Collection, processing and long-term storage of biological samples in UK Biobank
• Baseline (and repeat) samples give an accurate representation of the biology of the individual at the time of collection.
• Clear criteria for inclusion/exclusion of sample types.
  • Peripheral blood, spot urine, (mixed saliva)
• Protocol considered cost, future proofing and minimal modification of the samples.
• Consequences of scale
• Processing and archiving managed centrally.
• Extensive piloting demonstrated the protocol generated samples that were fit for purpose.
• Analysis of the samples at the time of collection was minimised.
Importance of pre-analytical variables

- Selection of anticoagulants and clot accelerators
- Impact of haemolysis from delayed processing
- Control of clotting
- Use of preservatives and stabilising agents
  - RNAse and protease inhibitors
  - Metabolic inhibitors (e.g. Fluoride Oxalate)
  - Borate/azide anti-bacterials
- Choice of cryoprotectants for cell line production
- Processing – time and temperature
- Archiving temperature
- Impact of freeze-thaw cycles
Sample collection protocol – phase 1

- K$_2$EDTA
- Silica
- Li/Hep
- Acid citrate dextrose
- K$_2$EDTA

- 4°C Transport
  - Plasma, Buffy coat, Red cells
- 18°C Transport
  - Serum
  - Plasma
  - PBLs
- 4°C Transport
  - Haematology
  - Urine analytes
Sample collection protocol – phase 2

- **K$_2$EDTA**
- **Silica**
- **Li/Hep**
- **Acid citrate dextrose**
- **K$_2$EDTA**

**4°C Transport**:
- Plasma, Buffy coat, Red cells

**18°C Transport**:
- Serum
- Plasma
- PBLs

**4°C Transport**:
- Urine analytes
- RNA
- Saliva
## Sample collection protocol – phase 2

<table>
<thead>
<tr>
<th>Collection tube</th>
<th>Fraction</th>
<th>-80°C</th>
<th>Nitrogen vapour</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>K⁺EDTA (X2)</strong></td>
<td>Plasma</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Buffy coat</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Red cell fraction</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td><strong>Li-Heparin (PST)</strong></td>
<td>Plasma</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td><strong>Silica clot activator (SST)</strong></td>
<td>Serum</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td><strong>Acid citrate dextrose</strong></td>
<td>Whole blood/DMSO</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td><strong>Urine</strong></td>
<td>Mid-stream urine</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td><strong>EDTA</strong> (whole blood – haematology)</td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td><strong>RNA stabilisation tube</strong></td>
<td>Lysed cell – stable RNA mix</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td><strong>Saliva tube</strong></td>
<td>Mixed saliva</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>17</td>
<td>19</td>
</tr>
</tbody>
</table>
Sample collection protocol – process demands

- **700 Participants per day**
- **4,900 Vacutainers per day**
- **25,000 aliquots produced per day**
- **15 million 0.85ml aliquots**

Reliable, cost effective, capacity to continually process, store and retrieve samples and data in a form suitable for future scientific research.
Central vs local processing

<table>
<thead>
<tr>
<th>Central</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased quality and consistency in processing and processes</td>
</tr>
<tr>
<td>Increased achievable throughput</td>
</tr>
<tr>
<td>Robust data trail</td>
</tr>
<tr>
<td>Cost</td>
</tr>
<tr>
<td>Processing is as rapid as is achievable – preservation of most species</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Local</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delay in processing may result in loss of labile species</td>
</tr>
<tr>
<td>Increased shipping costs</td>
</tr>
<tr>
<td>QA/QC from manual processing at high throughput</td>
</tr>
<tr>
<td>Robustness of data trail</td>
</tr>
<tr>
<td>Risk to locally stored samples</td>
</tr>
<tr>
<td>Challenges of sample distribution</td>
</tr>
<tr>
<td>Regulatory issues of local storage</td>
</tr>
<tr>
<td>Cost – staff and hardware</td>
</tr>
<tr>
<td>Impact of freeze thaw if samples are not processed</td>
</tr>
</tbody>
</table>
The protocol was extensively piloted.

Immediate transfer

Maintenance of whole blood/serum and urine at temperature for defined period

Processing

Biochemistry
Haematology
Genomics/5’ RNA
Immortalisation
GC-MS
$^1$H-NMR
Sample collection protocol – process demands

- **700 Participants per day**
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Reliable, cost effective, capacity to continually process, store and retrieve samples and data in a form suitable for future scientific research.
UK Biobank – sample processing and archiving centre
Average processing time (collection to archiving) = 24.6 (1SD=2.1)
Samples are stored in a fully automated working archive.

ULTC Spatial Temperature Uniformity

Effect of Accessing a Drawer for 30 seconds
...and a manual off-site back up
Samples are picked automatically in a cold environment.