

- What is the purpose and scope of this toolkit?
- Learn the rationale for PK data in Covid-19 clinical trials, pharmacokinetic basics, and trial design considerations

#### Background and rationale for PK data in Covid-19 clinical trials

- Pharmacokinetic basics
- Trial design considerations
- Matrices and assays
- Other data points for PK studies

#### Common errors and how to mitigate them

Pharmacokinetic (PK) sample processing and transport between laboratories

Toolkit

Blood

pharmacokinetic

sample collection,

processing and

transport in COVID-

19 clinical trials

# How?

- Learn about common errors and how to mitigate them
- Consider the facilities, equipment, consumables and staffing required for the sampling process
- Guides on documentation, data management and end of trial activities

## Pharmacokinetic sampling in the clinic

- Facilities, equipment and consumables
- Staffing and the sampling process itself
- Documenting dosing and sampling

Data management, analysis and end of trial activities

#### About

#### About this toolkit





This toolkit is not prescriptive and may be adapted for use by anyone according to need. We would appreciate feedback on any errors or suggestions as to how it may be improved.

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processing and transport in Covid-19 clinical trials v1.0

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**ADR:** Adverse Drug Reaction AE: Adverse Event AUC: Area under the concentrationtime curve **Cmax:** Maximum (drug) concentration Cmin: Minimum (drug) concentration **CRF:** Case Record Forms ECG: Electrocardiograph/ electrocardiogram **GCP:** Good Clinical Practice **ISF:** Investigator Site File **PK:** Pharmacokinetic **SOP:** Standard operating procedure T<sup>1</sup>/<sub>2</sub>: Half life **Tmax:** Time of maximum (drug) concentration

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#### ABBREVIATIONS



# DEFINITIONS

Area under the curve: time integral of a concentration versus time profile, which provides a measure of total exposure, incorporating both amount and duration of the drug concentration [1] Bioavailability: fraction of drug compound dosed by an extravascular route that reaches the systemic circulation [1] Half-life: time taken for the drug concentration to decrease to half its initial value [1]

**Pharmacodynamics (PD)**: the study of the biochemical and physiological effects of drugs on the body, the mechanisms of drug action in the body and the relationship between drug concentration and drug effect. ('what the drug does to the body'). [2]

**Pharmacokinetics (PK)**: The study of a drug's absorption, distribution, metabolism, and excretion (ADME) in the body ('what the body does to the drug'): [2]

- Absorption: the process by which drugs enter the body.
- Distribution: the process by which drugs move around the body.
- Metabolism: the process by which drugs are chemically altered to make them sufficiently water-soluble for excretion in urine or faeces (via the biliary tract).
- Excretion: the process by which drugs leave the body.

[1] Davies M, Jones RDO, Grime K, Jansson-Löfmark R, Fretland AJ, Winiwarter S, Morgan P, McGinnity DF. Improving the Accuracy of Predicted Human Pharmacokinetics: Lessons Learned from the AstraZeneca Drug Pipeline Over Two Decades. Trends Pharmacol Sci. 2020 Jun;41(6):390-408

[2] The International Union of Basic and Clinical Pharmacology (IUPHAR) Pharmacology Education Project. Available from: https://www.pharmacologyeducation.org/four-phasespharmacokinetics (Accessed 15 Jun 2020)

### BACKGROUND

1. What?

#### **b** PURPOSE/SCOPE

While a trial protocol will describe which pharmacokinetic (PK) samples are to be collected and when, and how such samples will be prepared for analysis, it is important that site staff understand the rationale and best practice for PK sampling to help ensure robust results.

This toolkit provides comprehensive generic guidance for blood sampling for PK analyses from the protocol through processing in a clinic/local laboratory and onto an analytical laboratory, to support trial-specific instructions or standard operating procedures (SOPs).

Special attention is given to trials with intensive PK sampling schedules where participants are brought in, in groups. Sample preparation for specific drug assays or the assays themselves are not covered, nor are other samples (e.g. urine).

#### PHARMACOKINETIC BASICS

For a drug to be effective, it needs to achieve adequate concentrations in the target organ, with optimal dosing for relevant sub-populations and minimisation of adverse drug reactions (ADRs).

All these issues rely on a thorough understudying of the drug's PK profile, in terms of its movement in, through, and out of the body.

Drug concentration data in the blood will allow for calculation of parameters such as the minimum concentration (Cmin), maximum concentration (Cmax), half-life (T½), time of maximum concentration (Tmax) and area under the curve (AUC).

These in turn underpin information about the drug's absorption, distribution, metabolism and excretion, which are dependent on its chemical properties, but also patient-related factors that are either predictable (e.g. sex, weight or body composition, age, genetics, renal or hepatic function, pregnancy, smoking or alcohol) or unpredictable (because they are individual or idiosyncratic).

Taking blood PK samples in trials informs subsequent trials, and evidence about a drug's accumulation (or its products of metabolism, the metabolites), drug-drug interactions (which are especially important for frequently co-administered drugs) and food-drug interactions that can also effect bioavailability.[**3**] Accurate measurement of drug concentrations is essential to ensure optimal dosing and understand the relationship between PK results and clinical response (the drug's pharmacodynamics, PD), and whether any ADRs are dependent on a particular dose.



Plasma Concentration

#### TRIAL DESIGN

2. What?

## **c**ONSIDERATIONS

Covid-19 is a novel SARS-CoV-2 viral infection with no drugs currently registered for its prevention or treatment. While there are investigational drugs under clinical development, various drugs marketed for other conditions are also under evaluation or being used off-label. Participants may be healthy or unwell (of different severities), outpatients or inpatients.

Depending on the trial's objectives and what is already known about the drug, the PK sampling schedule may involve multiple samples per visit at very rigid time points, or a limited number of samples taken with more flexibility in the timing. The former is typical of early phase trials, that often involve single and multiple-ascending doses to characterise a concentration-time curve (Figure 1), or trials aimed at investigating useful synergistic drug combinations or harmful interactions.



#### Figure 1: Schematic of an expected PK plasma concentration-time curve (J. Scott Daniels)

A theoretical time/concentration curve after a single dose obtained from PK sampling data (NB there will be variations depending on the formulation, whether oral, intravenous etc.)

#### Legend:

AUC: area under the curve Cmax: maximum concentration Tmax: time at the maximum concentration T1/2: half life Cmin: minimum (trough) concentration





3. What?

Should there be specific toxicities of interest, appropriate assessments (e.g. ECGs to detect cardiac anomalies) may be scheduled at the estimated Tmax as that is theoretically when the risk is highest. Even though some such trials involve healthy volunteers, there are ethical limits to intensive blood sampling in terms of the maximum total blood volume, pain and discomfort (and this is also very relevant for trials involving children).

Sparser sampling is more feasible in larger populations, complex or challenging clinical environments, for children and later phase trials. Both scenarios contribute to aggregate or individual patient data (IPD) meta-analyses, whereby data from multiple studies are combined to answer research questions that cannot be answered from the individual trials. This does, however, rely on harmonisation of methods.

Many drugs have been considered for re-purposing or positioning for Covid-19, which is advantageous as data about their PK and safety, together with preclinical (laboratory and animal) data, are readily available.[4] There are, for instance, useful existing data for oral chloroquine (and for its metabolite, desethychloroquine) about suggested PK sampling times from antimalarial studies.[5] However, as for a new infection such as Covid-19, it may be that dose, dosing frequency and/or duration of dosing will be different, especially for different pharmacodynamic targets (site of action in the body) and typical patient co-morbidities.

[4] Serafin MB, Bottega A, Foletto VS, da Rosa TF, Hörner A, Hörner R. Drug repositioning is an alternative for the treatment of coronavirus COVID-19. Int J Antimicrob Agents. 2020 Jun;55(6):105969.

[5] World Health Organization, 2011 Methods and techniques for assessing exposure to antimalarial drugs in clinical field studies. Available from: https://www.who.int/malaria/publications/atoz/9789241502061/en/ (Accessed 15Jun2020)





4. What?

There are various so-called biological matrices used for PK sampling, including plasma, serum, venous blood, and venous capillary blood. The latter is often collected as dried blood spots from finger-prick samples, which are particularly useful for low-resource settings. In general, as with other diseases, the matrix in which the highest concentrations can be measured will allow for simpler, more cost-effective analytical techniques, but this should be balanced against measuring concentrations at the drug's target site. For example, chloroquine is present in plasma at very low concentrations as it is preferentially distributed to red blood cells.[5]

Drugs being used to prevent or treat Covid-19 will have their own considerations as to which matrix is appropriate. Validated assays are then used in the analytical laboratory to measure concentration of the trial drug as per the methods detailed in the protocol. These assays have been published for chloroquine and other drugs being considered for Covid-19, such as hydroxychloroquine, some macrolides, ivermectin and the antivirals remedesivir, favipiravir, and lopinavir / ritonavir, from studies in other disease (e.g. malaria, HIV, influenza and Ebola Virus Disease), which will inform Covid-19 trials. Moreover, PK data from studies using these drugs in Covid-19 patients are now emerging, with some suggestions of different profiles to the registered indication.[6]

#### OTHER DATA POINTS FOR PK STUDIES

Critical trial data points for interpreting PK concentration data that must be measured accurately include the amount and time of the drug dose(s), the volume and time of the blood samples, and the body weight for calculating a mg/kg dose. However, there may be multiple other assessments and activities. So in planning any trial, but particularly complex ones, it is recommended that team members draw up the assessment schedule together so that it is ethical and workable (see Tables 1 and 2 for examples of relatively simple and more extensive flow charts with PK sampling). This will ideally include investigators, laboratory staff, pharmacists, nursing staff, data managers and statisticians.





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5. What?

**Table 1**: Example of a simple trial flow chart with limited PK samples

|                                 | -                      |       | -     | -      |        | -      |             |  |  |
|---------------------------------|------------------------|-------|-------|--------|--------|--------|-------------|--|--|
|                                 | Screening/<br>baseline | Day 3 | Day 7 | Day 14 | Day 28 | Day 42 | Unscheduled |  |  |
| Informed consent                | Х                      |       |       |        |        |        |             |  |  |
| Medical history                 | Х                      |       |       |        |        |        |             |  |  |
| Demography                      | х                      |       |       |        |        |        |             |  |  |
| Body weight                     | х                      |       |       |        |        |        |             |  |  |
| Physical exam                   | Х                      | Х     | Х     | Х      | Х      | Х      | Х           |  |  |
| Vital signs, temperature        | х                      | Х     | Х     | Х      | Х      | Х      | Х           |  |  |
| Urine pregnancy                 | X                      |       |       |        |        | Х      |             |  |  |
| Trial-specific response measure | Х                      | Х     | Х     | Х      | Х      | Х      | Х           |  |  |
| Blood PK                        | Х                      |       | Х     |        |        |        |             |  |  |
| Study drug                      | Х                      |       |       |        |        |        |             |  |  |
| Adverse events                  | XX                     |       |       |        |        |        |             |  |  |
| Other medication                | XX                     |       |       |        |        |        |             |  |  |

TABLE 2.

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6. What?

**Table 2**: Example of an extensive trial flow chart with multiple PK samples

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| Study Phase      | Screen    | Baseline | Treatr      | nent                  | and Fo  | llow | -up |   |   |   |   |    |    |    |    |     |     |     |     |     |     |
|------------------|-----------|----------|-------------|-----------------------|---------|------|-----|---|---|---|---|----|----|----|----|-----|-----|-----|-----|-----|-----|
| Visit numbers    | 1         | 2        | 3           | 3 4 5 6 7 8 9 10      |         |      |     |   |   |   |   |    |    | 10 |    |     |     |     |     |     |     |
| Study days       | -28 to -2 | -1       | 1           | 1 2 3 5 7 10 14 19 26 |         |      |     |   |   |   |   |    | 26 | 29 |    |     |     |     |     |     |     |
| Time (h)         |           | -24      | Pre-        | 0                     | 0.5     | 1    | 2   | 3 | 4 | 6 | 8 | 12 | 24 | 48 | 96 | 144 | 216 | 312 | 432 | 600 | 672 |
|                  |           |          | dose        |                       |         |      |     |   |   |   |   |    |    |    |    |     |     |     |     |     |     |
| Informed consent | Х         |          |             |                       |         |      |     |   |   |   |   |    |    |    |    |     |     |     |     |     |     |
| Medical history  | Х         | Х        |             |                       |         |      |     |   |   |   |   |    |    |    |    |     |     |     |     |     |     |
| Demography       | Х         |          |             |                       |         |      |     |   |   |   |   |    |    |    |    |     |     |     |     |     |     |
| Physical exam    | Х         | X        | Х           |                       |         |      |     |   |   |   |   |    |    | Х  | Х  | X   | Х   | X   | X   | Х   | X   |
| Hep B/C, HIV     | Х         |          |             |                       |         |      |     |   |   |   |   |    |    |    |    |     |     |     |     |     |     |
| Pregnancy test   | Х         | X        |             |                       |         |      |     |   |   |   |   |    |    |    |    |     |     |     |     |     | X   |
| Body height      | Х         |          |             |                       |         |      |     |   |   |   |   |    |    |    |    |     |     |     |     |     |     |
| Body weight      | Х         | X        |             |                       |         |      |     |   |   |   |   |    |    |    |    | X   |     | X   |     |     | X   |
| Temperature      | Х         | X        | Х           |                       |         | Х    |     |   | Х |   |   |    |    | Х  |    |     |     |     |     |     | X   |
| BP, heart rate   | Х         | X        | Х           |                       | Х       | X    | Х   | Х | Х | Х | Х | Х  | Х  | Х  | Х  | X   | Х   | X   | X   | X   | X   |
| Triplicate ECG   | Х         | X        | Х           |                       |         | X    | Х   | Х | Х | Х | Х |    | Х  | Х  | Х  | X   |     |     |     |     |     |
| Safety bloods    | Х         | X        | Х           |                       |         |      |     |   |   |   |   |    | Х  | Х  | Х  | X   | Х   | X   |     | X   | X   |
| Urinalysis       | Х         |          | Х           |                       |         |      |     |   |   |   |   |    | Х  | Х  |    |     |     | X   |     |     | X   |
| Microscopy       | Х         | Х        |             |                       |         |      |     |   |   |   |   |    |    | Х  |    | Х   |     | X   |     |     |     |
| Study drug       |           |          |             | X                     |         |      |     |   |   |   |   |    |    |    |    |     |     |     |     |     |     |
| Blood PK         |           |          | Х           |                       | X       | X    | X   | X | X | Х | X | Х  | Х  | X  | Х  | Х   | Х   | X   | Х   | X   | Х   |
| Urine PK         |           |          | Х           |                       |         |      |     |   | X |   |   |    |    |    |    |     |     |     |     |     |     |
| Adverse events   |           |          | As required |                       |         |      |     |   |   |   |   |    |    |    |    |     |     |     |     |     |     |
| Other            | Х         | X        | X           | As ı                  | require | d    |     |   |   |   |   |    |    |    |    |     |     |     |     |     |     |
| medication       |           |          |             |                       |         |      |     |   |   |   |   |    |    |    |    |     |     |     |     |     |     |

## Common errors and how to mitigate them

FIGURE 1

7. How?

Figure 1: Schematic of an expected PK plasma concentration-time curve (J. Scott Daniels) Legend:

AUC: area under the curve Cmax: maximum concentration Tmax: time at the maximum concentration T1/2: half life Cmin: minimum (trough) concentration





Figure 2: Actual PK plasma concentration-time curves showing implausible results (P Denti)

A theoretical time/concentration curve after a single dose obtained from PK sampling data is given in Figure 1 (NB there will be variations depending on the formulation, whether oral, intravenous etc.), while Figure 2 shows actual curves indicating implausible results likely from mislabeled, swapped or missed samples.



## Common errors and how to mitigate them



PK TRIALS

8. How?

By the time the samples are assayed the clinical phase of the trial may be far along or even over, so it is important to identify and prevent avoidable errors, especially systematic errors that suggest underlying problems in trial design or conduct.

Some errors are not preventable (e.g. if a participant refuses a sample), but it is important to also record the reason for these to help explain the final report, and participants may be given guidance as to how their behaviour impacts data if appropriate (e.g. for healthy volunteers to be on time for assessments or avoid prohibited food). However, the trial never overrides participants' safety, and autonomy etc. See Table 3 for common errors and ways to mitigate them.

#### Table 3: Common errors in PK trials and ways to mitigate them



| Common errors         | Mitigation strategies  |
|-----------------------|--|
| Incorrect dosing data | - A pre-dose PK sample is taken to confirm there are no residual levels of the trial         |
|                       | drug from a previous treatment   |
|                       | - Staff understand the PK sampling schedule in relation to time since dose(s)                |
|                       | - If oral dosing in clinic and appropriate, a mouth check to ensure participant              |
|                       | swallowed dose   |
|                       | - If doses are taken at home:  |
|                       | <ul> <li>Diaries to capture times of doses, post-dose vomiting, re-dosing, food</li> </ul>   |
|                       | consumption etc. are ideally designed with participants, and staff review                    |
|                       | diary entries with participants to understand and document discrepancies,                    |
|                       | with clarity on which data is considered final for the CRF                                   |
|                       | <ul> <li>Source data templates and CRFs are unambiguous as regards definitions of</li> </ul> |
|                       | fields such as 'last dose'. Ideally staff role-play how best to explain to                   |
|                       | participants whether to take a dose before coming to the clinic or at the                    |
|                       | clinic (for instance) and then capture the data  |
|                       | <ul> <li>If budget allows, automated dosing containers record opening at home,</li> </ul>    |
|                       | and there is a plan to interpret such data in relation to verbal reports                     |
| Incorrect PK sample   | - Staff perform quality control (QC) checks on sampling consumables and labelling            |
| data                  | - Data collection forms are ideally pre-printed to correlate with tube labeling              |
|                       | - Staff understand the importance of only using trial-specific sample equipment and          |
|                       | how to use it to get the required volume and maintain integrity of the sample                |
|                       | - The schedule is achievable with the number of staff for the activities required,           |
|                       | with role-play for complex sampling schedules  |
|                       | - Atomic clocks are used, or there is a process for synchronising clocks at start of         |
|                       | day/sampling as appropriate between the pharmacy (if the drug is being                       |
|                       | compounded or mixed at site), the clinic, and the processing laboratory                      |
|                       | - A process is in place to confirm participant identifiers are consistent on blood           |
|                       | collection materials and all related forms just prior to sampling                            |
|                       | - Indwelling catheters are used to negate discomfort from multiple blood draws,              |
|                       | with a plan in place for handling unexpected problems (e.g. to call back up for              |
|                       | Derticinants understand their role in the campling schedule where appropriate                |
| Spoilt sample         | - Participants understand their role in the sampling schedule where appropriate              |
| spont sample          | - start is well-trained, with role-play of sample from bedside to processing                 |
|                       | - Staff understand storage conditions (e.g. the correct temperature or humidity              |
|                       | filter namer storage in a correctly labelled hag with /without desiccant as ner the          |
|                       | laboratory conditions) and stocks are sufficient   |
|                       | - Team routinely review the extent of haemolysis, missed/late samples, delays in             |
|                       | processing etc. to identify and correct systematic errors                                    |
|                       | - Staff and/or couriers understand, are equipped, gualified or experienced, to               |
|                       | comply with protocol and regulatory conditions for road or air transport of samples          |
|                       | within and between facilities (especially for infectious samples)                            |
|                       | - Documents, such as shipping logs and permits, are adequate to prevent delays at            |
|                       | receiving lab, customs etc. or confusion about sample identification                         |
| Other data            | - Staff are trained to explain the rationale for fasting, disallowed medicines / food /      |
|                       | drinks or need for luggage checks on admission to the facility if appropriate                |
|                       | - There are SOPs for obtaining accurate body weight and other important clinical             |
|                       | data that will be interpreted with the PK data   |
|                       | - Staff understand how best to elicit other participant-reported subjective data e.g.        |
|                       | about concomitant medicines and health conditions (to identify accurate medical              |
|                       | histories and adverse events, AEs)   |

### PK sampling in the clinic



### SAMPLING 0 FACILITIES, EQUIPMENT AND CONSUMABLES

As Covid-19 is a highly infectious disease, there should be proper planning to prevent cross-infection between patients and staff, particularly while sampling. See openaccess resources contributed by the MRC Unit in The Gambia through the Global Health Network.



9. How?

Figure 3: Minivette® POCT, Sardstedt Calibrated sampling suitable for finger- blood PK samples prick samples



Figure 4: Example of a card for triplicate finger-prick

Suitably trained member(s) of the trial team should be delegated responsibility for ordering and/or labelling medical stock and equipment:

- Stock checklists (Appendix 1) should be developed with careful attention to the protocol or analytical laboratory's requirements. This will include phlebotomy supplies (syringes. butterflies and/or cannulas sets and their related consumables, with guidance on needle gauge) and the blood sample container. For venous blood tubes, considerations are the volume, whether glass or plastic, and with or without coagulant. For venous capillary blood it may be the pipette or graduated capillary tube volume, including coating (e.g. coagulant), or type of filter paper (e.g. brand and whether/how it is chemically treated). See Figures 3 and 4 for examples of the latter. The analytical laboratory will also advise on the use of desiccants and bags for filter paper storage.
- Blood collection containers are then labelled according to the trial's requirements. As analytical laboratories receive samples from multiple trials, a combination of the trial number, participant number, trial period (if relevant) and sample time-point is useful (e.g. for trial DDI, participant 01, sequence 1, day 0, hour 01 blood sample: DDI01S1d0H01). This will then correlate with other consumables and documentation, such as subsequent sample containers after processing (e.g. cryovials - tiny laboratory tubes for plasma or serum that may be frozen), source documents, CRFs and shipping logs
- Labels for cryovials/eppendorfs that go into fridges or freezers should be suitable for wet conditions or water-resistant pens used
- It is very important to proofread label templates before printing to prevent errors
- In addition, there should be spare consumables in case a repeat sample is needed, which can be labelled in real-time according to the same convention
- For intensive sampling of multiple grouped participants (such as in early phase or bioequivalence trials), wrist identity bands and bed labels are recommended, to correlate with a bed plan (Appendix 2) and other trial labeling and documentation
- If blood samples need chilling before processing, there should be a plan for sourcing ice and keeping bedside ice containers filled throughout the trial
- For PK trials with strict dietary considerations, there will be specific arrangements for standardised food or drink. A dietician can draw up menus that comply with regulatory standards, but also consider common allergies and traditionally acceptable foods.[7]
- Again, for strict trials, it may be necessary to arrange for alcohol, caffeine, cotinine/nicotine and drugs of abuse screening as these are usually exclusion criteria or important to measure to explain their effect on drug concentration data
- Other key or useful equipment are clocks (ideally in the pharmacy, clinic and laboratory, and with hours, minutes and seconds), which can be synchronised or are atomic, entertainment for participants spending a long time in the facility, and hand warmers to help blood flow for multiple samples
- For complex trials a guick reference guide for the clinic is useful for key processes and safety alerts (Appendix 3)
- All records relating to stock and equipment (QC check lists, specifications, calibration records and servicing documentation) will be filed in the Investigator Site File (ISF) throughout the trial (or a note to file indicating where they are stored)

### 10. How?

# Staffing and the sampling process itself

# TRIAL TEAM

The Principal Investigator should ensure the team is suitably qualified and experienced, but the level of staffing will depend on the complexity of the protocol. Dosing delays can have a serious knock on effect for subsequent activities in trials with intensive PK schedules and participants in groups, and this is compounded where eligibility relies on review of data from assessments done just prior to dose. In these trials there needs to be a clear plan on when and how such reviews are done, with the appropriate staff available (e.g. a cardiologist if necessary). There should also be back-up staff who can be brought in in case of illness, rather than postpone a whole group of participants, and attention should be especially paid to when sample times overlap.

#### TIMING

Flow charts such as the one in **Table 2** appear as though multiple assessments or sampling points are concurrent, but this is not feasible, and measurement of the key data end point(s) will take priority. E.g. if PK is the primary endpoint, PK blood sampling is done at the exact protocol-scheduled time with the coscheduled assessments (e.g. vital signs and ECG) in the minutes leading up to that time point (NB this is also preferable as ECGs should be done before a blood draw to get an optimal measurement).



# COMPLEX TRIALS

#### MULTIPLE TIMEPOINTS/ PARTICIPANTS

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In complex trials with multiple timepoints & participants, there must be enough staff available and this can be achieved through dosing multiple participants at exactly the same time point (for drugs with known safety profiles), or staggered intervals (with a sentinel dose in early phase trials). In the former each participant has 1 or 2 staff members assigned for multiple tasks (dosing, blood sampling, BP, ECG etc.), while for the latter, staff is assigned a specific role (e.g. dosing or blood sampling or BP, ECG) and move bed to bed in sequence.

#### STAFF-TASK SCHEDULE

See an example staff-task schedule for dosing day of an intensive Phase 1 trial of 10 participants (2 reserves) in **Appendix 4** with built-in calculations for dosing at 8 minutes apart to populate cells. Each staff has a dedicated colour.



## Documenting dosing and sampling





1. How?

#### DOCUMENTING

#### o DOSING & SAMPLING

The level of documentation will again match the complexity of the protocol and may be a simple record of dosing and date and time the sample(s) is taken (with attention to use of unambiguous time and date formats: DD-MMM-YYYY and 24h format for time being preferable):

Figure 5: Example source document for simple record of dose and PK sample

See **Appendix 5** and **6** for a process and example of a source document for more intensive PK sampling.





| Drug dosing                            |              |                           |             |              |         |      |  |
|--|--------------|---------------------------|-------------|--------------|---------|------|--|
|  | Date of dose | Time of dose              | Food/drink* | Dose vomited | Re-dose |      |  |
|  |              |                           |             | after dose?  | Amount  | Time |  |
| Dose 1 (day before visit)              |              |                           |             | Y/N          |         |      |  |
| Dose 2 (after PK 01 sample this visit) |              |                           |             | Y/N          |         |      |  |
| No tablets in packet                   |              | Reason for<br>discrepancy |             |              |         |      |  |

\*Indicate briefly food/drink consumed within an hour either side of dose (e.g. meal, biscuit, milk) \*\* If Y, record as AE

| Venous PK sample (2ml)            |                 |  |  |  |  |  |  |  |
|-----------------------------------|-----------------|--|--|--|--|--|--|--|
| Blood sample number               | Time collected  |  |  |  |  |  |  |  |
| 01 (before dose at clinic)        | <u>h</u> h: mm  |  |  |  |  |  |  |  |
| 02 (x hours after dose at clinic) | hh: mm          |  |  |  |  |  |  |  |
| 03 (y hours after dose at clinic) | <u>,</u> hh: mm |  |  |  |  |  |  |  |

#### 12. How?

## Local PK sample processing and transport between laboratories

PROCESS CHAIN OF CUSTODY

Ideally the interim or sample processing lab will be in, or close to, the clinic. After a sampling time point has been completed, a member of the trial team should make sure required samples are present and place them in the relevant storage or deliver them to the laboratory technician for processing according to the protocol or laboratory-specific instructions. All sample movement should be documented on a chain of custody form (Appendix 7) and if necessary, a stopwatch (or equivalent) used to ensure timelines are adhered to

It can be useful to distill information from the protocol into laboratory job aids (**Appendix 8**) as the lab staff may be working on multiple trials

#### BACKUPS AND INVENTORIES

While any storage facility should have equipment and processes to maintain conditions (e.g. backup generator, alarms to indicate temperature excursions etc.), it may be necessary to send samples periodically to a more secure interim storage facility if the clinic or local laboratory suffer frequent power outages. In this case, a backup sample should be retained until samples have reached the next facility and a copy of the chain of custody form should accompany samples. Both laboratories should also maintain their own inventories of samples (see Appendix 9 for an example plate map for cryovial storage). Ultimately these documents will be archived in the ISF with laboratory accreditations, temperature, maintenance and service records, and records of protocol deviations

#### INVENTORIES





samples can be done using ice, liquid nitrogen or dry ice; however, it can be difficult to maintain constant supplies and integrity. A mobile fridge or freezer can be plugged into a car battery. Whichever mode of transport there should be constant monitoring of the temperature either with a digital min/max thermometer whose records can be downloaded and printed, or with a trial team member manually keeping a record of the temperature using a probe.

Figure 3: Campmaster -20°C Fridge/ freezer



#### REGULATION

Sample transport will need to adhere to national and/or international safety and customs regulations (e.g. the International Air Transport Association, export and/or import permits of the different countries) and site or laboratory staff may need particular qualifications to pack or carry samples. Ideally there should be budget for an courier company experienced in transporting clinical trial samples.

Analytical laboratories will require an inventory (sometimes called a shipping record) which details each sample by its identity number, position in the box, drug to be analyses and volume (**Appendix 10**).



#### 13. How?

## Data management, and end of trial activities

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DATA DATA DATA MANAGEMENT

The data manager should have been involved in design of the source documentation and the CRF to ensure that all relevant fields are accounted for and the CRF may need to be designed with a view to supporting regulatory submissions (or subsequent secondary analyses) through standardised fields such as the CDISC (See an example as such in **Appendix 11**). Similarly, while some data points are participant-specific, other methodological variables are trial-specific meta-data which are important to record to understand the data fully and to also facilitate subsequent reviews and meta-analyses.

All Essential Documents for the conduct of a clinical trial should then be archived as per site and sponsor requirements and in accordance with relevant GCP guidelines and regulations. Depending on the conditions of the protocol and informed consent, left over samples may either need to be documented as destroyed, put into long-term storage for subsequent studies or sent to a biobank or central repository. Similarly, the IPD may be contributed to a relevant repository, such as The **Infectious Diseases Data Observatory (IDDO)**. A suggested text for adaptation for informed consent documents (subject to ethical review) is below (with consideration of participant initials next to each box that is ticked):

#### Sharing of results so that they can be combined with other studies

Medical journals require us to share anonymised information from studies like these. In addition, we would like to ask if you agree to us sharing the anonymised information with those wanting to combine our results with other similar studies. This is useful for understanding more about the study medicine. These combined results may also be discussed at meetings or published but you will never be identified by name. Please note, if you withdraw your consent during or after the study we will not be able to take back the data that has already been shared with others in this way.

By signing this consent form, I give permission for the use, access, and sharing of my personal medical information as described in the section "Confidentiality". Optional: Please let us know what you would like us to do about sharing of anonymised information with those wanting to combine it with other similar studies (you can still be part of this study, even if you choose not to share your anonymised information for this purpose):

□ I give permission to share my anonymised information for combining with other similar studies □ Do not share my anonymised information for combining with other similar studies]

At the end of the study unused blood samples will be stored and, if you agree, may be used in future investigations for understanding the effects of [treatment]. You can still be part of this study, even if you choose for your unused samples to be destroyed after the study has ended. Approval from the ethics committees will be sought before the stored blood samples are used for any such future investigations. Samples from those who do not give consent for use of their blood samples after the study has ended will be destroyed. Please let us know what you would like us to do with any samples left over at the end of the study:

Destroy all left over blood samples

Keep samples for use in future research to understand malaria and how best to treat or prevent it

#### References and appendices list









Examples only for illustrative purpose and adaptation for each trial:

Appendix 1: Stock and clinic set up lists

Appendix 2: Bed plan

14. How?

**Appendix 3**: Quick reference guide for complex trials

**Appendix 4**: Staff-task schedule for intensive PK sampling with multiple

participants

**Appendix 5**: Process for intensive PK sampling

Appendix 6: Source document for

intensive PK sampling

**Appendix 7**: PK sample chain of custody form

Appendix 8: PK sample processing job aid

**Appendix 9**: Cryovial plate map for PK samples

Appendix 10: PK analytical laboratory

shipping template

Appendix 11: PK case record form

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