STARmeds
Systematic Tracking of At-Risk Medicines

# CONDUCTING RANDOMISED FIELD SURVEYS OF MEDICINE QUALITY USING MYSTERY SHOPPERS: A PRACTICAL GUIDE AND TOOLKIT

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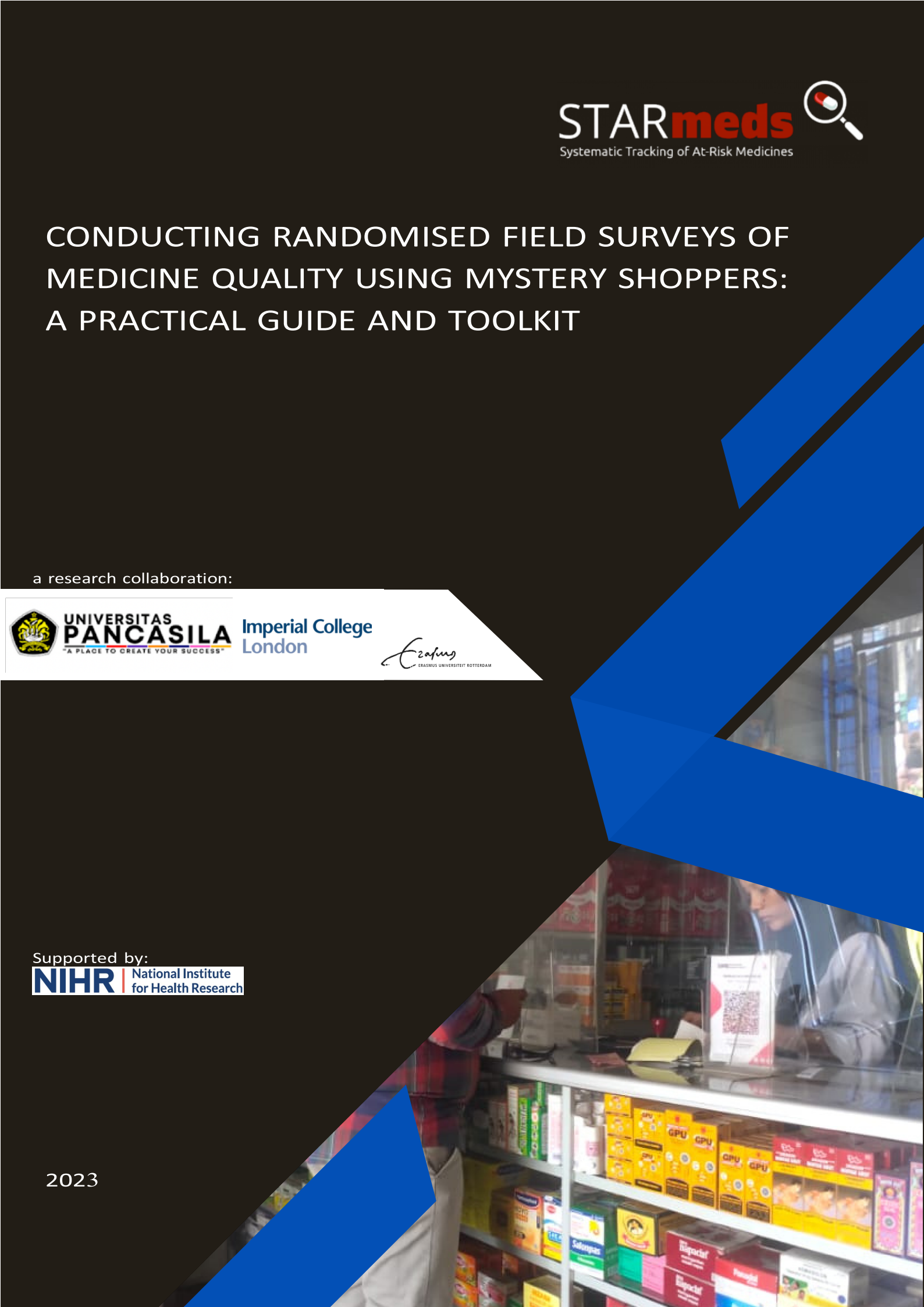


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# Conducting Randomised Field Surveys of Medicine Quality Using Mystery Shoppers:
## A Practical Guide and Toolkit

Version 1

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This toolkit was prepared by Jenny Pontoan, Mawaddati Rahmi, Ayu Rahmawati, Hesty Utami, Esti Mulatsari, William Nathanial and Elizabeth Pisani.



We recommend viewing the repository in "Tree" view (not "Table" view). In this document, files in the Repository are referred to in the following format:

Repository/Folder/Filename, where "Repository" is https://doi.org/10.7910/DVN/OBIDHJ. You can download all the files in the toolkit at once by choosing "Access Dataset", then "Download ZIP"

## Acknowledgements

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## Feedback

We consider this to be a "living document" and warmly welcome feedback, including corrections and suggestions for alternative or improved workflow or processes. Please send feedback to info@medswatch.org. We will revise this document as necessary, acknowledging the source of suggestions and improvements.

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# Chapter 1: Introduction

This Toolkit is intended to provide practical guidance and tools for academic researchers and others as they plan and carry out studies of the quality of medicines at the point where they are available to patients. It builds on broad guidance on the conduct of medicine quality studies provided by the World Health Organisation,[1] as well as on earlier guidance from academics.[2]

Our intention is not to replace existing guidance, but simply to share experience and practical tools developed in a recent series of studies, in the hope that some of the forms, software and methods we used may be useful to others planning to undertake similar work. The current toolkit focuses on testing the quality of medicines bought by "mystery shoppers" from randomly-selected outlets, including the internet. We hope the toolkit may be of use during the planned updating of existing guidance.

## *A note on definitions*

Throughout this toolkit we use specific terms with the following meanings:

**Medicine**: A pharmaceutical product for human use, containing an active pharmaceutical or biological ingredient. It includes medical products used for prevention or prophylaxis, such as vaccines and hormonal contraceptives.

**Poor quality medicines**: This refers to medicines that are either substandard or falsified.

**Substandard medicines**: Authorized medical products that fail to meet the specifications and standards set out in their market authorisation.

**Falsified medicines**: Medical products that deliberately and fraudulently misrepresent their identity, composition or source.

**Unregistered medicines**: Medical products that have not undergone evaluation and/or approval by the National or Regional Regulatory Authority for the market in which they are marketed/distributed or used, subject to permitted conditions under national or regional regulation and legislation.

**Sample**: One unit of analysis in a medicine quality study. It comprises:

- one medicine, *e.g., amoxicillin*
- of one dosage (strength and formulation), *e.g., 500 mg tablets*
- of one brand, *e.g., Supermoxy, or unbranded generic*
- from one market authorisation holder, *e.g., Modern Pharma Inc*.
- and one batch number, *e.g., TR26BX*
- collected at one location, at one time, *e.g., bought at Rainbow Pharmacy, on June 20th, 2022.*

The number of units (pills, bottles, vials etc.) included in a single sample will depend on the molecule and the tests that are planned.

**Unbranded generic**: Medicines that are marketed using only the name of the active ingredients (the International Non-proprietary Name). Also referred to as **INN generic.** All unbranded generics should nonetheless be registered to a market authorisation holder in the local market.

**Branded medicine:** Patented or originator brand medicines as well as generic or biosimilar medicines sold using a proprietary name.

## *Why measure the quality of medicines?*

Medicines stand at the core of all health systems. National medicine regulatory authorities (NMRAs) aim to ensure that medicines are safe and effective before they allow their manufacture, import or use in a country. They set and enforce rules for Good Manufacturing Practice to ensure that medicines are made correctly, while overseeing distribution to reduce the chance that medicines will degrade before they reach patients, and to keep falsified medicines out of the supply chain. Despite these efforts, poor quality medicines are found in almost all countries. Many regulators thus also sample medicines which are already on the market, testing them to ensure that they meet the standards promised by manufacturers. This activity, known as post-market surveillance, aims to deter the production and trade of poor-quality medicines, as well as to detect problematic products so that they can be removed from circulation, thus protecting patients. Regulators may therefore focus their sampling on locations or products that they believe to be at highest risk.[3,4]

Academic studies of medicine quality are more frequently designed to answer specific research questions, most commonly to estimate the proportion of particular medicines in a particular market that are substandard, falsified or illegal. Useful information about the conduct and reporting of such studies, including a discussion of a broad range of possible study designs, already exist, [1,2] and further updates are planned.

In this Toolkit, we focus largely on one of the more common study designs: the quality testing of medicines sampled from a random selection of outlets where patients obtain medicines. The proportion of samples that fail tests of quality can be combined with information about the volume of medicines of each brand dispensed by different outlets to give accurate estimates of the risk that patients will be exposed to poor quality medicines.

The data collection forms, log sheets and other research tools referred to in this guide can be downloaded in electronic format from the Toolkit Repository, https://doi.org/10.7910/DVN/OBIDHJ. They were developed for use in a large, multi-site study in Indonesia, but are designed to be easily adaptable for use in other settings.

The Toolkit includes information on:

- Planning a study, including seeking approval from authorities
- Choosing medicines to be studied
- Choosing a study design and developing a sample frame
- Survey preparation, including budgeting and logistics
- Data collection tools
- Fieldworker recruitment and training
- Data collection, including sample handling and real-time monitoring
- Visual inspection and laboratory testing
- Data analysis

# Chapter 2: Planning a study

Study planning must be based around several interdependent elements:

1) The **aim** of the study: this will determine the study design, and influence the choice of medicines chosen;

2) The available **budget:** this will influence the choice of quality tests and sample sizes, as well as medicines and formulations;

3) The available **testing infrastructure**: this will influence the choice and cost of quality tests;

4) The available **human resources**: these influence how much can be done, and in which locations;

5) The local **pharmaceutical market and health system structure**: this influences feasibility. It also interacts strongly with the aim of the study, since it determines how representative samples are likely to be of the medicines taken by patients in a country.

Practically, in academic research for which funding must be sought, these issues are considered iteratively. This toolkit assumes that funding for a survey of medicine quality has been secured; that the purpose is broadly to provide information about the extent of the threat posed to patients by poor quality medicines in a country; and that a decision has been made to use randomisation in the selection of sampled outlets.

Once those key factors are in place, more detailed study planning takes place, as shown in Table 1, and detailed below. Some of these steps may have been taken while developing a research proposal.

*Table 1: Steps involved in planning a study*

| | **Activity** |
|---|---|
| 1 | Situation assessment |
| 2 | Consultation with potential data users |
| 3 | Study design: choose molecules, outlets, locations, sample size etc. |
| 4 | Choose laboratory tests and pharmacopeia |
| 5 | Choose laboratory |
| 6 | Ethics and administrative approvals |
| 7 | Construct sample frame |
| 8 | Detailed budgeting |
| 9 | Design/adapt data collection forms |
| 10 | Design/adapt Standard Operating Procedures |

## *Step 1 Situation assessment*

All medicine markets and health systems are different. An understanding of the structure of the local health system and medicine market will help inform choices about which types of outlets to sample from. This knowledge is also needed once study results are available, in

order to understand the implications for patients, and to inform potential policy recommendations.

A situation assessment is likely to involve some or all of the following elements:

1) Reviews of:

- national legislation related to medicine distribution, dispensing and retailing;
- procurement rules and practices in the public sector;
- any volume or pricing data related to the national medicine market, potentially including data from the national health or procurement system, commercial pharmaceutical data aggregators, market research companies and industry or professional associations;
- press reports relating to medicine marketing, distribution, consumption or quality;
- public domain regulatory records on medicine quality, including product recalls and pharmacovigilance reports;
- academic publications (including in local language journals) relating to medicine distribution, dispensing, retailing or quality.

2) Formal or informal interviews with:

- pharmaceutical industry associations, manufacturers or distributors;
- pharmacists and medicine traders;
- health care providers
- patients

3) A mapping of the "journey" of medicines in the local medicine market, from production to consumption.

### *Step 2 Consultation with potential data users*

Most medicine quality studies are (or should be) undertaken with the ultimate aim of better understanding the degree and distribution of the threat poor quality medicines pose to patients. Academic researchers may be able to identify concentrations of risk, and suggest policy changes that could reduce the risk, but they are rarely in a position to effect those changes. When planning research on medicine quality, academic and other non-government groups should therefore try to ensure that their research addresses questions considered important by the policy and market actors who could use study results to inform and implement change. These actors will generally include the medicine regulator and other health authorities, as well as professional associations (pharmacists, doctors, nurses), and industry.

Consulting with these groups early in the study planning process (sometimes through interviews conducted as part of the situation assessment) may help refine specific research questions and study design, for example suggesting priority medicines or geographic areas for study. Early engagement may also facilitate quicker action by the regulator or industry to protect patients in cases where the study identifies medicines suspected or demonstrated to be of poor quality. The research budget should be adequate to cover the costs of engagement, including meeting expenses of travel as needed.

## *Step 3 Study design*

Final study design requires detailed decisions about sampling locations and levels, as well as about which products to sample, and how many samples should be collected. These will all flow from the overall purpose of the study, and available resources.

### Study aim

Studies that collect and test medicines from a random sample of outlets at which patients access those products generally aim to measure the proportion of samples that do not meet quality standards; or the proportion of outlets that dispense or sell medicines that do not meet quality standards; or both. Within that broad goal, a study may also be designed to compare measures of quality across a number of different dimensions, for example:

- geographic area of sale
- therapeutic class
- price point or brand status
- type of outlet or source
- country or area of production

If the intention is to compare prevalence on any of these dimensions, then it is necessary to ensure that sample sizes for each group (for example for each province, or for domestically produced and imported medicines) is large enough to allow for a statistically significant difference to be measured (see section on sample size calculation below).

### Choosing medicines

Medicine quality testing involves the use of a (usually expensive) reference standard, and a validated testing protocol, the latter specific to the formulation of a medicine (for example, it differs for tablets, capsules or dry syrup formulations of the same molecule). This usually limits the number of molecules and formats that can be sampled in any study. In practice, the choice of medicines is often dictated by the institutional interests of the providers of research funding. However, in order to maximise utility to countries where research takes place, other factors should also be considered when choosing medicines.

**Public health importance**

Medicines may be chosen for study based on the magnitude of the risk to public health if that particular medicine were found to be substandard or falsified. Measuring public health importance is not straightforward. It can include measures of:

- Disease prevalence: how many people are affected by the condition the medicine treats?
- Patient vulnerability: does the condition affect especially vulnerable people, such as young children, or people most likely to lack health insurance or access to public services?
- Medical consequences of failure: how severely would a patient's health be affected if the medicines were substandard? For example, the consequences of substandard paracetamol may be a prolonged headache, while substandard chemotherapy may lead to death. Medicines with a "narrow therapeutic index" -- including those that are toxic if over-dosed -- may have especially severe consequences.

- Secondary effects of poor quality: for example, substandard antimicrobials could contribute to antimicrobial resistance, so that even quality medicines become ineffective.
- Budgetary impact: does the medicine represent a high burden on the national or on family budgets?

**Quality risk**
Some medicines are at higher risk for being substandard or falsified than others, either for reasons inherent in the product, or because of market factors. Studies may wish to focus on molecules at higher risk, though if this choice is made, it is important not to imply that the prevalence of poor quality in these molecules represents all medicines on the national market.

Potential indicators of increased risk for substandard products include:

- Chemical composition: some molecules are less stable than others; less-stable molecules and those which are temperature-sensitive are especially likely to degrade;
- Formulation: complex production techniques or sterile formulations may be at particular risk for production errors;
- Variety of producers: the more producers there are of a locally-marketed molecule (including producers in other countries), the more likely it is that some producers will fail to meet quality standards;

Potential indicators of increased risk for falsified products include:

- Medicines with severely controlled or restricted distribution: restrictions may apply because medicines are used recreationally, or for purposes not authorised locally. Narcotics, psychotropics, steroids and abortifacients often fall into this category;
- Medicines that are very expensive, and not covered by health insurance

**Feasibility**
The choice of medicines have important implications for feasibility of sampling. Before finalising the choice of study medicines, the following issues should be considered:

- Affordability: can the medicine be bought and tested within the available budget?
- Accessibility: can the medicine be easily acquired from the outlets included in the study design, in the volumes necessary for testing? This consideration often rules out the inclusion of controlled medicines such as narcotics, and in some settings makes it difficult to sample some antibiotics;
- Handling needs: it may not be practical to include medicines that must be stored and transported in particular ways, for example cold-chain products;
- Capacity for testing: is there a laboratory able and willing to test the medicines and formulations chosen?
- Political acceptability: global health organisations, research funders and governments may have programme priorities that do not reflect local public health needs very closely. It will usually be easier to get support for the investigation of medicines that treat or prevent conditions that are current political priorities, as well as to engage potential users with the results of such studies, than it will be to study medicines relating to health areas that are not currently in fashion.

To the extent possible, all of these decisions should be based on recent data. In terms of public health importance, for example, data about procurement volumes and values can provide a crude ranking of the importance of a medicine in the public system. Bear in mind, however, that raw volumes do not translate easily into disease prevalence or patient exposure, because pills per patient vary, and medicines for chronic conditions may be taken indefinitely, while those for acute conditions will be taken only for a short period.

The consultations described in Step 2 on page 8 are essential in order to access reliable, recent data, as well as to canvas opinions about which factors to prioritise in choosing study medicines.

## Choosing study areas

The choice of geographic areas in which to collect samples will be influenced by the overall purpose of the study.

Choice of geographic area may be part of a multi-stage random sample design (see section on randomisation techniques on page 18). However, this is likely to be expensive, and feasibility may be low. The alternative is to choose sampling areas purposively.

**Explanatory potential**
The areas included in the study have an important bearing on the interpretation of the results. These include:

- Geographic diversity: even if a study is not designed specifically to compare prevalence rates between areas, researchers may wish to ensure that different regions are included, based on population density, economic development, ethnic or other demographic profiles, or other factors;
- Political or administrative diversity: in countries with decentralised health systems, it may be useful to include areas with different models of medicine procurement or dispensing.
- Comparative data: some areas may be richer than others in information which would add to the learning generated from the study (for example previous studies of medicine quality, or of medicine procurement or dispensing).

**Supply chain and quality risks**
In some country settings, falsified (and in rarer cases substandard) medicines may cluster geographically. For example, unregistered and other smuggled medicines might be found in areas bordering countries with weaker medicine regulation or greater availability of affordable medicines. Similarly, informal markets -- more easily penetrated by falsifiers -- might be concentrated in a particular district or along a trade route.

Studies may wish to include or focus on these higher risk areas. If this choice is made, it is important not to imply that the prevalence of poor quality in these areas represents all medicines on the national market.

**Feasibility**
Issues to consider include:

- Density of outlets and stock levels: in some areas, for example remote rural districts, it may be difficult to buy enough pills to meet testing needs, or to sample from a large enough variety of outlets;

- Local support: the willingness of local authorities or research partners to support or allow the research may increase the likelihood that study results contribute to useful policy changes if needed.

Data that may help inform the choice of districts includes data on population density and per capita measures of health service availability and use, together with regulatory data on the historical distribution of detected cases of falsified or substandard medicines.

## Choosing outlet types

The country context and the study design will influence decisions about which types of facilities data collectors will get samples from.

**Representativeness**
As with choice of geographic area, the included outlet types will influence the extent to which any measured prevalence can be generalised to a nation or region. Things to think about include:

- Inclusiveness: do the outlets chosen represent all the sources from which patients acquire medicines in the study area? Many national authorities restrict post-market surveillance to the regulated supply chain which they oversee. However, in many countries, patients also buy medicines from sources not technically authorised to sell them, such as street vendors, internet vendors, or private midwives, nurses or doctors. All of these *de facto* sources of medicines should be considered when choosing outlets for sampling.
- Patient exposure: do the outlets chosen represent the sources from which patients get most of their medicines, by volume? In some settings, a small number of outlets account for a significant proportion of dispensed medicines. (For a detailed description of exposure-based sampling see Dewi et al., 2022)[5]

**Quality risks**
In most countries, falsified products are much more commonly found in the unregulated supply chain (including unlicensed internet vendors and informal markets) than in regular outlets such as hospitals or pharmacies which are subject to rules and oversight. Studies may wish to include or focus on these higher risk outlets. If this choice is made, it is important not to imply that the prevalence of poor quality in these outlets represents all medicines on the national market.

**Feasibility**
Not all outlet types are equally accessible to sampling staff. Issues to consider include:

- Availability of target medicines: some medicines are only available in hospital settings, or other service-specific settings. In addition, some types of outlets do not maintain significant stocks of medicines, so it may be difficult to acquire enough pills, bottles or vials to make up a viable sample.
- Permissions and ethical challenges: sampling from some outlets, often including hospitals and health centres, may require additional permissions; "mystery shopper" sample collection techniques may not be possible so overt sampling may be needed. In areas with limited stocks, there is a risk that taking samples for the study might deprive patients of medicines they need -- a situation that must be avoided for ethical reasons.
- Data sources for sample frame: random sampling presupposes that each outlet has an equal chance of being selected; a full listing or mapping of potential outlets is thus

needed. Some outlets, such as itinerant medicine vendors, may be especially difficult to include in a random design if resources for mapping are not available.

### Sample size calculations

The number of samples required depends on the questions researchers want to answer. If the study aims to make statistically valid comparisons between the prevalence of poor quality among medicines with different characteristics (for example comparing the quality of antibiotics with that of cardiovascular medicines, or comparing medicine quality in rural areas with that in urban areas), each comparison must be taken into account when calculating the minimum sample size.

Free, on-line tools that calculate the sample size needed to estimate a **single proportion** (prevalence) or the **difference between proportions** are available from several sources. Examples include https://statulator.com/ and the Statcalc function in EpiInfo (https://www.cdc.gov/epiinfo/support/downloads.html). These require users to input the desired levels of accuracy and an estimate of the baseline prevalence of poor-quality drugs, or to determine the difference between proportions.

As a general rule of thumb, and following the equations for single proportions described in the sources above, 138 samples would be needed to be 95% confident that a measured prevalence of 10% substandard or falsified medicines reflects the true proportion of poor-quality medicines.

Calculating sample sizes to estimate the difference between two proportions accurately requires researchers to decide what level of difference is worth measuring. For example, if we wanted to be able to measure a 50% difference in prevalence between rural and urban areas -- assuming for example that 14% of medicines in rural areas are substandard compared with 8% of medicines in urban areas, we would need to sample 929 medicines *in each area* to be 95% confident that our estimates reflect the true difference.

The number of units (pills, bottles or vials) required for each sample is discussed under testing parameters, in the next step.

## *Step 4 Testing parameters*

Although laboratory testing can not take place until after samples have been collected, several decisions related to these tests have to be made early on, both because they have a major affect on the study budget, and because they affect subsequent planning and timelines.

### Choosing which tests to perform

Table 2 shows the tests that are often, or sometimes, conducted in studies of medicine quality. The order in which they are presented broadly reflects the relative frequency with which they are undertaken/ reported, with the most frequent at the top.

The choice of medicines may affect the choice of tests. Uniformity of content, which is a proxy for the even distribution of the active ingredient through a batch of medicine, is more important for low dosage pills, for example, or those with a narrow therapeutic index (where small deviations in dosage may lead to therapeutic failure or toxicity). Impurities testing may be especially important for unstable molecules at high risk of producing toxic degradants.

Impurities testing is particularly expensive, because it requires procurement of additional reference chemicals against which to benchmark the impurities or degradants.

*Table 2: Laboratory tests commonly undertaken in medicine quality studies.*

| Test | Definition | Notes |
|---|---|---|
| Identification | Presence of the labelled active ingredient | This does not quantify the active ingredient, and can often be measured using screening devices |
| Assay | % of labelled amount of active ingredient actually present in sample | Requires quantification equipment, e.g. HPLC |
| Dissolution | % of labelled amount of active ingredient dissolved within specified time frame | Solid formulations only. Proxy for bioavailability. |
| Uniformity of content | Variation in % of labelled active ingredient among individual tablets/capsules in a sample | Tablets or capsules with dosages < 25 mg or < 25% |
| Uniformity of weight | Variation in weight between individual tablets/capsules in a sample | |
| Impurities | Presence of specific impurities associated with a medicine, often because of degradation | |

*HPLC: High performance liquid chromatography

### Number of units in each sample

The number of units (pills, bottles or vials) needed in each sample varies according to the tests planned. Table 3 provides an illustration of common tests, the types of medicines for which the tests are commonly conducted, and the minimum number of units per test.

*Table 3: Minimum units for common tests of medicine quality: an illustration*

| Molecule | Dosage and form | Parameter | | | Units needed | |
|---|---|---|---|---|---|---|
| | | Identification and assay | Dissolution (3 stages) | Uniformity of content | Minimum | Ideal |
| Amlodipine | 5mg tablet | 5 | 24 | 30 | 59 | 80 |
| Amoxicillin | 500mg tablet | 5 | 24 | N/A | 44 | 70 |
| Amoxicillin | 125mg dry syrup, 60ml bottle | 3 bottles | N/A | N/A | 3 | 5 |
| Simvastatin | 10mg tablet | 5 | 24 | 30 | 59 | 80 |

N/A: Not applicable

Laboratories commonly request additional units so that they have a back-up in case of error. Researchers must balance the value of "insurance" samples against cost and feasibility. Note that the number of units required for academic research are commonly lower than those used for regulatory testing. While academics should report results to regulators and may also report to manufacturers, they are not in a position to take regulatory action, and do not need to retain samples to support that action.

### Choosing a pharmacopeia and reference standards

Pharmacopeial testing is carried out to identify whether the sampled medicines meet the specifications in their market authorisation. Medicines are tested against a "pure" form of the molecule, known as a reference standard. The tests should be performed using methods that

are laid out in detail in monographs specific to a single molecule and formulation. These are gathered in medicine testing manuals known as a pharmacopeia. Confusingly, there are at least 50 different pharmacopeias available globally and their contents are not identical, either in the medicines and formulations they cover, or in the methods and quality standards prescribed. (Even the word is not always spelled the same: pharmacopoeia and pharmacopeia are both used.) Among the most commonly used are the pharmacopeias of the United States, Britain, Europe, Japan and China. National regulators can choose which pharmacopoeia to use in assessing drug quality in their area of authority. Researchers can also choose which pharmacopeia and reference standards to use. They should be aware that if they choose one that differs in methods or quality standards from the nationally-designated pharmacopeia, the results of the study may be called into question by national authorities.

If there is no monograph available in the selected pharmacopoeia for the sample molecules or formulations to be tested, researchers must agree with the laboratory on methods, specifications and test protocols, and method validation may be needed, as described below.

The choice pharmacopeia can have significant cost implications, because it determines the choice of reference standards. These vary widely in price from one pharmacopeia to another; if imported they may attract significant import duties. Reference standards must be handled with extreme attention to maintaining correct temperatures, humidity levels etc. If they need to be imported, procurement should start in good time, so that they are ready when study samples start to arrive at the laboratory.

### Choosing a laboratory

Medicine quality testing is a specialised field. Not all medicine regulators have access to national laboratories that can guarantee good laboratory practices; the same is true of many academic institutions. The World Health Organisation runs a prequalification scheme for medicine quality testing laboratories, with qualified laboratories listed at https://extranet.who.int/pqweb/medicines/medicines-quality-control-laboratories-list. Other certification schemes, such as national ISO accreditation schemes certifying laboratory and data management processes are also available.

Issues to consider when choosing a laboratory include:

- Certification: is the candidate laboratory WHO prequalified or does it have other quality certification?
- Ownership: is the laboratory independent? If not, might its ownership carry a risk of bias in testing, or potentially restrict publication of results (for example if owned by the national regulator, or by a conglomerate whose products are included in the sample)?
- Location: is it in the country of sample collection? International shipment of samples may require material transfer agreements and/or customs clearance; the latter may incur extra expense (import taxes) and time (including when samples are impounded).
- Equipment: does the laboratory have the equipment and expertise needed to perform tests according to the chosen pharmacopeia?
- Workload: can the laboratory guarantee that it can dedicate resources (equipment. manpower) to processing study samples within the agreed timeline.
- Cost.

- Oversight and transparency: is the laboratory willing to provide raw data as requested, as well as to be audited by the study team?

It is logistically simpler to use a single laboratory for a study. If the workload must be split, it is best to process each molecule in a single laboratory. If no WHO-prequalified laboratory is available for the samples as a whole, and budget and samples suffice, a subset of samples might be re-tested at prequalified laboratory as a quality control measure.

### *Step 5 Ethics and administrative approvals*

Researchers should ensure that they have secured permission from research ethics review boards and from other authorities as necessary in the country and locations where research will be conducted. If research funding comes from other countries, or researchers from overseas institutions are involved, it may also be necessary to seek approval from research ethics review boards in those countries.

The process of seeking ethical review and administrative permissions to conduct research locally may run in parallel with other preparatory activities. It can be time-consuming, so start early.

#### Ethical considerations in medicine quality studies

The basic principles of research ethics apply. Some issues particular to medicine quality studies may need special consideration and planning.

**Creation of shortages**
Researchers should avoid creating localised shortages of medicines needed by patients. Where overt sampling is used, for example in public health facilities or hospitals, data collectors may provide replacement medicines rather than payment.

**Reporting of suspect or proven poor-quality products**
Study results should be reported to the medicine regulator. However, there are ethical issues involved in deciding when and what to report, as well as who else to report data to. These issues are covered in more detail in Chapter 6.

**Use of mystery shoppers**
Some ethics committees have concerns about studies in which data collectors pose as patients or relatives of patients, because they involves a degree of pretence or deception. However, overt sampling from pharmacies or the internet carries the risk that sellers might conceal products that they suspected of being of dubious quality. World Health Organization guidelines suggest that the benefit of gathering unbiased data on medicine quality outweighs any ethical obligation to report to sellers how the medicines bought from them at retail prices will be used.[1] Despite this, there are considerations to note around:

- Feasibility: "Mystery shopper" techniques are rarely feasible in outlets that provide treatment directly for patients in care, such as hospitals or health care providers. In these cases, bias in overt sampling may be reduced by sampling all available brands of a target medicine.
- Protection of field staff: we are unaware of any instances in which data collectors in a medicine quality study have been threatened with harm because they are suspected of deception. However, researchers should give mystery shoppers copies of all administrative and ethical permissions; train them in techniques for diffusing tense situations; and provide real-time supervision to deal with any problems that arise during fieldwork.

### Administrative permissions

The need for administrative permissions is extremely site-specific and will also depend on outlets sampled. In some countries, permission to conduct research from a local ethics review board may be enough, especially if sampling is exclusively from pharmacies and the internet. The consultations described in Step 2 (see page 8) should have informed other important actors of the study aims. In some settings, it may be helpful get explicit permission to conduct research from some or all of the following:

- National or regional medicine regulator(s)
- National or local health departments
- Hospital directors or hospital research review boards

## *Step 6 Construction of sample frame*

The sample frame derives from the study design but requires more detailed data. The level of detail will depend on the sampling design.

Randomisation of outlets requires a full listing of current outlets. Table 4 provides suggestions for potential sources of information for different types of outlets.

*Table 4: Source of listings for different outlet types*

| **Outlet types** | **Source** |
|---|---|
| List of pharmacies in area | - District health office<br>- Association of Pharmacists<br>- Internet directories or mapping services |
| List of hospitals in area | - District health office<br>- Health information websites<br>- Internet directories or mapping services |
| List of clinics | - District health office<br>- Health information websites<br>- Internet directories or mapping services |
| List of health providers | - District health office<br>- Association of doctors<br>- Association of midwifes |

Pharmacies and clinics can shut down or move, and doctors move their practices, so it is rare to find a listing that is complete and up-to-date. Data should be triangulated across all available sources to achieve the most complete listing. If no listings are available as a starting point, physical mapping may be needed.

### Verification of listed outlets

Verification of listed outlets - particularly pharmacies and clinics of general practitioners and midwives - greatly increases the efficiency of sample collection, reducing time, costs and staff frustration. It should be conducted prior to randomly selecting the study outlets.

Where possible, start with the sources listed in Table 4 above.

Consolidate listings of outlets from all sources, removing obvious duplicates. If phone numbers are available, it may be possible to verify the continued existence and correct address of outlets by phone. Venues that have not been verified by phone should be verified physically, preferably by field staff who know the target area well. If the outlet is not found in the expected location, neighbours may be able to provide information on the business (did it close down or move to another location?). Local informants may also provide information about newly opened pharmacies.

The sampled outlets should be drawn from the list of verified locations.

### Multi-level randomisation

Some sample designs minimise the burden of listing and mapping by first randomly choosing smaller geographic units such as a sub-districts or city wards. A full listing of all outlets is then only needed for those districts.

Where pharmacies or other outlets are concentrated within just a few sub-districts, this process is risky, because it may result in the selection of areas with few outlets and exclude those where most medicines are sold or dispensed.

#### Probability proportional to size

One work-around is to consider the distribution of outlets by city ward (or other geographic unit) when selecting districts. Wards are weighted so that those with few outlets will have a lower probability of being selected than those with many outlets. Technically, this procedure requires full verified listings before it can be implemented. However, existing (though imperfect) listings likely provide data robust enough to allow for the weighting of wards and a first-level selection of wards for more detailed sampling and mapping. An exception would be where there is reason to believe that inaccuracies in listing vary substantially between wards, for example because one area has experienced radical redevelopment since the most recent listing, where others have not.

We have copied a useful WHO worksheet showing how to perform random selection using probability proportional to size into the STARmeds Toolkit Repository: (Repository/01_Sample_frame/01_WHO_probability_proportional_to_size.pdf). Document details are provided in the References.[6]

Once detailed geographic areas have been chosen for sampling, efforts to obtain and verify detailed data allowing for a full listing of all targeted outlets in the chosen areas, including physical mapping if necessary, should continue.

### Random selection of outlets

Once outlets have been verified, make a final, numbered list for each study sampling area (for example each city or province included in the study). Now use the random function in a statistical or spreadsheet software (e.g. the =RAND( ) function in Microsoft Excel) to select the required number of outlets.

The number of outlets selected will depend on the total target sample size, and the number of samples collected at each site. It is wise to randomly select more outlets than strictly necessary, labelling additional outlets as alternates, in case some selected outlets are unable to provide the study medicines.

In the Repository, we provide Stata format code for the randomization process, including generating alternates. The code is annotated so that it can be easily adapted by other users.

(Repository/01_Sample_frame/02_Stata_code_for_randomisation.do). Also provided are example input and output spreadsheets, so that users can try running the code.

### Distribution of medicine samples by outlet and sample collector

Once outlets have been selected, a working sample frame can be drawn up. The sample frame distributes target medicines (usually by molecule, and in some cases also dosage, form and brand) between venues and specifies which data collector will visit each outlet. Issues to consider:

- **Security of study staff**
  Target outlets and medicines should be distributed so that "mystery shoppers" do not arouse suspicion, for example by buying the same product at several adjacent market stalls or by buying therapeutically incoherent combinations of medicines.
- **Feasibility of workload**
  As long as security can be assured, grouping target outlets geographically will allow a single data collector to collect more samples in a day. Payment structures should take into account feasibility and varying transport time between venues.
- **Coherence of medicine grouping**
  Target medicines should be assigned in ways that are therapeutically coherent (for example, a "patient" should not try to buy four different antimalarials at once, or buy medicines for high blood pressure and low blood pressure at the same time). They should also be economically consistent (a single shopper may target all high-priced brands or all INN generics, but usually not both at once).
- **Feasibility of medicine-outlet pairing**
  Not all outlets carry the same stock (for example, newer antibiotics may not be available from informal vendors, while public health facilities may dispense only unbranded generic medicines). While always trying to avoid bias, it may be necessary to distribute the sample purposively according to likely availability of some items.

Each mystery shopper can then be provided with a personalised sample frame, showing:

- The outlets they should visit, with address;
- The products they should buy in each individual outlet (by molecule, dose form, brand or price-point, according to the study design);
- Optionally, for some study designs, the preferred day or time of sample collection.

These sample frames may be provided for the study as a whole, or as a daily worksheet. Figure 1 shows an example of a sample frame/worksheet for a single data collector. A soft copy can be found at (Repository/01_Sample_frame/05_daily_sample_frame.xlsx)

Worksheets may also include information on diseases and symptoms associated with the target medicines and expected brands and price range, to support mystery shoppers in credibly requesting medicines.

| *Prescription Available* | *Area* | *Pharmacy* | *Address* | *Medicine* | *Dose* | *Price point* | *Number of tablet/ bottle* | *Is there more than 1 brand?* |
|---|---|---|---|---|---|---|---|---|
| (1) | (2) | (3) | (4) | (5) | (6) | (7) | (8) | (9) |
| **Surveyors name: 2b** | | | | | | | | |
| **Day/date: Friday, 05 August 2022** | | | | | | | | |
| Non Prescription | Subdistrict 1 | Pharmacy 1 | Sejahtera street, 21st | Molecule1 | 100 | Pricey | 60 tablet | |
| | Subdistrict 1 | Pharmacy 1 | Sejahtera street, 21st | Molecule4 | 5 | Pricey | 90 tablet | |
| | Subdistrict 3 | Pharmacy 2 | Panjang Umur Street, no. 73 | Molecule2 | 300 | Pricey | 40 tablet | |
| With Prescription | Subdistrict 6 | Pharmacy 3 | Sawah street no. 12 | Molecule1 | 100 | Cheaper | 60 tablet | |
| | Subdistrict 6 | Pharmacy 3 | Sawah street no. 12 | Molecule2 | 300 | Cheaper | 40 tablet | |
| | | | | | | | | |
| | | | | | | | | |
| Notes : | | | | | | | | |

*Figure 1: Example of daily sample frame for a single data collector*

These sample frames are also useful for estimating the amount of money that each data collector will need to acquire the target medicines.

## *Step 7 Detailed budgeting*

*Table 5: Items likely to be included in fieldwork budget*

| **Item** | **Notes** |
|---|---|
| Engagement and permissions | May include cost of organising meetings, travel to visit local authorities before fieldwork, fees for approvals or documentation |
| Outlet verification | First cut may be done by phone, but final physical verification by locally-based field staff is recommended |
| Field staff fees and expenses | Includes day rates for training and verification; day rates or per-sample rates for data collection, and operational expenses, e.g. transport and communications, in accordance with local standards. |
| Fieldstaff training | Includes trainer fees, accommodation, sample medicine for simulation |
| Research hub hire | Accommodations rental fee: near the sampling area is recommended |
| Logistics and consumables | Stationery, storage box, data logger, data entry equipment, resealable plastic bag, sample container |
| Purchase of medicines | Adjust to the target, prescription costs, buy medicines, and add shipping cost if you buy online |
| Sample shipment | Packaging and shipping costs |
| Study staff travel and expenses | Transportation, lodging accommodation in the sampling area, daily fees/living costs, data and communication packages |
| Contingency | Fieldwork is unpredictable: add budget for unexpected expenses! |

## *Step 8 Design or adaptation of data collection forms*

The increasing use of mobile phones globally and the availability of smartphone apps which also allow for offline data entry mean that electronic data collection is possible in almost every setting. While it is still possible to use paper data collection forms, it is strongly recommended that electronic data collection forms are used. Advantages include:

- **Efficiency**
  Electronic data capture means that manual data entry is not needed, saving time and money
- **Accuracy**
  Automatic skip patterns, picklists and autocomplete fields greatly reduce the likelihood of data entry errors
- **Flexibility**
  Forms can be updated in real time, in case errors are discovered or new data collection needs emerge early in the research
- **Convenience**
  Many of the available tools allow for barcode reading, geo-positioning and photographs, meaning that different types of data can be captured in a single app, and more easily managed and analysed
- **Real-time monitoring**
  In most settings, electronic data collection tools allow for instant upload of data to the cloud, meaning that progress in sample collection can be monitored in real time, and adjustments to forms, sample frame or instructions to field staff made instantly.

**Questions and instructions**
In all research, there is a trade-off between what is feasible for data collectors and respondents (usually less), and what is desirable for researchers (always more!).

We recommend splitting data collection forms into two; a minimalist form for completion in the field, and a more comprehensive form for completion by data entry staff at the research hub. The field form should contain exclusively "need to know" information -- the minimum needed to record location details and price paid, and to allow for real-time monitoring. The hub form can include detail needed for more detailed analysis ("nice to know" information), as well as product photographs. The two forms can be merged on barcode.

### Choice of data collection tool

At the time of writing (2022) available electronic data collection tools include KoboCollect, RedCap, Dharma Platform, Google Forms and many others.

Some, including KoboCollect, are free, open source, and based on Open Data Kit (ODK) standards, so that researchers can easily develop data entry forms using complex skip patterns and multiple languages, using nothing more than an Excel spreadsheet.

An example data collection form containing questions for data commonly collected in medicine quality surveys is available at Repository/02_Fieldwork/06_sample_collectors.xlsx, while the equivalent form for photography and more detailed data entry by office-based data entry staff is at Repository/02_Fieldwork/07_data_entry_staff.xlsx. These forms are in English and Indonesian, to demonstrate the structure of multi-lingual forms. We have provided some specific and some non-specific choices for molecule, brand etc (e.g. allopurinol/Zyloric as well as Molecule 2/Brand 2a) to demonstrate the ease of adaptability.

These are in ODK format, and can be freely adapted and uploaded to any platform using ODK standards for data collection. The forms translate into a user-interface which automatically navigates through question choices according to the responses chosen, as shown in Figure 2.

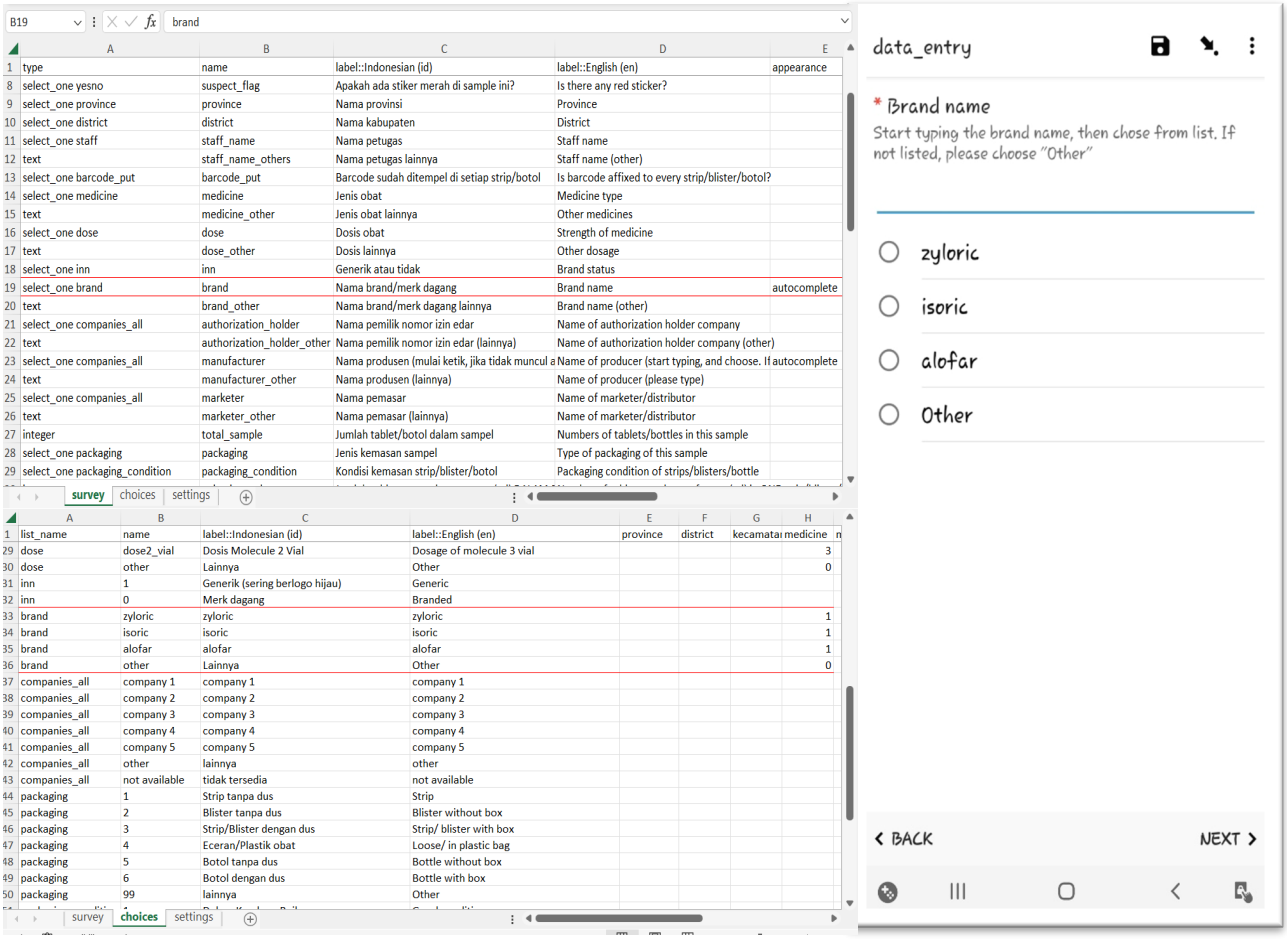


*Figure 2: Illustration of part of an ODK-based spreadsheet and resulting user interface.*

Figure 2 shows how the ODK files relate to the user interface on a smartphone or tablet. Every ODK data collection workbook consists of three sheets, called "survey", "choices" and "settings". General setting such as the default language appear in “settings” sheet (it is possible to run the same survey in multiple languages -- users simply choose on their phone which language they would like to see the questions in). The "survey" sheet shows the questions that will appear in the form, and also stipulates skip patterns, the question type (for example multiple choice, or numeric), and other aspects of the survey. The “choices” sheet gives the options that will appear in the multiple choice lists. In the example shown, row 19 in the “survey” sheet asks the brand of the sample, while rows 33-40 in the “choices” sheet lists all the possible brands. The options that will show on the screen depend on the answer to an earlier question about which medicine has been collected. (Variable name: "medicine".) Column H lists which brand applies to which medicine, so if the answer to the earlier medicine question was 1, then only those brands relevant to medicine 1 will appear in the pick-list on the data collector's screen.

Excel forms must be uploaded to the Kobo platform and deployed before data collectors can use them. Permissions allow different people to have access to different forms.

*Table 6: Types of information collected in different forms*

| Type of data | Field form | Hub form |
|---|---|---|
| Barcode | ✓ | ✓ |
| Basic identity of medicine (molecule, dose form, brand, manufacturer) | ✓ | ✓ |
| Detailed identify of medicine (batch number, expiry date, manufactured date, photos of medicine packaging) | ✗ | ✓ |
| Geography (city, location, outlet name, GIS data) | ✓ | ✗ |
| Basic facility of outlets (ac or non, pharmacist availability, cleanliness, prescription requirement) | ✓ | ✗ |
| Medicine price (selling price) | ✓ | ✗ |

Both questions and instructions should be in **lay language**, avoiding medicine industry jargon (for example use "medicine" rather than "API", and "unbranded generic" rather than "INN").

Use **picklists** (lists of pre-defined answers which data collectors can select from) wherever possible: they reduce effort for data collectors and minimise data entry errors. ODK-based forms make the use of picklists quite easy. For long picklists (such as products with hundreds of possible brand names) use **autocomplete** options for rapid form completion. Avoid asking data collectors to type in responses; this greatly complicates data cleaning and analysis.

**Field testing**

All forms should be tested by study staff before training of data collectors or piloting of study procedures. Forms can easily be tested by buying cheap, over-the-counter products such as paracetamol, and entering, extracting (and where more than one form is used merging) data for a handful of samples.

## *Step 9 Design or adaptation of standard operating procedures*

Standard operating procedures (SOPs) differ from guidelines by being specific to a particular research project. An SOP is a clear and precise instruction manual providing a detailed description of workflow. It is designed to ensure consistency of procedures across different study personnel and sites.

It is helpful to have written SOPs for each of the major aspects of field work, as well as for laboratory testing of medicine quality. These should be:

- In a language that all site supervisors and study implementation staff can read
- Accessible to all study staff and data collectors as relevant, (for example stored in a shared directory)
- Available in hard copy at the data collection hubs or lab

SOPs for laboratory work, including steps for any verification or further investigation of out of specification samples, should be developed and agreed together with laboratory staff. The agreed SOPs should form an integral part of the contract with the testing laboratory.

Table 7 lists the research stages for which SOPs should or may be developed or adapted.

*Table 7: Possible standard operating procedures*

| Research area | Topics covered | Urgency |
|---|---|---|
| Sample collection | - buying medicine<br>- dealing with problems in the field<br>- storing and delivering collected samples<br>- downloading and updating data entry forms<br>- filling and submitting forms | Essential |
| Sample handling, research hub | - registering incoming samples<br>- other intake procedures<br>- filling and submitting forms, including protocols for photography<br>- sample verification | Useful |
| Visual inspection | - packaging check<br>- checks for unexpected values or formats in batch numbers, expiry dates and maximum retail prices<br>- recording suspicious samples | Essential |
| Sample storage and shipping | - storage condition (temperature, humidity)<br>- packing samples for shipment to lab<br>- choosing a shipper | Useful |
| Laboratory protocols | - validation of testing protocols<br>- protocols for sample preparation and testing for each molecule and formulation<br>- investigating unexpected values<br>- data reporting formats | Essential |

The folder Repository/04_Example_SOPs provides examples of standard operating procedures for mystery shopping, hub data entry staff, and laboratory process, as well as a full laboratory testing protocol for one molecule. These are in .docx format, and can be downloaded and adapted as necessary.

# Chapter 3: Final preparations for fieldwork

Table 8 shows the steps involved in the final preparation for fieldwork. Like the steps above, some of these can overlap. However, it is not advisable to continue with this part of the work until all previously described steps have been completed.

*Table 8: Steps involved in preparing fieldwork*

| | **Activity** |
|---|---|
| 10 | Logistics |
| 11 | A-Z piloting of field work |
| 12 | Hiring and training of data collection and entry staff |

## *Step 10 Logistics*

Logistic preparation includes buying and preparing all the materials needed for sample collection and handling, as well as the hiring and preparation of a study hub. Table 9 lists important items which are needed for research.

*Table 9: Preparing logistics*

| **Item/task** | **Notes** |
|---|---|
| *Preparation of research hub* | |
| Hire research hub | Desirable: location central to data collection area; separated quiet space for data entry preferred. |
| Equip research hub | Necessary items if not present:<br>• Table/workspace for sample intake<br>• Tables/desks for data entry<br>• Sufficient plugs & extension lead<br>• Additional stationery (labelling sticker, pen, scissors, permanent marker)<br>• Printer<br>• Magnifying loop<br>• Good lighting<br>• Wi-fi<br>• Bathroom<br>• Drinking water |
| *Preparation of field worker training* | |
| Training materials | Includes presentations, handouts, cheat-sheets, trial sample collection kits, trial data entry forms |
| *Prescriptions* | |
| Prescriptions | University medical department may be able to provide prescriptions under terms of ethics consent |

| *Preparation of sample collection kits* | |
|---|---|
| Design and print barcodes | Ensure waterproof printing on high quality sticker paper. Ask lab how many they need per sample: print that number, plus 20 extra |
| Buy sample Ziplocs | High quality resealable bags in clear plastic. Depending on target medicines and pills/bottles per sample you may need varying sizes. |
| Sticker sample Ziplocs | Stick one barcode **inside** top corner of Ziploc, and one on the outside. Put remaining barcodes in the bag, with a silica gel pack. |
| Other items for data collectors | For each data collector, prepare a kit containing:<br>• Their personalised sample frame<br>• Large Ziplocs for daily sample delivery<br>• Cheat sheets about medicines (for what illness, signs and symptoms, common brand names) and how to complete the field form<br>• Study team contact numbers<br>• Copies of research permits |
| Payment mechanisms, field expenses | Data collectors need money for medicines and operational expenses; either cash or electronic transfer mechanisms should be in place |
| *Sample processing and data entry* | |
| Prepare sample intake | Necessary/ useful items:<br>• Clipboards with pre-printed log sheets<br>• Pens and permanent markers<br>• Box cutter and scissors<br>• Magnifying glass<br>• Coloured stickers<br>• Spare sample Ziplocs with barcodes |
| Prepare data entry | Necessary/ useful items:<br>• Light box<br>• Minibox<br>• Scissors<br>• Pen<br>• Sticker label<br>• Magnifying glass<br>• Tablet and charger<br>• Power cables |
| Sample storage and shipment | • Sealable containers for safe storage and shipment.<br>• Delivery report listing samples by barcode, molecule and dose<br>• Temperature logger |

Figure 3 shows a sample collection bag, as given to data collector, and after processing.

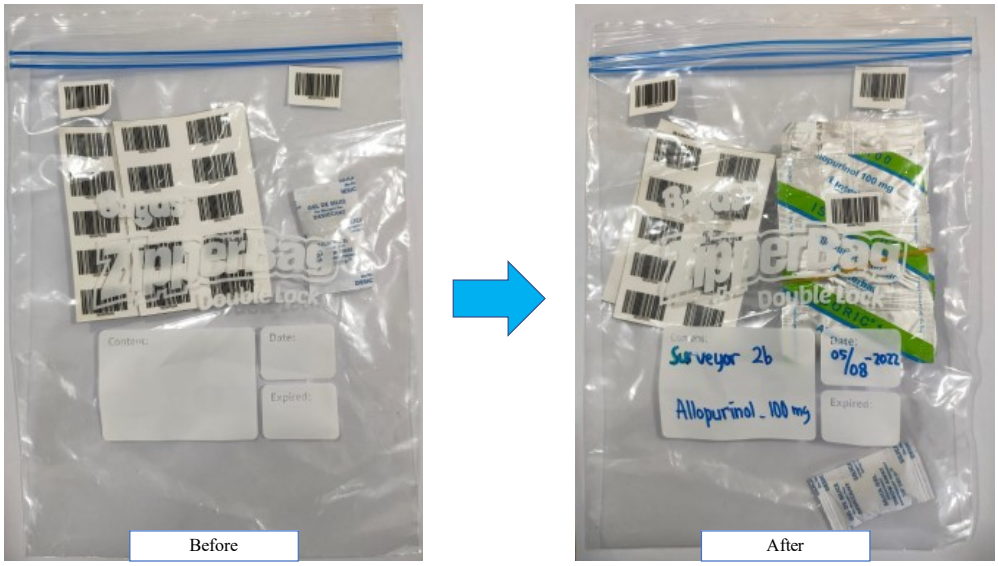


*Figure 3: Sample collection bag, "before" and "after"*

## Step 11 Piloting study procedures

Before training field workers and embarking on the study, it is wise for study staff to try a "dry run" of all the data collection procedures, buying medicines in the same class as those in the study, from outlets not randomly selected for the study.

This will test the feasibility and efficiency of study SOPs and will allow for any necessary changes to data collection forms, study materials and procedures before research begins.

## Step 12 Hiring and training of field staff

The number of surveyors is determined by the number of targeted samples, considering a reasonable workload for each surveyor. Determine the sample collectors' qualifications in accordance with study needs e.g.,

- communication skill, map-reading skill, ability to use certain software or mobile applications, driving license.
- previous experience in conducting fieldwork, especially familiarity with the importance of sampling plans, is helpful
- local data collectors (especially those who speak local dialects) may arouse less suspicion, and familiarity with the local area usually makes for more efficient data collection. However, in smaller towns this may compromise anonymity.

Training is conducted to provide basic knowledge and technical aspects of the study, and simulation of data collection. The training is compulsory for all sample collectors. While introductory material can be imparted online, face-to-face training is essential for role-play and for running through study procedures.

Study staff may use the simulation to assess the particular skills and capabilities of candidate data collectors, and assign them roles accordingly. For example, younger candidates more familiar with technology may be assigned to enter data at the research hubs or to buy medicines online, while those who drive motorbikes may be assigned to collect samples in harder-to-reach areas.

*Table 10: Topics covered in training*

| Item/task | Notes |
|---|---|
| Introduction | ✓ General overview of the study, and of the medicine market<br>✓ General overview of medicines collected in the study<br>• Type of medicine; generic/branded, cheap/pricey,<br>• Indications/symptoms, therapeutic effects, side effect, etc.<br>• Prescription status<br>• Samples of common brands and manufacturers<br>✓ General overview of medicine packaging; training in how to recognise:<br>• name of medicine, dose and formulation<br>• brand, market authorisation holder, manufacturer<br>• expire date<br>• batch number |
| Data collector tasks | Provide information and demonstrate each of the data collector's tasks including:<br>• Following the sample frame<br>• Approaching seller and buying medicine (demonstrated through role playing, see page 28)<br>• Filling out the data forms (field and office)<br>• Packaging and sending samples<br>• Communicating with study staff<br>• Record keeping, reimbursement procedures |
| Full Simulation | ✓ All data collectors must try to "buy" medicines from study staff at simulated pharmacies, then store and process medicines according to study procedures, filling both the field and the office data entry forms. |

### Roleplaying and sampling simulation

During this session, which requires a stock of study medicines, researchers play roles as healthcare professionals in the medicine outlets and the sample collectors become the mystery shoppers. Sample collectors are given a list of target medicines; they practice trying to buy these in the required quantity without raising any suspicions from pharmacy staff. Study staff acting as pharmacists should interact in ways expected in the field, so that data collectors can experience what could happen in reality.

*Table 11: An example scenario for role playing*

| **An example for role playing**<br>If you tell the seller you are buying this medicine for someone else, they won't get suspicious if you can't answer any questions about dosing, side effects etc. Here's an example: | |
|---|---|
| Surveyor | Hello, can I get some amlodipine, please? It's for my boss. |
| Seller | Sure. Is Amlopax ok? |
| Surveyor | How much is that? |
| Seller | 3.5 dollars per strip. |
| Surveyor | Is this your best brand? She always wants the best. |
| Seller | We've got this imported brand, Plusamlo, but it's more expensive of course. It's 6 dollars. |
| Surveyor | That's fine, I'll take 6 strips, please. |
| Seller | Oh, I'm sorry, it looks like I've only got 3 strips left. But I can order it in for this evening if you want to come back for it then. |
| Surveyor | Hmm, I'm not sure. She's quite fussy. Let me just call her and check. You've got stock of the other one, right? Remind me of the brand name. |
| Seller | You mean the Amlopax? Yes, we've got lots of that in stock. |
| Surveyor | Ok, hang on a minute while I give her a ring. |
| | Use this opportunity to ask the hub about what they prefer you to buy at this outlet |
| Surveyor | Sorry it took a while. She's leaving this afternoon, so she can't wait. I'll take 6 strips of the Amlopax, please. |
| Seller | Sure |

Other possible scenarios:

- For paediatric formulation target: “my child is sick”
- To buy an unusually large number of tablets:
    - “I'm buying for my cousin; she's a village midwife”
    - “My brother is going abroad for a job; he wants to take medicines he can trust”

## Contract settlement

Sample collectors who have the required qualifications and pass the training should be given a formal contract. This outlines their rights and responsibilities, the expected workload, the deliverables and the timeframe; lists equipment provided by the research team and by the individual sample collector (for example, they are expected to use their own phone, but the research team will provide a data quota for two weeks); and specifies amounts, timing and mode of payment. An example of a data collector contract is provided at Repository/02_Fieldwork/08_sample_collector_contract.docx.

# Chapter 4: Fieldwork

Once the study has been planned and fully budgeted, logistics are in place and staff are trained, core data collection activities can begin.

Table 12 shows the steps involved in the actual implementation of the fieldwork for the study -- the period in which medicine samples are collected and processed.

*Table 12: Steps involved while carrying out fieldwork*

| | **Activity** |
|---|---|
| 13 | Sample collection and handling |
| 14 | Ongoing monitoring and sample frame adjustment |
| 15 | Intake and visual inspection |
| 16 | Additional data entry |
| 17 | Sample verification and storage |
| 18 | Selection for testing and shipment to laboratory |

## *Step 13 Sample collection and handling*

An example SOP for sample collection staff is provided at Repository/04_Example_SOPs/19_SOP_mystery_shopping.docx.

### Daily preparation

At the start of each day, each data collector should go through the checklist to ensure they have the correct equipment and are adequately prepared for the day's work. Checklist items may include:

- **Do you know what you are buying?**
  Review your daily sample frame, make sure you are familiar with the days' targeted medicines, prepare appropriate scenarios, and ensure that you have the necessary prescriptions.
- **Are you dressed for the part?**
  You should be dressed appropriately for someone likely to be buying your target medicines (e.g. branded, cheapest-on-market, paediatric medicines).
- **Have you downloaded the latest versions** of the data collection forms?
- **Is your phone/tablet charged** (electricity and data), with research staff numbers entered and saved?
  It's always good to take a charger and battery pack
- **Do you have enough barcoded Ziplocs** for the day's samples?
- **Do you have copies of study documentation**, including local research permit?

### Buying medicines: in the store

Mystery shoppers should use prepared scenarios to buy the target medicines. If the target medicines are not available, they should communicate discreetly with the study staff for advice on what to buy, if anything.

Data collectors should have prescriptions available in case sellers request them. If researchers wish to collect data on compliance with regulations on prescriptions, they may instruct data collectors not to produce a prescription unless it is specifically requested by a pharmacist. Studies that aim to collect specific brands may make greater use of prescriptions.

Shoppers should pay in cash, and ask for a receipt if plausible. Receipts are needed for reimbursement, but can also be useful in checking for data entry errors.

### After leaving the store

Immediately after buying samples, sample collectors should find a safe and discreet place (e.g., small café, parking lot) to complete collection process. If geopositioning is being used, this location must be very close to the outlet.

- Put each sample in a separate, barcoded, Ziploc bag. If the data collector bought three samples in one outlet, they should put the medicines in three separate bags.
- Using a permanent marker, label each bag with the staff ID number, the date, and a truncated unique id number [for example, the last four digits of the barcode] in LARGE letters/numbers. This facilitates sample handling and checking later in the process.
- Working on one sample at a time:

    Open the data collection app (for example the kobo form);
    Scan the barcode on the Ziploc bag;
    Fill in the remainder of the field data collection form;
    Store Ziploc in daily collection bag;
    Submit form immediately if online; otherwise save
    Repeat for all samples, then move on to next outlet.

If data collectors are out of phone coverage range, forms can be saved and submitted as soon as they are back in range.

### At the end of each day

At the end of each working day, each sample collector should:

- Ensure that the daily collection bag includes all of the samples collected that day;
- Add any additional paper forms to the bag (for example, annotated daily sample frames, if these are being used);
- Using a permanent marker, label the daily sample collection bag with the staff ID number and the date;
- Deliver samples to the research hub, either in person or using a reliable courier.

After receiving all daily samples, the field coordinator should check that the number of samples matches the number of data collection forms submitted online. If there are any discrepancies, the issue should be followed up immediately so that missing forms or samples can be quickly located.

*Table 13: commonly occurring problems and possible solutions in data collection*

| Problem | Solutions | Notes |
|---|---|---|
| Outlet is not found | *Check in raw data that address on sample frame is correct; Redirect to outlet from alternates list .* | A more thorough verification process greatly reduces this problem |
| Target sample not available | Request alternative brand or molecule. *Adjust overall sample frame.* | Make a list of variations of drug brands on the market |
| Insufficient tablets available | Seek advice from support staff on purchase of fewer tablets. *Authorise or deny, considering factors such as rarity of brand and nature of outlet.* | It may be possible to prioritise key tests for samples with fewer tablets. |
| Limited variety of drug brands | *Real-time monitoring of samples may lead to alert to data collectors to avoid over-sampled brands*. | Data collectors should have lists of brand names of target medicines circulating in the market |
| The seller seems suspicious | Use scenarios practiced in role play, for example explaining that the medicine is for a friend or family member | It is best to avoid pretending to know too much about a medicine; pharmacists often ask difficult questions! |
| Out of cash | *Provide immediate cash transfer to data collector using digital wallet.* | |
| Communication problems (difficulty contacting the hub) | Delay sample purchase | Provide several contact persons in the hub |
| Problems filling field forms | Record the information manually, and immediately report error to hub. *Update forms as necessary, push to all data collectors*. | Data collectors should be advised to update forms by group message, and should individually confirm updates are complete. |

## *Step 14 Ongoing monitoring and sample frame adjustment*

### Real-time support

Sample collection rarely goes exactly according to plan. Each study location should therefor assign at least one staff member to provide real-time support to data collectors, helping them to resolve problems as they arise in the field. This staff member should also have access to real-time sample collection data as it is submitted, so that they can redirect data collectors as appropriate according to the overall sample composition.

Table 13 provides an overview of commonly occurring problems and possible solutions. Actions in italics are taken by support staff, while those in regular type are taken by data collectors in the field.

### Daily review and summary

Study staff should monitor progress at the **end of each day**, comparing the achieved sample against the sample frame and noting any shortfalls or over-samplings of medicines by any characteristic of interest, such as brand, price point, or country of manufacture.

Data collectors and study staff should gather at **the end of each day or the subsequent morning** in a meeting or group phone call to discuss any adjustments to sampling plans. Study staff can advise on revised data collection forms, troubleshoot common problems, answer questions, and reinforce SOPs, while data collectors can highlight problems arising in the field, suggest improvements to workflow, or share tips for effective data collection.

## *Step 15 Intake and visual inspection*

The progress of a sample through the processing hub is recorded on a hard-copy log sheet, in which each handler of the sample signs it out and back in, and on which flags relating to special circumstances are affixed, as shown in Figure 4. A soft copy of an empty English language log sheet for adaptation can be downloaded from Repository/02_Fieldwork/09_logsheet.docx.

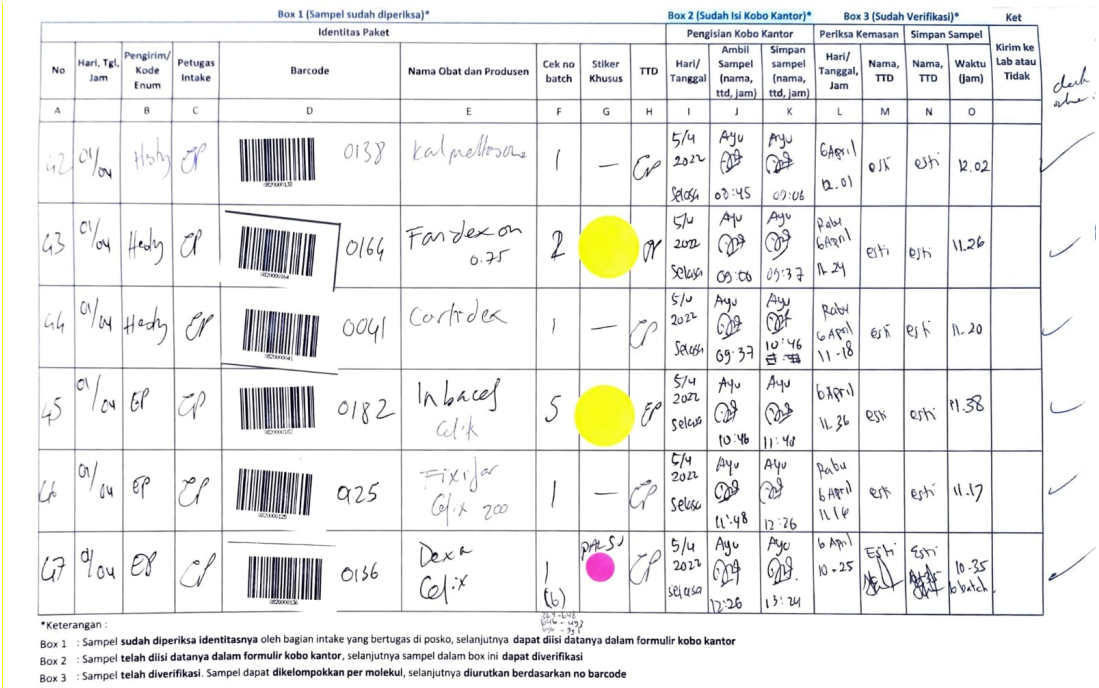


*Figure 4: Example of filled research hub log sheet*

When samples arrive at the research hub, they are deposited in the "Incoming Samples" box. the research staff charged with intake and visual inspection proceeds through the following steps. The process is completed for **one sample at a time**.

- Take a Ziploc containing one sample out of the Incoming Samples box.
- Remove one spare barcode from the Ziploc, and stick-on the log sheet
- Take all the medicines out of the Ziploc, and check whether they are all the same batch number. If not, put a coloured sticker (for example yellow) on the log sheet, and on the Ziploc. (This alerts the data entry staff that they need to process more than one batch number.)
- Check whether all the expiry dates are within the time period in which laboratory is expected to completed testing work. If any medicine is already expired or will expire three months or less after the target end date for laboratory testing, put a different coloured sticker (for example green) on the log sheet and Ziploc. (This alerts the lab to samples with short expiry dates and allows for easy triage of testing order).
- Carefully inspect packaging, using a magnifying glass/loop if necessary. Samples should be compared to reference packaging, lists of registered products, or previously collected samples of the same brands if available. Use a standardised form, adapted to the local market, to compile an "index of suspicion" (see below).

If the sample is suspect:

- Put a different coloured sticker (for example red) on the log sheet and Ziploc. (This alerts the data entry staff that there are likely to be notes in with the sample -- these stickers should be removed before shipping to the lab, to avoid biasing lab staff.)
- Note any details you would like added to the "notes" field in data entry on a piece of paper and put it in the Ziploc with the sample for study staff.
- Note the details of the sample (barcode, molecule, brand etc.) and the nature of suspicions in the study logbook.
- In some cases, it may be desirable to split a sample so that different blisters/bottles/strips etc are tested separately (see below). If a sample is split, also note in the log book the barcode to which is it split.

Once a sample has been processed, it should be signed off on the log sheet and transferred to the "Awaiting Data Entry" box, for further processing by data entry staff.

### Split samples

In some cases, the data entry staff may choose to split one sample into two or more for testing, or for later triage. Reasons for doing this might include:

- Shopper has mistakenly bought more than one brand in the same sample;
- The sample contains different versions of the same brand, for example the same brand, but in different packaging;
- There is a suspicion that some strips/blisters/bottles in the sample may be falsified, while other appears genuine;
- The sample contains more than the minimum needed number of pills and bottles of a single batch number, while also containing other batch numbers.

If a sample is split, the intake staffer should put the "split" or overflow tablets, bottles or vials into a new Ziploc with a new barcode and include a note for data entry staff giving the barcode of the sample from which it was split, for entry into the notes field.

(Note that in data processing, the field data collection form for the original sample must be duplicated so that the relevant information -- source of sample, GIS data, price etc -- can be applied also to the "offspring" sample. Stata format code for this is provided in Repository/03_Data_processing/12_special_cases.do, which runs on the example file 13_special_cases_example.xlsx in the same directory.)

Intake staff with serious suspicions about a product that may have serious implications for vulnerable patients (for example, a paediatric formulation sampled from a high turnover hospital) should alert the study supervisor for potential immediate action (see section on ethical considerations on page 16).

### Index of suspicion

The drivers of substandard production and falsification vary from country to country. It is often difficult to tell whether a poor quality medicine is substandard (made by a legitimate manufacturer, but failing to fulfil the standards laid out in its marketing authorisation) or whether it is falsified (being sold under a misrepresentation of identity or source). In addition, some falsified medicines, including those that have been illegally repackaged, may meet the pharmacopeial specifications for the brand that they are emulating.

Indications of falsification may include mis-spellings on packaging or other factors that can be checked for during visual inspection, especially if reference packaging is available. It is wise for a research team to develop a formalised framework ahead of data collection to systematise the visual inspection, and to guide decision-making about follow-up action, including early alerting of regulators, health authorities or manufacturers.

We provide an example of an index of suspicion framework at Repository/03_Fieldwork/10_index_of_suspicion.docx.

## *Step 16 Additional data entry*

Specialised data entry staff are tasked with completing data entry using software that can be integrated with the data collected in the field.

Data entry is a task that requires concentration. We recommend setting aside a quiet, well-lit room in the hub, with a strong wi-fi signal, for this task. It is best to use tablets with high-quality cameras, and to set photo resolution at high quality. We strongly recommend using portable light boxes, which provide a neutral background and good lighting. Ideally, each data collector should have their own data entry station, with tablet, light-box, and chargers.

Data entry staff process one sample at a time. They proceed as follows:

- Take a sample from the "Awaiting Data Entry" box and sign it out on the log sheet;
- Return to their station, open a new data collection form and photograph the barcode
- Open the Ziploc, take out the spare barcodes and the medicines, and stick one barcode to every strip/blister/bottle of medicine, as well as to any secondary packaging, before returning the medicines and remaining barcodes to the Ziploc.
- Fill in the data entry form, including photographing the products. If there are several batch numbers and expiry dates, each will need to be photographed.
- Fill in the notes section with any notes included in the Ziploc by intake staff

- Ensure that all medicines and barcodes are returned to the Ziploc, place the Ziploc in the "Entered; Awaiting Verification" box, and sign it off by barcode on the log sheet.

An example SOP for data entry staff is provided at Repository/04_Example_SOPs/20_SOP_data_entry_staff.docx.

Table 14 provides a list of data commonly captured at this stage. Some variables are duplicated from the field data collection form; this allows for cross-verification, but also accounts for any differences between the originally collected and finally processed sample, for example because samples have been split.

*Table 14: Information entered at additional data entry stage*

| Item | Entry data | Documentation (photo) |
|---|---|---|
| Sample identity (serial number /barcode) | ✓ | ✗ |
| Data entry staff | ✓ | ✗ |
| Samples name | ✓ | ✗ |
| Number of unit | ✓ | ✗ |
| Molecule name | ✓ | ✗ |
| Formulation | ✓ | ✗ |
| Dosage | ✓ | ✗ |
| Registration number | ✓ | ✓ |
| Market authorization holder* | ✓ | ✓ |
| Manufacturer | ✓ | ✓ |
| Packaging | ✓ | ✓ |
| Packaging note | ✓ | ✓ |
| Expired date | ✓ | ✓ |
| Batch number | ✓ | ✓ |
| Stickering notes (e.g. different batch number in one sample, past expiry date, or any special cases) | ✓ | ✓ |
| Any other notes from intake process | ✓ | ✗ |

*A Marketing Authorisation Holder (MAH) is a company, firm or non-profit organisation that has been granted a marketing authorisation in the country. Sometimes it is different from the producer/manufacturer. This is illustrated in the examples in Figure 5.

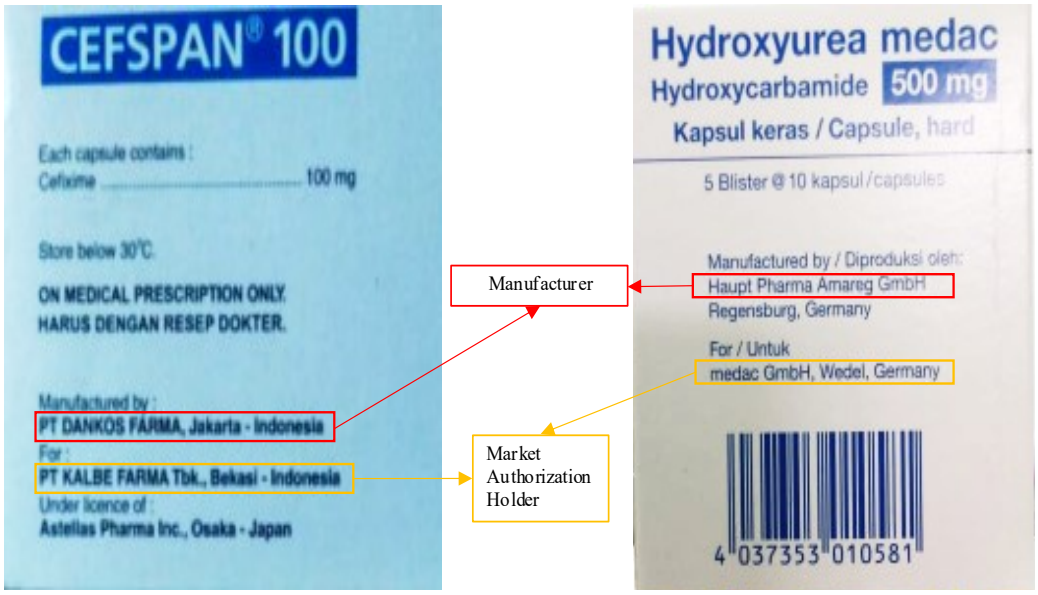


*Figure 5: Examples of packaging of contract manufactured medicines*

## *Step 17 Sample verification, storage and shipment*

The samples undergo a final verification step before being stored for shipment. This verification should be carried out by a new person, not the intake or data entry staff.

Samples are verified against the data recorded on the log sheet. Matching on barcode, verification staff should ensure that the molecule and brand match those on the log sheet. For each sample, they should verify:

- All batches numbers are the same; if not, Ziploc and log sheet are marked with correct coloured sticker.
- All expiry dates are more than three months after final target data for testing; if not, Ziploc and log sheet are marked with correct coloured sticker.
- Any stickers denoting suspicion of falsification or substandard production have been removed.
- All strips/blisters/bottles have been individually stickered with the correct barcode
- Any secondary packaging has been removed from the sample Ziploc (this should be stored separately)

If data is found that does not match between the log sheet and the physical sample, the field and further data collection forms should be checked, and any errors corrected.

Once a sample has been verified, it should be stored in a labelled box, sorted by molecule and barcode number. Samples should be stored and shipped in accordance with national or international Good Distribution Practice (GDP) guidelines, including ensuring temperature control during storage and shipment. A temperature logger should be included with the samples; this can be set to provide readings at regular intervals, for example every four hours. Samples should be hand carried or shipped through a reliable courier, with provision for temperature control and adequate insurance. Samples may be delivered directly to the processing laboratory, or to a central study site for further triage.

### *Step 18 Selection for testing; shipment to laboratory*

Testing is expensive, and the actual number of viable samples may have changed over the course of data collection (for example because some samples have been split). In addition, not all samples may include the ideal number of tablets/bottles/vials to allow for all tests. For these and other reasons, it may be necessary to exclude some samples from testing, while triaging others to prioritise particular tests.

It is wise to set clear, pre-determined criteria to guide the selection of samples to be excluded, and the order of tests for samples with limited volumes. An example of such criteria is provided at Repository/03_Fieldwork/11_laboratory_triage_example.docx.

Study staff may wish to repack samples in accordance with testing priorities before shipment to the laboratory (for example, medicines with close expiry dates might be packed at the front of the container, or all samples of a particular molecule which require dissolution testing prior to assay testing because of limited pill counts might be grouped together). Each container of samples should be clearly labelled, including with any prioritisation instructions, and should contain a hard copy list of the samples in the container, by barcode and molecule.

# Chapter 5: Laboratory testing

Table 15 shows the process steps involved in testing the sampled medicines. Note that several laboratory-related steps, including selection of tests, pharmacopeia and laboratory (see page 13), as well as preparation of standard operating procedures (see page 23), will have been carried out during the study preparation phases.

An example SOP for general laboratory workflow is available at Repository/04_Example_SOPs/21_SOP_laboratory_process.docx

*Table 15: Remaining steps involved in laboratory work.*

| Step # | Activity |
|---|---|
| 19 | Validating methods |
| 20 | Handling and testing of samples |
| 21 | Data entry and reporting |

## *Step 19 Validating or verifying methods*

If the laboratory is using an existing, validated monograph (for example, a monograph published by the International Pharmacopoeia or United States Pharmacopeia), methods do not need to be comprehensively validated, but they do need to be verified. Verification involves an individual laboratory performing "test run" testing, to demonstrate that it can correctly implement the existing monograph for the chosen medicine. Verification should be performed for every test parameter, and for each formulation and molecule (including impurities, if these are included in he study). Records from the verification should be made available to the research team.

In some cases, laboratories develop their own method, or vary existing methods because no monograph is available for a particular medicine or formulation (for example, a monograph is available for a tablet but not a capsule form). In this case, a more comprehensive validation is needed. This involves performing extensive tests to demonstrate that the method meets the requirements for the intended purpose, for example, that it measures assay percentages with acceptable accuracy. If the laboratory is not following a published monograph exactly for any given medicine and formulation, then it will need to validate the method for that particular medicine.

## *Step 20 Handling and testing of samples*

Laboratory procedures will be laid out in SOPs. They should cover:

### Reception of samples

- Download temperature data from data logger
- Log incoming samples, by barcode; check them off packing list
- Record number of pills per sample, with expiry date, by barcode
- Prioritise samples for testing. (This should be in accordance with prioritisation lists provided by study staff.)

### Visual inspection and physical tests

- Inspect pills for uniformity of colour, shape, identifying marks, any clear defects (such as partial disintegration of tablets); note outcomes

- Weigh individual tablets (if uniformity of weight test included)
- Inspect packaging, using microscope (if the laboratory has reference packaging; this step is more commonly undertaken by study staff at intake, see page 33).

### Pharmacopeial tests

These tests should be carried out according to the validated monographs and using the verified methods. To avoid bias in reading test results, the staff carrying out the tests should not know the identity (brand) of the product they are testing. Because some products carry logos or other defining characteristics, this may mean that the person preparing the sample (for example crushing and dissolving tablets) must be different from the person operating the testing machinery.

The sequence and completeness of testing should be laid out in the SOPs, and will depend on the aims of the study. For example, if the principle aim of the study is to estimate the proportion of medicines that are substandard, then testing of a sample will finish after any substandard result. In this case, if the assay tests show that the percentage of active ingredient is below the level considered acceptable in the chosen pharmacopeia, then no further tests (for example dissolution, impurity or uniformity of content) are needed. This case is illustrated in the laboratory flow chart shown in Figure 6, which prioritises assay testing.

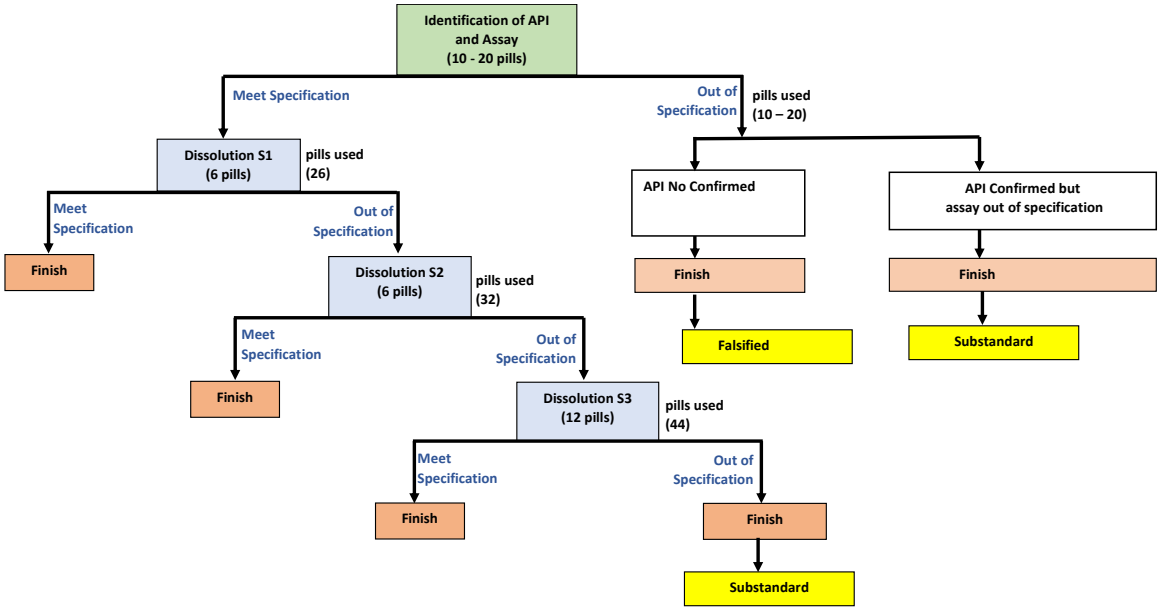


*Figure 6: Flow chart showing an option for testing sequence*

Researchers may, however, be interested in questions other than simple estimates of prevalence. If, for example, the study focused on the relationship between medicine price and bioavailability, then dissolution testing -- a proxy for bioavailability -- would probably take precedence over assay testing in the laboratory workflow.

## *Step 21 Data entry and reporting*

The final, formal reporting of test results by the laboratory usually takes the form of a formal Certificate of Analysis (or CoA). There is usually one CoA per sample, including information on barcode, sample identity, sample visual appearance, test method, test date, name of testing and quality assurance staff, specifications and headline test results with tolerance limits. For

ease of data entry, the laboratory should also provide a spreadsheet giving key results by barcode.

It is also important that researchers have access to the raw data underlying the certificate of analysis -- for example, for dissolution testing, the results per individual tablet or capsule. Researchers and laboratory staff should agree on a soft-copy data entry and reporting template for these data, as well as a timetable for provision of results. It is strongly recommended that raw data are provided to the research team as tests are completed, and before a final certificate of analysis is issued, in spreadsheet format. This allows the research team to monitor progress, and to spot any anomalies or unexpected results that may require rapid follow-up investigation by the lab. Raw data reporting should include sample barcode, molecule, dose and formulation, test date and analyst who carried out the test. Interim results will depend on the tests ordered but may include weighing data, dissolution and dilution data, system suitability test data, absorbance data for test results by spectrophotometry and peak area data for testing using HPLC.

An example of a full laboratory testing protocol for amoxicillin capsules is provided at Repository/04_Example_SOPs/22_pharmaceutical_analysis_protocol.doc.

# Chapter 6: Data management and reporting

If these guidelines are followed, it is likely that study data will be provided in several different files -- at least one file for laboratory results, and two from field data collection -- the data input by data collectors, and the additional data and photographs entered in the research hubs. There may additionally be files related to special cases or split samples.

Each of these files should eventually be structured in the same way -- one observation per barcode -- and the data may thus be merged on barcode. Some other data will be duplicated between datasets (generally the medicine, dose and formulation, and perhaps also the brand). Where there are conflicts, records should first be verified against photographs. If this does not resolve disparities, data entered by data entry staff at hubs are generally more reliable (they also account for split samples and other modifications during intake).

Some data cleaning and management may be needed before datasets can be merged: for example, data may need to be restructured from the output of an ODK-based data collection form that includes skip patterns.

We provide examples of Stata code that manages and merges data from Kobo and laboratory forms in Repository/03_Data_processing/14_manage_&_merge.do. The Readme file in the folder gives more details.

## Reporting to the regulator

Results should be reported to the national medicine regulator soon after verified laboratory results are available, although when strong suspicions arise during visual inspection or initial laboratory testing, and where those suspicions raise concern of immediate public health harm, provisional information should be provided to the regulator even before confirmed laboratory results (reported in certificates of analysis) are available.

When reporting proven or suspect substandard or falsified products to the regulator, The research supervisor should provide, at a minimum, the **medicines, dosage and formulation, brand, batch number, expiry date and geographical area of sampling**. The source of the sample should be shared for falsified products; it may not be necessary to share the source for substandard products.

Regulators should have a library of reference packaging and may be able to help verify the identity of any products that are suspected of being falsified.

## Reporting to market authorisation holder

Market authorisation holders are often best placed to verify whether a product suspected of being falsified is actually falsified or is genuine. Research staff should share with market authorisation holders, at a minimum, the **medicines, dosage and form, brand, batch number, and expiry date,** as well as **photographs of packaging.**

If a market authorisation holder confirms a product as falsified, researchers may wish to share further details such as source of sample date of acquisition etc.

## Reporting to the academic community

Reporting of medicine quality studies should follow the MEDQUARG guidelines (see Table 1 of 10.1371/journal.pmed.1000052).

The limitations cited by several important recent meta-analyses, including the different standards applied by pharmacopeia in different countries, underline the importance of providing full information on each sample (quantitative results for assay, dissolution, uniformity of content and any other test performed), rather than simply reporting numbers

passing and failing testing. An easy and useful way to do this is to share the dataset underlying the study in a research repository; this allows for the reuse of data by other researchers. An example of a medicine quality dataset shared at the level of individual sample data can be found at https://doi.org/10.7910/DVN/EBQYUB, File 7.

Note that any data shared in publicly accessible repositories must comply with the terms of the ethics approval for the research. This may require anonymisation or aggregation of certain parameters, such as brand name or outlet.

# References

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