT</td>
<td>13</td>
<td>12</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>LDH</td>
<td>153</td>
<td>150</td>
<td>145</td>
<td>172</td>
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## Abnormal Liver Function Tests

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<thead>
<tr>
<th>Chemistry</th>
<th>11/09/13 18/09/13 19/09/13 20/09/13 23/09/13 30/09/13</th>
<th>Units</th>
<th>Ref Range</th>
</tr>
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<tr>
<td></td>
<td>08:30 11:48 12:53 09:02 12:20 15:45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>140 139 139 139 141 139</td>
<td>mmol/L</td>
<td>[135-145]</td>
</tr>
<tr>
<td>Potassium</td>
<td>4.3 4.5 4.4 4.3 4.3 4.2</td>
<td>mmol/L</td>
<td>[3.5-5.5]</td>
</tr>
<tr>
<td>Chloride</td>
<td>103 102 102 103 104 101</td>
<td>mmol/L</td>
<td>[95-110]</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>24 24 27 27 28 25</td>
<td>mmol/L</td>
<td>[20-32]</td>
</tr>
<tr>
<td>Ca (corr)</td>
<td>2.33 2.35 2.42 2.39 2.33 2.34</td>
<td>mmol/L</td>
<td>[2.10-2.55]</td>
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<tr>
<td>Phosphate</td>
<td>0.9 0.9 1.4 1.1 1.3 1.3</td>
<td>mmol/L</td>
<td>[0.8-1.5]</td>
</tr>
<tr>
<td>Urea</td>
<td>6.8 5.0 5.3 6.4 5.7 6.4</td>
<td>mmol/L</td>
<td>[3.0-8.0]</td>
</tr>
<tr>
<td>Urate</td>
<td>0.42 0.33 0.32 0.42 0.36 0.32</td>
<td>mmol/L</td>
<td>[0.20-0.50]</td>
</tr>
<tr>
<td>Creatinine</td>
<td>103 99 95 102 86 98</td>
<td>mmol/L</td>
<td>[60-110]</td>
</tr>
<tr>
<td>eGFR</td>
<td>81 85 89 82 &gt;90 86</td>
<td></td>
<td>(&gt;59)</td>
</tr>
<tr>
<td>Random Glucose</td>
<td>6.4 7.5 5.7 5.7 4.8 3.8</td>
<td>mmol/L</td>
<td>[3.6-7.7]</td>
</tr>
<tr>
<td>Total Protein</td>
<td>69 73 70 71 70 70</td>
<td>g/L</td>
<td>[66-83]</td>
</tr>
<tr>
<td>Albumin</td>
<td>45 49 45 45 46 46</td>
<td>g/L</td>
<td>[39-50]</td>
</tr>
<tr>
<td>Globulin</td>
<td>28 28 28 28 28 28</td>
<td>g/L</td>
<td>[20-38]</td>
</tr>
<tr>
<td>T Bilirubin</td>
<td>21 H 12 16 12 7 8</td>
<td>umol/L</td>
<td>[4-20]</td>
</tr>
<tr>
<td>C Bilirubin</td>
<td>7 4 6 5 3 3</td>
<td>umol/L</td>
<td>(0-7)</td>
</tr>
<tr>
<td>ALP</td>
<td>44 51 48 48 45 61</td>
<td>U/L</td>
<td>(35-110)</td>
</tr>
<tr>
<td>AST</td>
<td>15 378 H 262 H 190 H 46 H 21</td>
<td>U/L</td>
<td>(10-40)</td>
</tr>
<tr>
<td>ALT</td>
<td>12 190 H 172 H 157 H 80 H 26</td>
<td>U/L</td>
<td>(5-40)</td>
</tr>
<tr>
<td>GGT</td>
<td>12 13 12 12 12 14</td>
<td>U/L</td>
<td>(5-50)</td>
</tr>
<tr>
<td>LDH</td>
<td>172 1138 H 520 H 298 H 181 232</td>
<td>U/L</td>
<td>(120-250)</td>
</tr>
<tr>
<td>Creatine Kinase</td>
<td>28365 H 16650 H 8817 H 1156 H 235</td>
<td>U/L</td>
<td>(45-250)</td>
</tr>
<tr>
<td>Magnesium</td>
<td>0.8 0.7 0.9 0.9 0.9</td>
<td>mmol/L</td>
<td>(0.7-1.1)</td>
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<tr>
<td>Haemolysis Index</td>
<td>5 7 8 13 2 18</td>
<td></td>
<td>(0-40)</td>
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## Abnormal Liver Function Tests

<table>
<thead>
<tr>
<th>Chemistry</th>
<th>D14</th>
<th>D21/EOS</th>
<th>D22</th>
<th>D23</th>
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<td>16</td>
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<td>8</td>
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<tr>
<td>C Bilirubin</td>
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<td>4</td>
<td>6</td>
<td>5</td>
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<td>1138 H</td>
<td>520 H</td>
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<tr>
<td>Creatine Kinase</td>
<td>29355 H</td>
<td>16650 H</td>
<td>8817 H</td>
<td>1156 H</td>
<td>235</td>
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<td>Magnesium</td>
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<td>0.7</td>
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<tr>
<td>Haemolysis Index</td>
<td>5</td>
<td>7</td>
<td>8</td>
<td>13</td>
<td>2</td>
<td>18</td>
</tr>
</tbody>
</table>

**Units:** umol/L, U/L, mmol/L  
**Ref Range:** (4-20), (0-7), (35-110), (10-40), (5-40), (5-50), (120-250), (45-250), (0.7-1.1), (0-40)

**Lifestyle restrictions:** Exercise ** PISCF
Fasting increases serum bilirubin levels in clinically normal, healthy males but not females: a retrospective study from phase I clinical trial participants

Bilirubin influenced by diet (males only)

Figure 3  Comparison of serum bilirubin levels between the fed and fasted cohort of males and females (****p<0.0001). Data are displayed as a box and whiskers plot (25th–75th centile, minimum to maximum with all data points shown). ULN, upper limit of normal; LLN, lower limit of normal.
Clinical Trials in Zika Virus

- **Flavivirus**
  - nonsegmented, single-stranded, positive-sense RNA virus
  - Spread by *Aedes aegypti* & sexual contact

- **GLS-5700** (NCT02809443 GeneOne Life Science, Inc.)
  - Synthetic DNA plasmid vaccine
  - Intradermal & electroporation (** Dengue Naïve adults**)

- **VRC-ZKADNA085-00-VP** (NCT02840487 National Institute of Allergy and Infectious Diseases (NIAID))
  - single closed-circular DNA plasmid (intramuscular)
  - wild type precursor transmembrane M (prM) and envelope (E) proteins from the H/PF/2013 strain of ZIKV
  - Variation – timing of prime & boost x 1 or 2
  - Safety monitoring & ZIKV-specific immune response
Clinical Trials in HSV2

- Herpes virus
  - Double-stranded, linear DNA genome
  - Spread by sexual contact
  - Surface expressed Glycoprotein D = target (Neutralising Ab & CMI)

- COR-1 (HSV-2) vaccine (ACTRN12613000831785 Coridon.Pty Limited)
  - Synthetic DNA plasmid vaccine DNA vaccine (gD2 codon optimized/ubiquitin-tagged)
  - Intradermal (Healthy HSV1 & 2 seronegative adults)
  - Antibodies & IFNα elispot

- Herpes Simplex Virus-2 (HSV-2) Deoxyribonucleic Acid (DNA) vaccine (ACTRN12615000094572 Admedus Vaccines Pty Ltd)
  - Same Vaccine (HSV2 patients) (Prime + 2 boost (4 wk)+ 4th boost (6 mo))

- Others – Live attenuated, ± adjuvant, novel vector
Clinical Trials in RSV

- **Pneumovirus**
  - negative-sense, single-stranded RNA virus
  - Spread by droplet infection (Seasonal)
  - RSV Fusion (F) glycoprotein = target

- **AK0529** (NCT02654171 Ark Biosciences Inc.)
  - NCE target RSV fusion protein
  - Oral (Healthy adults)
  - Safety & PK (SAD/MAD)

- **RSV F Protein Nanoparticle Vaccine**
  (NCT01960686/NCT01704365/NCT02266628 Novavax)
  - Nanoparticle RSV vaccines ± adjuvant (Prime + Boost)
  - Neutralising Ab – cross strains (RSV A& B), HAI titres, Competitive ELISA (Palivizumab = MoAb)

- Others – Live attenuated (Ad26/35.RSV.FA2, ± adjuvant, novel vector/delivery)
Pathology Testing is Pivotal in Clinical Trials

- Subject Selection & Safety Monitoring
- Each trial is different
- Frequency of testing varies with Trial Phase
- Reporting Requested tests
- Standard nomenclature
- Laboratory Data critical for Drug Registration

Thank you