MBIRA study training manual

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The name of the study MBIRA is an acronym for **M**ortality from **B**acterial **I**nfections **R**esistant to **A**ntibiotics. An mbira is also a “thumb piano”, played as a musical instrument across southern Africa.

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This manual is intended as a practical guide to aid execution of the MBIRA study, to bridge between the protocol document and the study data collection forms, both for Investigators and Research Staff. For more detail on the study background, please refer to the study protocol document, as available in the study Dropbox folder. The most recent versions of all the study data collections forms are also kept in the same location, plus various other supporting materials. If you do not currently have access to this Dropbox folder, please contact the study co-ordinators, Alexander Aiken (alexander.aiken@lshtm.ac.uk) or Lee White (lee.white@lshtm.ac.uk).

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1. Background to MBIRA study

Antimicrobial resistance is a major public health problem of the 21st Century. A key challenge for tackling this problem is that it is difficult for policy-makers in Low and Middle Income Countries (LMIC) to make a connection between high rates of antimicrobial resistance in bacteria and patient-level outcomes, such as risk of death (mortality) and prolonged or additional hospital admissions (morbidity). This disconnection is due, in part, to the lack of local research work in LMIC that makes a connection between microbiological measurement of antibiotic resistance in laboratories and patient-level clinical impacts in wards and clinics. For more extensive background information, see the literature review section in the study protocol document.

The MBIRA study aims to make a first multi-national attempt to bridge this gap between laboratory information on antibiotic resistance and clinical outcomes in sub-Saharan African countries. The study aims to include patients from hospitals across multiple different African countries, all collecting the same types of data prospectively over an (approximate) 1 year period in 2020-2022. The project is focussed on bloodstream infections (=bacteraemia) caused by Gram-negative enteric bacteria (Enterobacteria, such as *E. coli* and *Klebsiella pneumoniae*) and includes patients of all age groups, from neonates to adults. We hope to recruit a total of approximately 1,200 patients with bacteraemia across all sites in the study, with matching to approximately 2,400 non-infected patients in the same hospitals. The MBIRA study is **purely observational**, with the intention of only measuring what normally happens in routine clinical activity in the participating hospitals. At present time (as of May 2021), the participating hospitals are:

Site, country	Level of facility	Anticipated main support for blood cultures
Tygerberg Hospital / Stellenbosch University, South Africa	Tertiary hospital	Government
Kilifi District Hospital / KEMRI-Wellcome Research Programme, Kilifi, Kenya	District Hospital	Research programme
Korle Bu Hospital / University of Accra, Accra, Ghana	Tertiary hospital	Government+ Fleming Fund
National Hospital, Abuja, Nigeria	Tertiary hospital	Government
Hiwot Fana Hospital, Harar, Ethiopia / Haramaya University	Tertiary hospital	Research programme
Kilimajaro Christian Medical Centre / Kilimanjaro Clinical Research Institute, Moshi, Tanzania	Tertiary hospital	Government+ Fleming Fund
University Teaching Hospital, Lusaka, Zambia / Centre for Infectious Diseases Research, Zambia	Tertiary Hospital	Government+ Fleming Fund
Queen Elizabeth Hospital, Blantyre, Malawi / Malawi-Liverpool-Wellcome Research Program	Tertiary hospital	Research programme

The MBIRA study is funded by the Bill+Melinda Gates Foundation and is led by researchers at the London School of Hygiene and Tropical Medicine in the UK. This current study is the second part of the MBIRA study work – an initial pilot study was conducted in 2017-18, using historical laboratory and clinical data from 6 African hospitals, 3 of which have continued to participate in this current MBIRA study (manuscript published Jan 2021 see https://academic.oup.com/jacamr/article/3/1/dlaa130/6104122).

2. Overview of data collection forms in MBIRA study

The main work in the MBIRA study revolves around identification of new patients with positive blood cultures and recording information on their antibiotic treatment and outcomes. Any patient with a blood culture (taken for routine clinical diagnostic purposes) that is **positive for any bacterial species within the Enterobacterales order** (other than Salmonella species) is eligible for inclusion in the study and should be approached to ask to participate. See Introduction to Microbiology (section 14 of this manual) for full description of all relevant bacterial species – **the most typical organisms in this group are *E. coli* and *K. pneumoniae,* but there are many others***.* Each patient with a positive blood culture (a bacteraemia patient) is matched to 2 comparison patients without currently-known bacteraemia (matching patients) who are in hospital at a similar time, to form groups of 3 patients ("triads"). The non-infected patients are included in the study to allow us to adjust for other factors causing ill-health in the hospitalized population. All of these patients are followed up together for a period of up to 30 days or their eventual discharge from hospital, whichever is the later. Most hospital admissions last less than 30 days, so the 30-day follow up will usually occur some time after the discharge from hospital, when patients will be contacted by phone. The design of the study is a type of **cohort study** with matching between the infected and non-infected patients. The study is not a case-control study design, and we avoid calling the patients either "cases" or "controls" as this increases the confusion. Additional data is collected in this study about the hospital that the study is being performed in – this provides important context information to help understand the patient-level data being collected. The data collection forms used in the study are as follows:

- **Case Record Form (CRF**). This is the main patient-level data collection form. A separate copy of this form is used for each individual patient in the study. The same form is used for both infected (bacteramia) patients and non-infected (matched) patients.
- **Pharmacy Form**. This form collects information about the availability of antibiotic drugs in the local hospital pharmacy, to reflect actual current drug availability. This form does not contain patient-level information. The data collection for this form should be performed monthly, ideally at the start of each month in conjunction with a local Pharmacist.
- **Hospital Form**. This form collects information about the Hospital where the study is taking place. This form includes descriptions about the physical size and activity levels in the hospital, information about the laboratory and descriptions about Infection Prevention and Control (IPC) and Antimicrobial Stewardship (AMS) activities in the hospital. For IPC and AMS activities, the MBIRA study makes use of questionnaires developed in other recent studies, with summaries of results (and scanned copies of the forms) being entered. All the data for the Hospital Form should be collected once at the start of the study and a second time at the end of the study, about 12 months later.
- **Laboratory Monitoring Form**. This very simple form collects information about the performance of blood cultures in the laboratory of the hospital. This form should be completed each month, based on the blood cultures performed in the previous month. To allow completion of the laboratory identification work, this form should be collected in the middle of each calendar month in conjunction with Microbiology staff in the laboratory.

The most recent paper-based versions of all these forms are kept in the study Dropbox folder. Once the relevant information has been collected, the information is entered to a Redcap database. The same Redcap database can also be used for direct electronic data entry of the forms, using a tablet device. Participating sites can use either paper-based or electronic data capture, as suits locally. This manual gives further detailed instructions on completion and entry of these forms, plus a series of linked training exercises.

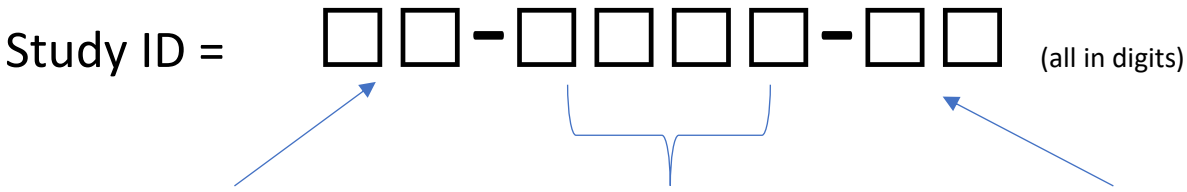
Collecting information about clinical cases or activities in African hospitals can be challenging, especially if documentation in medical records is poor. We have tried to focus these forms on what is both potentially important in the analysis of this study and also realistic to collect. If there are major obstacles that you can

predict in data collection or minor improvements that you can suggest, we would like to hear from you! Please contact the study co-ordinators with any suggestions – see section "25. Feedback" in this manual.

Activity: now download from Dropbox and print out paper copies of the four different types of MBIRA study forms. These copies will be used in some of the subsequent Training Exercises, which are easier to do with paper versions of the forms.

3. Main study reference number format

For individual patients in the MBIRA study, we will use a unique study reference number for tracking the participating patients in the database. The names of these patients not be recorded electronically for purposes of preserving confidentiality, though these can be written on paper copies of the CRF to assist with locating patients on study wards. Hospital inpatients will have hospital medical record numbers (MRN or similar) and there may also be other reference numbers relating to other research studies – these other numbers are not relevant to this project, unless being used for tracking of bacterial isolates in freezers or linking other data. The MBIRA study reference number (the Study ID) has the following format across all sites:



This first part of the study ID relates to the study site, and will always be the same in that site for the duration of the study. The numbers are as follows

01	South Africa
04	Nigeria/Abuja
05	Kenya
06	Ghana
08	Ethiopia
09	Tanzania
10	Zambia
11	Malawi

This second part of the study ID relates to the "triad" of patients – one bacteraemia case and their corresponding matched uninfected patients. These numbers will be assigned sequentially, starting from 0001 for the first "triad" in each site

This third part of the study ID relates to the "type" of patient.

00 = bacteraemia patient
01 = match #1
02 = match #2
03 = match #3 (if needed)
04 = match #4 (if needed)
…

The bacteraemia patient in each triad is number 00. Normally, we aim to match each bacteraemia case to 2 non-infected patients – the first two matches approached are assigned as 01 and 02. Occasionally, individuals identified as potential matches may decline to participate, in which case a 3rd or a 4th matched individual should be approached (and numbered 03, 04 etc), until 2 matched patients consent to participate in the study.

This study ID is recorded at the top of the CRF. The study ID should be assigned to a bacteraemia case as soon as the laboratory identifies a suitable positive blood culture, even before the patient has been approached to participate, so that all consecutive positive blood cultures (for the appropriate bacteria) are given a study ID.

Allocation of MBIRA study ID numbers for bacteraemia cases can be done in the Microbiology laboratory, either by directly accessing the Redcap database to determine the next relevant ID number (with -00 at the end for a bacteraemia case), or by creating a separate Excel spreadsheet file with a record of the relevant numbers, so that the next number can be easily predicted.

Example of possible laboratory enrolment log:

	C	D	E	F	G	H
1	**MBIRA number to be assigned**	**Date of positive culture**	**hospital number**	**ward**	**Name**	
2	03-0001-00	02/11/2020	24352455	Paediatrics	Thomas Dlamini	
3	03-0002-00	05/11/2020	98797974	Adult- male	David Bakageso	
4	03-0003-00	12/11/2020	43456346	Neonatal	Grace Bojang	
5	03-0004-00					
6	03-0005-00					
7	03-0006-00					
8	03-0007-00					
9	03-0008-00					

4. Inclusion+exclusion criteria for bacteraemic patients in MBIRA

Inclusion criteria

All consecutive patients identified to have proven bacteraemia caused by species of Enteric bacteria (technically, bacteria in the Enterobacterales order – typically E. coli and K. pneumoniae, but many other minor species – see Introduction to Microbiology section 14) are eligible to participate in this study and should be included, if possible. Patients with bacteraemia caused by Salmonella species (either Salmonella typhoid or non-typhoidal Salmonella species) are **not** eligible for inclusion.

All age-groups are eligible, from neonates through to adults. Patients who were previously included in the study can be enrolled again, so long as this represents a distinct episode of bacteraemia – the patient should have at least completed the 30-day follow-up period before being eligible to be enrolled again.

Note that blood cultures typically take 2-3 days between collection from a patient and identification of the bacteria – this is because the culture are based on bacterial growth, which typically takes at least 12-24hrs. Patients who have died in the interval between blood culture collection and a positive identification of a suitable pathogenic bacteria **are still eligible for inclusion in the study** and should be retrospectively included where-ever possible. This may present some challenges for data collection, but death after blood culture collection is not an exclusion criterion in itself.

Exclusion criteria

Repeat isolation of same organism in same patient. A repeat positive blood culture of the same species within 30 days of a previous positive blood culture is not eligible for inclusion as a new study patient – we consider this to represent a recurrence of incompletely treated infection rather than a new disease episode.

Outpatients. The MBIRA study requires that patients with bacteraemia are hospital inpatients. A positive blood culture for an individual who was not a hospital inpatient at the time the blood culture was collected is therefore not eligible to be included in the study. We define “hospital inpatient” as someone who spent at least one night in hospital, or intended to do this (a patient may die before 24 hours has elapsed). Some high-risk outpatient groups (eg. renal dialysis patients) may be detected to have bacteraemia whilst in an outpatient setting – these patients are not possible to include in the MBIRA study.

Mixed pathogens. Where there are 2 or more recognized different pathogens identified in the same blood culture sample (including 1 enterobacteria and 1 or more other non-enterobacteria pathogen), these bacteraemic individuals are not eligible for inclusion in the MBIRA study. These patients are excluded because it would be too difficult to interpret impacts arising from these mixed infections. It is acceptable to

include bacteraemia patients where there is a mixture of 2 or more different enterobacteria (eg *E.coli* and *K.pneumoniae* in same blood culture) or an enterobacteria and a recognized contaminant species (eg. coagulase-negative Staphylococci). See Intro to Microbiology section 14 for more detail on the pathogen and contaminant species.

Consent: note that all patients in the MBIRA study, both bacteraemia and matching patients (or their next of kin) will be asked to provide informed consent to participate. Some of the participating hospitals are conducting surveillance studies under different research protocols, which may allow collection of the necessary information for the MBIRA under a separate consent form. There are no particular procedures or risks involved in the MBIRA study, but it does represent some different activities to normal clinical care. Patients / next of kin are, of course, entitled to decline to participate, though we hope this will be rare.

A CRF form should be started for all eligible bacteraemia patients – if they decline to participate, stop filling the CRF at the relevant point.

5. Matching non-infected inpatients in MBIRA study

A key feature of the MBIRA study is the matching of infected patients with bacteraemia to otherwise similar hospital inpatients who do not (as far as we know) currently have bacteraemia. This matching process allows us to establish a "baseline" risk of mortality and duration of hospital admission in what should be otherwise similar hospital inpatients.

This matching process will be challenging to do initially, so it is vital that project staff performing this matching activity are suitably trained, first by reading this section of the manual and then by performing the following training exercise (next section).

The principle for matching is that the non-infected patients should be picked such that they are matched to the patient with bacteraemia, in terms of

- **Time-period of admission** – i.e. they are admitted to hospital on an approximately similar date as the bacteraemia case (within 2 weeks before or after by calendar date is ideal, though longer periods than this are acceptable). This criterion is flexible if the bacteraemia patient has a long admission prior to a positive blood culture – the matching patients should be "as close as possible" in terms of date of admission.
- **Hospital location at recruitment**. For example, if the bacteraemia case patient is currently in the Paediatrics ward at time of enrolment into the study, the matching patients must be recruited from the same ward. The patient physical location at time when the blood culture was collected is not relevant.
- **Age category** (grouped as neonate (0-28 days) / infant (29-364 days) / child (1 – 14 yrs)/ adult (>14yrs)). For example, if the bacteraemia case is an infant, only infants are eligible to be matches. It is acceptable in some circumstances for a patient in an "adjacent" age category to be included (eg. for an "infant" bacteraemia case to be matched to a "neonate" or "child" who is close in age).
- **Time-in-hospital**. This is the most difficult part of the matching to understand. This means that at time of recruitment, a potential matching patient must have been in hospital for at least as long as the time from admission to development of bacteraemia (defined as the day the blood culture was collected) in the corresponding bacteraemia case. Further description and examples of how to calculate this in practice are given in the Training exercise.

Sex of patient is not a matching criteria, so in a mixed sex ward, a bacteraemia patient can be matched to a patient of a different sex.

Patients must be alive **at time of selection** for being potential matches in the MBIRA study – do not attempt to include patients who are already deceased when selecting potential matches. Some matched patients will die after being selected and recruited into the study – this is an expected occurrence.

Exclusion criteria for potential matching patients – patients known to have bacteraemia (any form of disease-causing bacteria) at any point in their hospital admission are not eligible for inclusion, but patients with any other form of infection (eg. pneumonia, UTI, suspected "sepsis", chronic infections such as TB or HIV) are eligible to be in the study. Patients that have already died are not eligible for matching (as above), but patients that are severely unwell can be approached for matching if eligible based on above criteria.

In practical terms, matching patients should be identified and recruited as soon as possible after a bacteraemia case is recruited. If a bacteraemia case has already died by the time of recruitment of potential matches on the ward, it is still possible to seek potential matches for a deceased patient.

A simple approach to use is to make a list of all the other inpatients in the same ward as the bacteraemia case and to rule out those that do not meet the matching criteria or have any exclusion criteria present. This will generate a "short list" of 2 or more possible matches, though it is possible that there will be zero or only one suitable matches available.

If there are >2 potential matches available, the patients to be approached should be **selected at random** from the available patients and approached in this order. An easy approach to this is to use a free Random number generator app – we suggest the "Random: All Things Generator" app, but many alternatives exist.

For example, if there are currently 8 patients on the ward who are suitable to be approached to be matches in the study:

1. Write these patient names in a list, numbered 1 to 8
2. Use the random number generator app to pick a random number between 1 and 8
3. Approach this patient first to seek consent to participate (record as number as 01 within the triad)
4. Repeat steps 2 and 3, numbering patients approached as 02, 03, 04 etc until two are recruited

If only 2 suitable patients are available on the ward at time of potential recruitment, it is not necessary to randomize. If only 1 or zero suitable patients are available, then it will be necessary to visit the ward again on subsequent days until at least one (and preferably two) suitable matching patients are identified and recruited. If a bacteraemia case cannot be matched to at least one uninfected patient, this bacteraemia case should still be followed up in the study, but it will limit their usefulness in the analysis. If only one matching patient can be identified, this is better than zero, but not as useful as 2. There is no need to recruit more than two patients who consent to participate in the study.

Activity: now download a random number generator app of your choice to your phone or data-collection tablet. If you don't have a device that can use apps, a dice might be a simple alternative.

Link for "Random: All Things Generator" app – various other apps also are available and suitable to use.
Android: https://play.google.com/store/apps/details?id=com.yahenskyi.random
Apple: https://apps.apple.com/us/app/random-all-things-generator/id1128190780


or

→ use the Number # function.

6. Training exercise 1 – mock matching to select non-infected patients

This is an exercise to test your understanding of the process of identifying suitable matching patients for the MBIRA study.

The most difficult aspect is to ensure that only patients with the same Time-in-Hospital interval as the bacteraemia case are considered for matching. For example, if the bacteraemia patient was admitted to hospital on the 1st March and had a blood culture (which subsequently became positive for a relevant bacteria) on the 6th of March, then the time-in-hospital interval is 6th March– 1st March = 5 days. This would mean that only non-infected patients who have already been in hospital for at least 5 days are suitable.

The scenario below is based on recruiting on a mixed-age Paediatrics ward on **10th January 2020**. Patient ID 1 was admitted on the 1st of January and has a positive blood culture for *E. coli* that was taken on 6th January 2020. Some other patients have also had blood cultures performed and the results are indicated in the relevant column. All patients are currently alive and currently in the same ward at Patient ID 1. Some dates of birth are unknown and their estimated ages are indicated.

ID	Date of birth	Age	Age group	Date of admission	Admission to current date interval	Date of blood culture	blood culture result
1	23/04/2019			01/01/2020		06/01/2020	E. coli
2	11/11/2019			27/12/2019			
3	02/03/2019			28/12/2019		28/12/2019	negative
4	14/12/2011			03/01/2020			
5	07/07/2019			07/01/2020			
6	08/02/2017			02/11/2019			
7	03/01/2020			04/01/2020			
8	10/05/2008			09/01/2020			
9	20/06/2019			30/11/2019		03/12/2020	negative
10	06/10/2019			04/01/2020			
11	unknown	est. 6 months		25/12/2019			
12	29/10/2019			08/01/2020			
13	04/02/2017			07/10/2019			
14	08/06/2019			04/01/2020		02/01/2020	Staph aureus
15	unknown	est. 2 years		05/01/2020			

Activity

1. Work out the ages and age-groups of all patients as per study definitions (age-groups: neonate 0-28 days ; infant 29-364 days ; child 1 – 14 yrs ; adult >14yrs. Write these in the Age and Age-group columns. Cross out any patients which are now not suitable matches to the bacteraemia case.
2. Work out the interval (in days) from admission to the current date for all remaining suitable patients and write this into the relevant column. What is the interval from admission to bacteraemia for the bacteraemia case? Which additional patients are now not suitable matches?
3. Referring back to the previous section, apply any other relevant exclusion criteria for the study. Which additional patients are now not suitable matches?
4. Give sequential numbers (i.e. 1, 2, 3 etc … as needed) to any remaining suitable potential matches and then use your random number generator to pick 3 of these to approach to seek consent, indicating the order in which they were chosen.

***** DO NOT TURN OVER UNTIL YOU HAVE COMPLETED ALL STAGES OF THE ACTIVITY *****

Answers: You should have ended up with a table that looks like this (note scenario dated is 10th Jan 2020).

ID	Date of birth	Age	Age group	Date of admission	Admission to current date interval	Date of blood culture	blood culture result
1	23/04/2019	8 months	infant	01/01/2020	Not relevant	06/01/2020	E. coli
2	11/11/2019	2 months	infant	27/12/2019	14		
3	02/03/2019	10 months	infant	28/12/2019	13	28/12/2019	negative
~~4~~	~~14/12/2011~~	~~8 years~~	~~child~~	~~03/01/2020~~	~~7~~		
~~5~~	~~07/07/2019~~	~~6 months~~	~~infant~~	~~07/01/2020~~	~~3~~		
~~6~~	~~08/02/2017~~	~~3 years~~	~~child~~	~~02/11/2019~~	~~69~~		
~~7~~	~~03/01/2020~~	~~7 days~~	~~neonate~~	~~04/01/2020~~	~~6~~		
~~8~~	~~10/05/2008~~	~~11 years~~	~~child~~	~~09/01/2020~~	~~1~~		
~~9~~	~~20/06/2019~~	~~6 months~~	~~infant~~	~~30/11/2019~~	~~41~~	~~03/12/2020~~	~~negative~~
10	06/10/2019	3 months	infant	04/01/2020	6		
11	unknown	est. 6 months	infant	25/12/2019	16		
~~12~~	~~29/10/2019~~	~~2 months~~	~~infant~~	~~08/01/2020~~	~~2~~		
~~13~~	~~04/02/2017~~	~~2 years~~	~~child~~	~~07/10/2019~~	~~95~~		
~~14~~	~~08/06/2019~~	~~7 months~~	~~infant~~	~~04/01/2020~~	~~6~~	~~02/01/2020~~	~~Staph aureus~~
~~15~~	~~unknown~~	~~est. 2 years~~	~~child~~	~~05/01/2020~~	~~5~~		

Step-by-step guide.

1. For the ages and age-groups, you can calculate these from the dates of birth and the current date (10th of January 2020) and apply the age-group criteria. The bacteraemia case (ID 1) is an "infant", so any patients that are "child" or "neonate" (ID numbers 4, 6, 7, 8, 13, 15) can be crossed out. Note that patients where the precise date of birth is not known can also be ruled in or out on this basis.
2. The interval from admission to current date can be worked out by subtraction from the date of admission to the current date and written into the column. For the bacteraemia case, the relevant date interval is between the date of admission (1st Jan) and the date of blood culture collection (6th of Jan) = 5 days. The interval to the current date is not relevant for the bacteraemia patient. Patients whose time from admission to current date is less than 5 days have not been in hospital as long as the time-to-bacteraemia in the bacteraemia case, so are not suitable matches. This should lead to patients ID 5 (interval = 3 days), ID 8 (interval = 1 day) and ID 12 (interval = 2 days) being crossed out as these are all less than 5 days.
3. Which other exclusion criteria are relevant? Patient ID 9 was admitted to hospital in November 2019, which is much more than 2 weeks ago, so should be excluded (so long as alternative matches are available). Patient ID 14 has a positive blood culture with Staph. aureus bacteria – this is a genuine pathogen (not to be confused with coagulase-negative Staphylococci eg. Staph epidermidis, which is normally a contaminant), so this patient has a proven pathogenic bacteraemia – so should not be a potential match. Patient ID 3 has also had a blood culture taken, but this had a negative result – so the patient is still eligible to be a match.
4. You should have now indicated 1, 2, 3, 4 on the four remaining possible matches (ID numbers 2, 3, 10, 11). You should have assigned these numbers before you did randomization. Using your random number generator (you need to set the range to 1 to 4), you should have picked three of these and indicated which one was picked first, which 2nd and which 3rd. These patients would now be approached in this order to seek consent to participate in the study. **You do not need to record the details of the process of random selection of the matching patients.**

7. Introduction to main CRF

In the MBIRA study, there is a single Case Record From (CRF) that captures all of the information at individual patient-level. This CRF has been designed to try to be straightforward to collect, and mainly include information that is already available in medical and nursing records in most participating hospitals.

The same form is used for both patients with bacteraemia and uninfected matched patients. The same form is used for all age groups, from neonates up to adults – this will present some challenges, as some information (eg. birthweight, prematurity) will only be relevant for younger patients, while other parts of the form (eg. Charlson Comorbidity Index) are primarily designed for adults. We are attempting to collect the same types of information for all patients in the study, so unless otherwise indicated, try to complete all sections of the form for all patients.

This form (if printed out) is 6 sides of paper long and contains different sections of information to collect, though some information is only needed for patients with bacteraemia. The sections are

1. Identifiers + telephone contact details of the patient,
2. laboratory information about the bacteraemia (bacteraemia patients only)
3. clinical information
4. antibiotic use information (bacteraemia patients only)
5. outcome of hospital admission and 30-day outcome

Notes for specific sections – it will be helpful to have a printed out copy of the CRF when reading this.

a) Identifiers:

The names of patients are not intended to be entered to the final study database (for anonymization of the data), but it is reasonable to record the name on a paper-based version of the CRF for practical purposes during data collection.

The “date of visit” is the first date that the patient (or their relatives) are first approached to seek consent for participation in the study. It is not the same as date of enrolment – see clinical information section.

Phone numbers – try to record as many different relevant contact phone numbers as possible for the patient and / or immediate relatives. Space is allowed for up to 4 contact phone numbers.

b) Laboratory Information

The bacterial species and the antibiotic sensitivities are the key information to record here. Please record results for all antibiotics tested in routine local work. These are currently written as “drug 1” to “drug 12”– these should be replaced with the names of the drugs actually used and extra rows added or deleted as needed – see microbiology training section. It is not necessary for any extra testing to be done for the purposes of the study. For the antibiotic sensitivities, record either the zone size (in mm) or MIC (in (µg/mL), as per the local testing method used.

It is very important to record a date and location of where this bacterial isolate is stored in a freezer so that it can be located at the end of the study. We expect that laboratories will have their own existing record keeping system for recording sample locations in freezers – as far as possible use the existing systems for freezer locations and write “freetext” information to describe the location in this space eg “freezer A, box B, tray C, position D7”.

c) Clinical information

The “Date of Enrolment” in the study is a difficult date to understand – it relates to the matching process used in the study. It is not the same as the “date of visit”, which is when the individual was first approached by a study staff member.

For a bacteraemia patient, the "Date of Enrolment" will always be the same as the date that the blood culture (which later became positive for the Enterobacteria) was taken. If the blood culture was taken on the day of admission, then "Date of enrolment" will be the same as "Date of admission". If the blood culture was taken some time after admission, then "Date of enrolment" will be that later date. When first collecting data about the patient in the study, "Date of enrolment" for a bacteraemia case will always be at least a few days in the past, because blood cultures typically take 2-3 days to get a positive identification.

For a matched patient, the "Date of enrolment" is more challenging. For these patients, it is the "date of admission" PLUS the number of days from "date of admission" to "date of blood culture" (the interval) in the bacteraemia case that they are matched to. If the bacteraemia patient had their blood culture taken on day of admission, then the "date of enrolment" will be the "date of admission" for both the bacteraemia patient and the matching patients.

In this study, the "Date of Enrolment" will usually be prior to the actual date on which the patient gave consent to participate in the study – this is expected.

Activity: Look back to section 5 to the practical example. For patients ID 1, 2, 3, 10 and 11, what would have been the "Date of Enrolment" for these patients, if they had been included in the study? What was the date they were actually approached to participate in the study?

When you have worked out these dates, see answers on next page.

Weight and Height (or length). Ideally, collect these information from clinical notes, but if it has not been recorded so far, the research study nurse should use locally available equipment to measure these, or failing that, make an appropriate estimation. If all of these are not possible, record as "unknown".

Prior healthcare exposure questions. This information will probably not be clearly recorded in medical notes, so it may be necessary to clarify with the patient / their relatives with further questions.

The Charles Comorbidity Index (CCI). This is recorded for all patients. The Charlson Comorbidity index predicts the one-year mortality for a patient who may have a range of comorbid conditions, such as heart disease, AIDS, or cancer (a total of 22 conditions). Each condition is assigned a score of 1, 2, 3, or 6, depending on the risk of dying associated with each one. Scores for individual conditions are added up to provide a total score to predict mortality. Many variations of the Charlson comorbidity index have been presented and there are various alternative scoring systems.

Clinical conditions and associated scores for the CCI are as follows:

- 1 each: Myocardial infarct, congestive heart failure, peripheral vascular disease, dementia, cerebrovascular disease, chronic lung disease, connective tissue disease, ulcer, chronic liver disease, diabetes.
- 2 each: Hemiplegia, moderate or severe kidney disease, diabetes with end organ damage, tumor, leukaemia, lymphoma.
- 3 each: Moderate or severe liver disease.
- 6 each: Malignant tumor, metastasis, AIDS, tuberculosis

We have also included some supplementary questions on other diseases that we think will likely be relevant amongst the patients in the MBIRA study – these are not part of the normal Charlson score.

>>

Answers to "Date of enrolment" question from previous page

Patient ID 1 = bacteraemia case – hence Date of Enrolment = date of blood culture = 6/1/20

The "interval" is 06/01/2020 (date of blood culture) – 01/01/2020 (date of admission) = 5 days

Therefore, Date of enrolment for other patients is

ID 2 = 27/12/2019 + 5 days = 01/01/2020

ID 3 = 28/12/2019 + 5 days = 02/01/2020

ID 10 = 04/01/2020 + 5 days = 09/01/2020

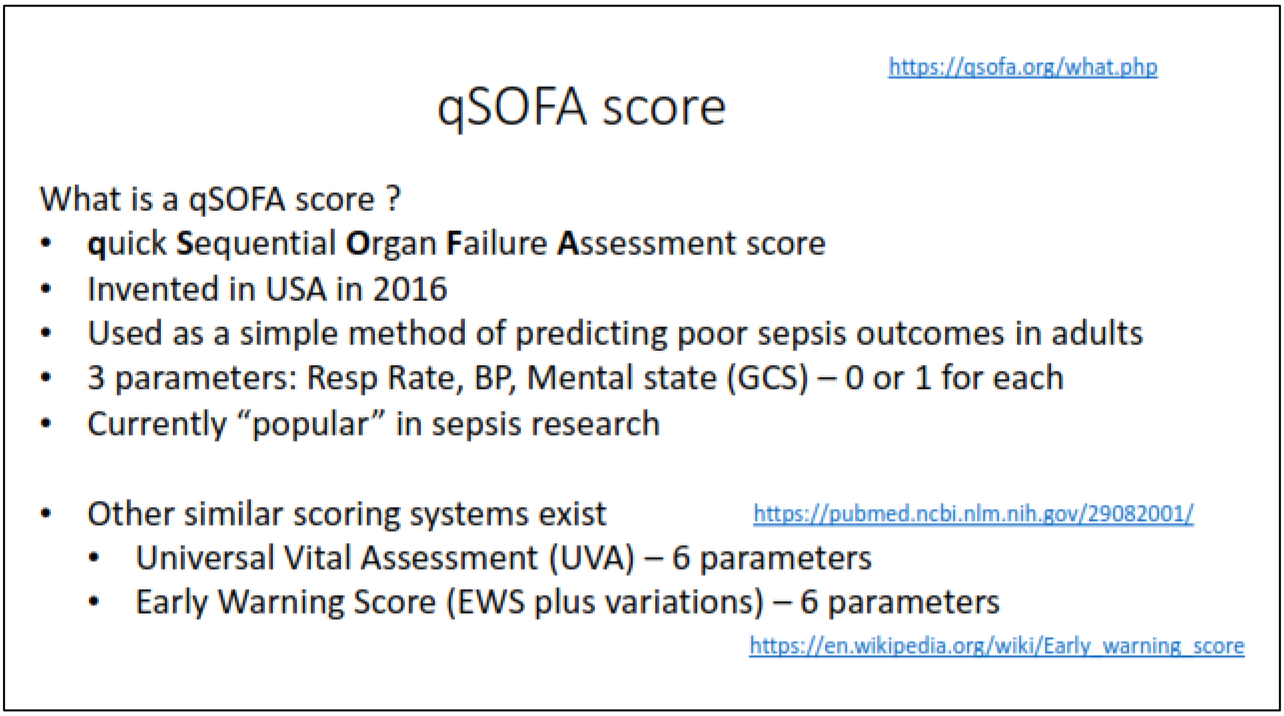
ID 11 = 25/12/2019 + 5 days = 29/12/2020

All these patients would have been approached to be involved in the study on or after the 10/01/2020, so in all cases, the “date of enrolment” was before this date.

>>

RVD = Retroviral Disease = HIV. We have used this terminology to help protect confidentiality.

The qSOFA score. This is recorded for bacteraemia patients only. The Quick SOFA Score (quickSOFA or qSOFA) was introduced by the Sepsis-3 group in 2016 as a simplified version of the SOFA Score as an initial way to identify patients at high risk for poor outcome with an infection. The qSOFA simplifies the SOFA score drastically by only including its 3 clinical criteria. The score ranges from 0 to 3 points. The presence of 2 or more qSOFA points near the onset of infection is thought to predict a greater risk of death – but we are not aware if it has ever been used with bacteraemia patients in African hospitals previously. We have used adapted criteria for younger patients, based on published guidelines – a paediatric quick SOFA (p-qSOFA).



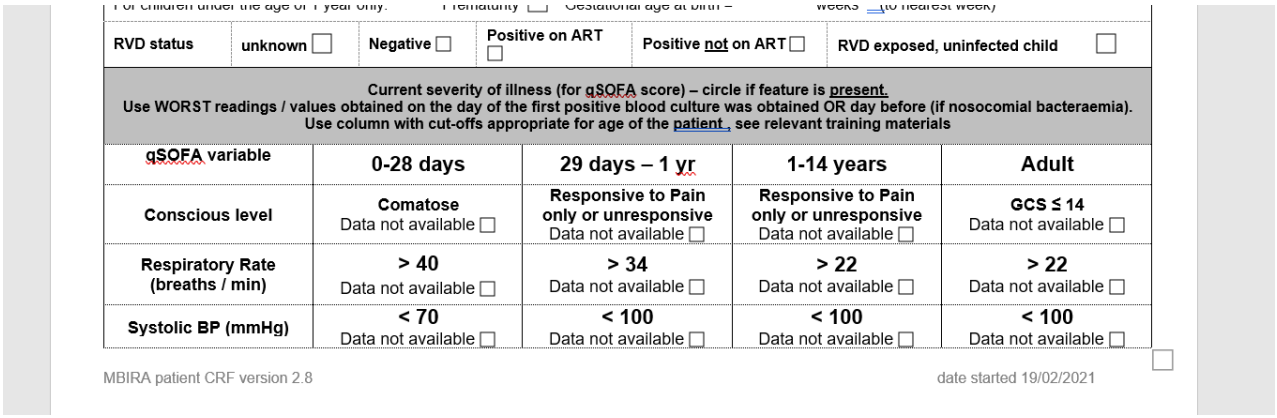
For scoring the qSOFA score, this requires some degree of clinical judgement. We are seeking the worse value of each of the three parameters that was recorded on the day the first positive blood culture was taken OR the day before. It does not matter if these values were obtained at different times on these days.

Conscious level in qSOFA. For neonates (0-28 days), we consider conscious level to be either “Normally responsive” = 0 points or “comatose” = lethargic/no spontaneous movement = 1 point.

For both infants (29d – 1yr) and children (1-14yrs), we are using an AVPU scale (Alert, responsive to Voice, responsive to Pain, Unresponsive) for recording consciousness.

Alert / responsive to voice = 0 points, responsive to pain/unresponsive = 1 point

** We acknowledge that it will, in some circumstances, be difficult to gather relevant information on clinical parameters for the qSOFA score as suitable information from a few days earlier was not collected/recorded. Documentation of patient observations can be erratic in some hospitals and paper-based records can get lost. We have therefore added the option of recording "Data not available" for all the qSOFA parameters. This box should be "ticked" in the CRF and the Redcap database if the best judgement of the person extracting these data is that suitable information cannot be found to determine if the relevant factor was or was not present. There is a corresponding option in the REDCAP database to record this information.



For children under the age of 1 year only: Prematurity ☐ Gestational age at birth – weeks (to nearest week)

RVD status	unknown ☐	Negative ☐	Positive on ART ☐	Positive not on ART ☐	RVD exposed, uninfected child ☐

Current severity of illness (for qSOFA score) – circle if feature is present.
Use WORST readings / values obtained on the day of the first positive blood culture was obtained OR day before (if nosocomial bacteraemia).
Use column with cut-offs appropriate for age of the patient , see relevant training materials

qSOFA variable	0-28 days	29 days – 1 yr	1-14 years	Adult
Conscious level	Comatose Data not available ☐	Responsive to Pain only or unresponsive Data not available ☐	Responsive to Pain only or unresponsive Data not available ☐	GCS ≤ 14 Data not available ☐
Respiratory Rate (breaths / min)	> 40 Data not available ☐	> 34 Data not available ☐	> 22 Data not available ☐	> 22 Data not available ☐
Systolic BP (mmHg)	< 70 Data not available ☐	< 100 Data not available ☐	< 100 Data not available ☐	< 100 Data not available ☐

MBIRA patient CRF version 2.8 date started 19/02/2021

Source of bacteraemia. This information is a clinical judgement and may be recorded in the medical notes, or may require some discussion with treating clinicians or the local Lead Investigator. In some patients, it may not be clear what the most likely source of bacteraemia is – in these patients, it is reasonable to record an "Unknown" source.

In neonates, it is particularly hard to identify sources of bloodstream infection, so for the majority of bacteraemic patients in this age-group, the source of infection will be "unknown". If in a neonate, the infection occurs with the first 72 hours of life and there is a clinically compatible maternal illness (eg choriamnionitis), then the infection can be recorded as a "maternal infection". Neonates with bacteraemia that is associated with a recognized infection at another body site (eg meningitis, thrombophlebitis, NEC) can be recorded with a source corresponding to the appropriate infection site from other options given.

Indwelling devices at time of enrolment. This requires a retrospective evaluation of what medical devices were (probably) being used for the patient on the "Date of Enrolment" – a best estimation is reasonable.

d) Antibiotic use information

This section collects the day-by-day use of antibiotics for the bacteraemia patients from the day before they had the blood culture taken until the end of antibiotic treatment or 30 days. This will require frequent visits (we suggest alternate days or Mon/Weds/Fri) back to the hospital ward where the patient is being treated to collect this information from the patient's medical records and / or drug chart.

This section is not to be completed for non-infected patients and no drugs apart from antibiotics need to be recorded on this section. Instructions for how to record this information are given on the CRF itself.

When entering this data in the database, there is an additional piece of information about "appropriateness" of antibiotics, based on the antibiotic resistance of the bacteria from the blood culture. This section should only be completed by the lead investigator for each site. An introduction to this aspect are given in sections 12 and 13 below, and a more comprehensive set of materials are given in the "MBIRA study: Guide to

scoring appropriate-ness of antibiotic use v1.1" (written in December 2020) – this document is now attached as "Appendix 2" to this version of the Training Manual.

e) Outcome of hospital admission and 30-day outcome

This information collects that main outcomes of the study – length of time in hospital and risk of death, either in hospital, or at 30 days from enrolment. It is therefore vitally important that this information is always fully collected and recorded.

Discharge from hospital. This is the date on which the person completed their medical care in hospital and was considered "permitted to leave", and will normally leave hospital on the same day. In some circumstances, a patient may physically remain in hospital after this date, for social reasons (eg neonate whose mother is still inpatient or a patient waiting to settle hospital bill). In these circumstance, best judgement should be used to determine when the patient was considered "medically discharged".

Occasionally, patients may be transferred to other hospitals or abscond (or self-discharge) before medical treatment is completed. If this occurs, record the date and manner they left the study hospital.

Death of patients. This should be recorded as the date of a medically confirmed death in hospital. See section 24 for further notes about handling patient deaths in the study.

Always record whichever was the first hospital outcome to occur – for example, if the patient was first discharged and then later readmitted and/or then died or absconded, the first outcome was "discharged".

30-day outcome. This is to record the mortality status (alive or dead) of the patient only at 30 days after the "Date of enrolment" (see above) into the study. For most patients, they will have left hospital by this time, and hence we will use telephone contact to gather this information. Occasionally, some patients with long hospital admissions will still remain as inpatients, so a direct inspection in hospital will be sufficient.

For contacting patients / family members by telephone, this should be done in a professional manner, considering the following

- Timing and tone of phone call. Any date from 30 days after enrolment is suitable to call.
- Sensitivity of information – we are essentially finding out if a patient has died

Multiple phone numbers for the patient and relatives should have been collected – all of these can be used.

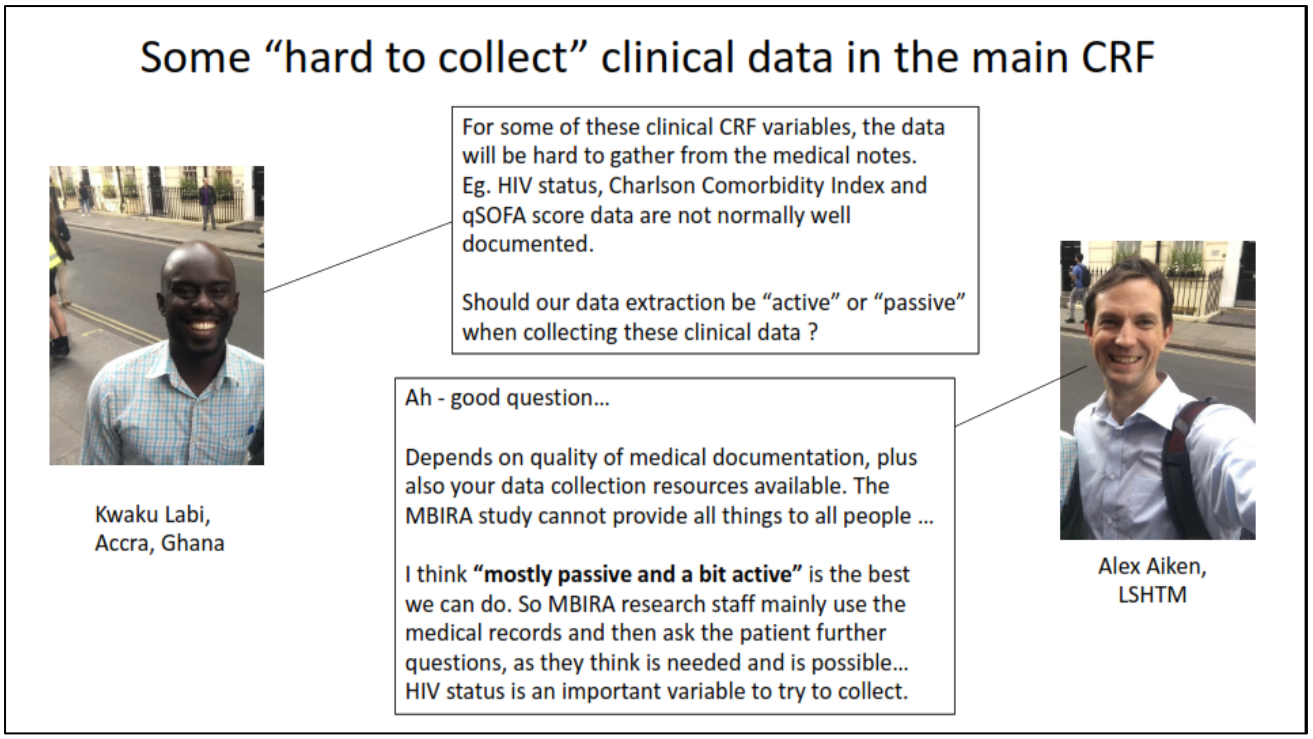
There is no need to collect any information beyond the vital status of the patient, but obviously patients / their relatives should be given appropriate information in response to questions about the study.

Try on up to 3 different days to contact an appropriate person to get this information. If unable to make contact with anyone suitable by any of the phone numbers after this time, only then record the 30-day outcome as "unknown".

** We acknowledge that some of these data in the MBIRA study may be hard to collect. This depends on the quality of medical record keeping, what information was available to the medical staff, what information is routinely documented in the medical notes and so on. Some information is likely to be more difficult to extract than others, and this is liable to vary between the MBIRA study sites – we cannot control this.

As far as possible, we advocate "passive" use of information that is already routinely recorded in the medical records, but where necessary, we encourage MBIRA investigators to "actively" seek out important pieces of information that are not recorded or seem inaccurate. This is likely to be more time consuming, but will result in better quality study information. This might take the form of discussing with a treating clinician for their opinion on the most likely source of the patient's bacteraemia, or getting a height or weight measurement for a patient where this has not been recorded, or making sure that an HIV test is offered to a

patient and/or ensuring that the result of HIV-status is recorded in the notes. This takes time, effort and clinical judgement.



8. Training exercise 2 – practice CRF data extraction from mock records

For purposes of this training exercise, we are going to extract data from "mock" medical notes onto the CRF. These are not intended to represent the exact format of medical records, just something with sufficient similarity to a medical record to allow practice data extraction. These "mock" cases are quite rough – so apologies in advance for any inconsistencies.

In the MBIRA study, you may want to set up direct electronic data entry, which is possible to do, but this requires special configuration if using an offline device. If using a portable device with a live internet connection, the Redcap database behaves in the same way as for a static computer. Use of an off-line data collection tool is covered in the next section – it is up to site leads to decide what formats of data collection to use. For the purposes of this training exercise, it is probably easier to use paper-based materials, just to build initial understanding of the forms. You will need two copies of the CRF for the two patients you will collection information on.

Activity: start with collection of data about a bacteraemia case.

We have created two "mock" bacteraemia medical records (one adult, one infant) and two "mock" matching patient records (one adult, one infant) for practicing data collection in the MBIRA study. Alternatively, you could use medical records from actual patients from your own institution, but do not collect any "patient identifiable" information in this case.

Choose either the infant bacteraemia case or adult bacteraemia case or a local record of a patient with proven bacteraemia of a relevant species. The "mock" records are in the Dropbox folder under training materials. These mock records include fictitious drug charts, observations charts and a laboratory report – obviously these will all have different formats in your local hospital.

Activity: for the bacteraemia case, collect the information for the CRF on the paper copy of the form, including all dates, laboratory results and drug treatments. Record the eventual outcome of the hospital

admission and the 30-day outcome. Do not record a study ID number yet – this is generated in the MBIRA study database and is specific to your site.

When you have finished recording as much data as you are able onto the CRF, check for any incomplete information and then tick the appropriate boxes in the "CRF checking" section.

Activity: now perform collect data collection for a non-infected matching case.

The "mock" medical records for four non-infected matching cases for purposes of practicing data collection for the CRF are in the Dropbox folder as matching cases #1 and #2 (paediatric matches) and #3 and #4 (adult matches). Choose one out of the relevant matching cases, based on the age-group that you chose for the bacteraemia case – the matching patients need to be in the same age-group as the bacteraemia case.

Activity: for one matching case, collect the information for the CRF on the paper copy of the form, including all dates and clinical details. Note that laboratory results and drug treatment information is not needed for a matching case. Record the outcome of the hospital admission and the 30-day outcome.

Again – when you have finished, check through the form for any incomplete information and then tick the appropriate boxes in the "CRF checking" section.

9. Introduction to Redcap database + data security

The MBIRA study uses a database system called Redcap to collect the data for the study. This is an online database, so to access the Redcap database, you need a computer with a working internet connection. The information in the MBIRA Redcap database is physically held on an LSHTM server, which is based in the MRC Unit in the Gambia in west Africa – this institution is now a part of LSHTM. Redcap is a database system that is well-suited to multi-site medical research studies, especially clinical trials; here we are using it for an observational study. Redcap contains many built-in features to support high-quality data collection and entry and many security features to protect accidental data sharing or loss.

In preparation for the study, we used a "Development" version of the MBIRA database for training and finalization of the layout of the forms. This allowed us to enter "mock" or "dummy" data to practice using the database and test for any problems. From the start of the study, since approximately November 2020, we have switched to using the "Production" version of the database, which collects the real information for the study, but otherwise looks very similar. The "Development" version of the database remains available.

You should have received a Redcap username and password for the MBIRA study database by this time – if not, please speak to your local site lead or contact Lee White (lee.white@lshtm.ac.uk) . In terms of data security, do not share usernames for the study and do not leave a username+password written in a place where someone else might find it. If you lose your password, Redcap has a password recovery system.

Log onto the "Development" MBIRA database (on the MRC Gambia server) at the following location :

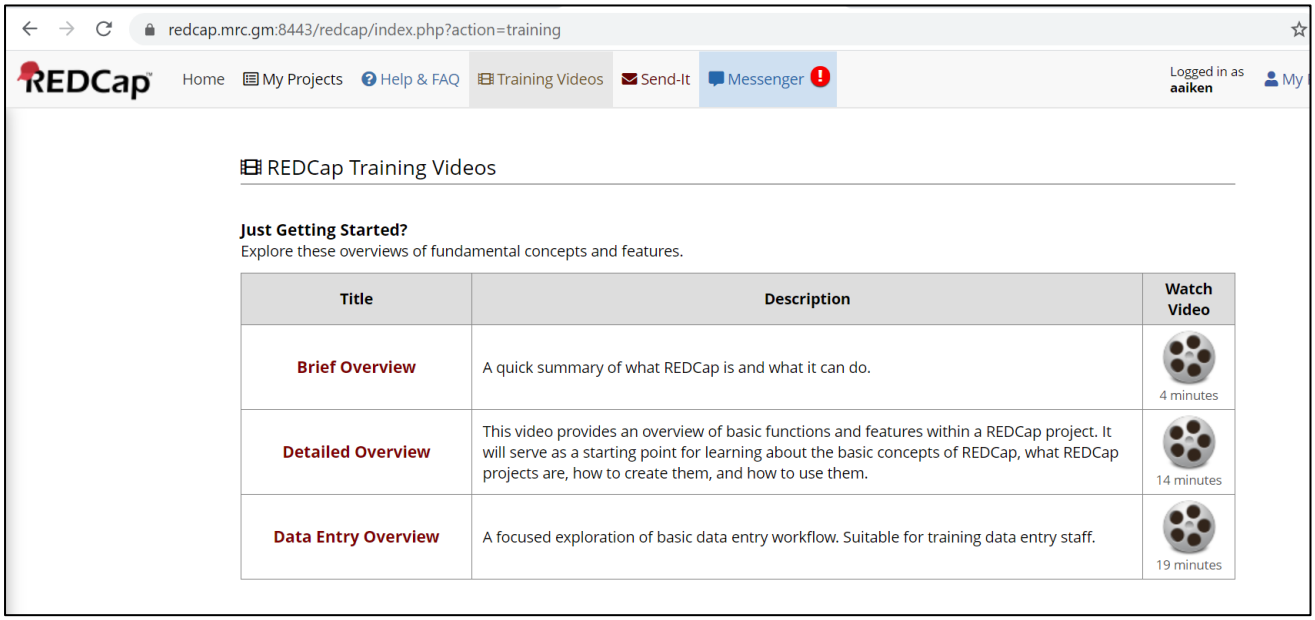
https://redcap.mrc.gm:8443/redcaptest/index.php

The "production" (or "live") version of the database is now (since November 2020) held at location :

https://redcap.mrc.gm:8443/redcap/index.php

Redcap terminology describes each section of data entry in a study as a "project" – so one whole form in the study (eg the whole CRF form) corresponds to one "project" in the Redcap database.

Activity: even if you are previously familiar with using Redcap, please watch all three introductory training videos as below, available on the "Training Resources" page.

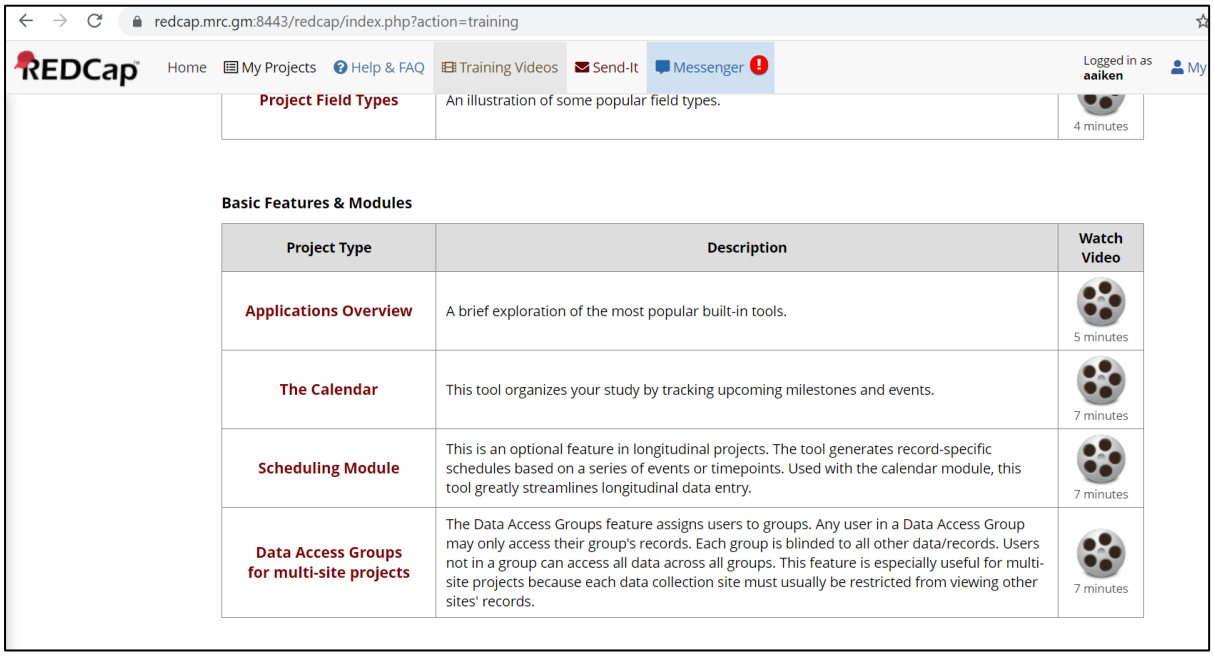


There is also an extensive "Help & FAQ" section about how Redcap works – see top bar.

For data security in Redcap in multi-site studies, users are assigned to Data Access Groups (DAG) which limit their access to data just from the site in which they are based. Project administrators can access data from all DAGs.

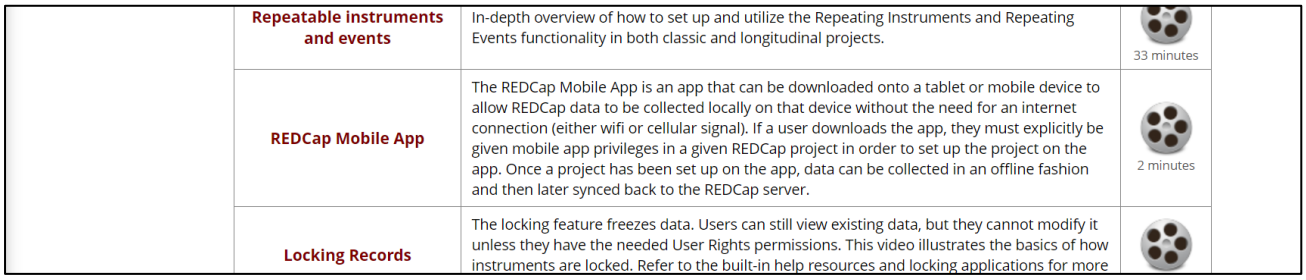
Activity: watch the training video about "Data Access Groups for multi-site projects".

If you want, you can also watch other training videos about other features of Redcap.

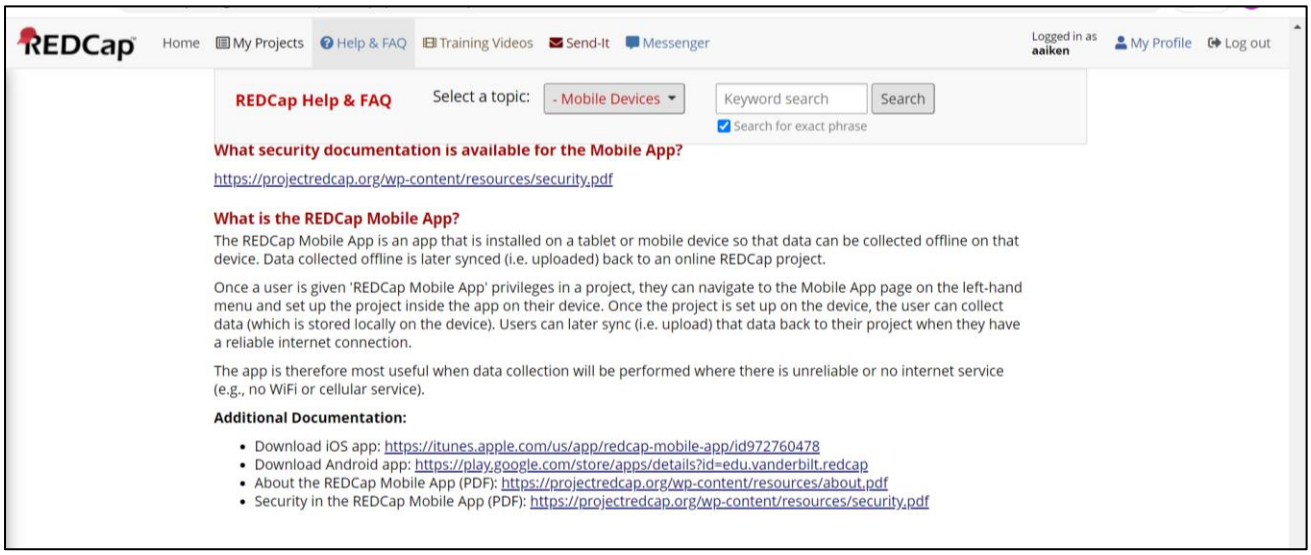


One of the features of Redcap is that it allows both paper-based data collection (with subsequent entry to the database at a computer with internet connection) or direct electronic data entry, either to a mobile device with (online) or without (offline) an internet connection. However, if using a mobile device without an active internet connection, this requires some additional set-up of the "project" on the mobile device.

Activity: If you intend to use <u>offline</u> electronic data collection on any mobile device (ie using a device without a current internet connection), please watch the initial video on the Redcap Mobile App …



… and then read the further materials on "What is the Redcap mobile app?" in the Help and FAQ section.

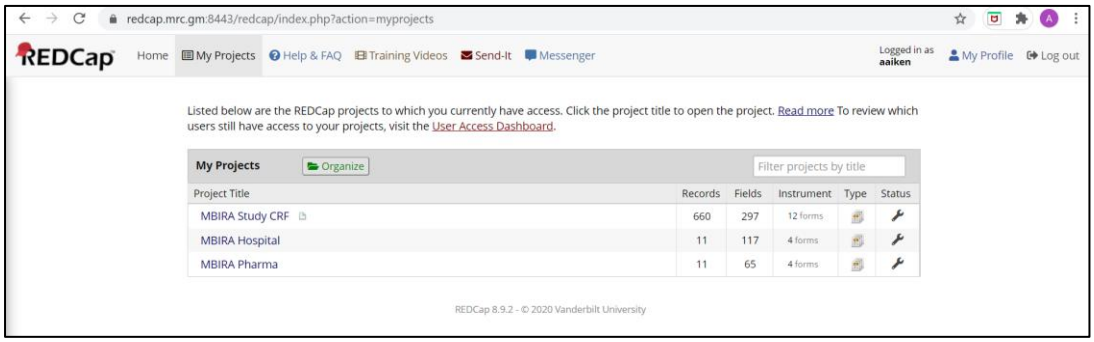


Important note: running a project using offline data-collection devices may be more difficult to set up than using paper-based data collection and also requires appropriate mobile devices, probably tablets. The decision about what format of data collection to use should be made by the site lead before the start of the main project, in discussion with the LSHTM central team.

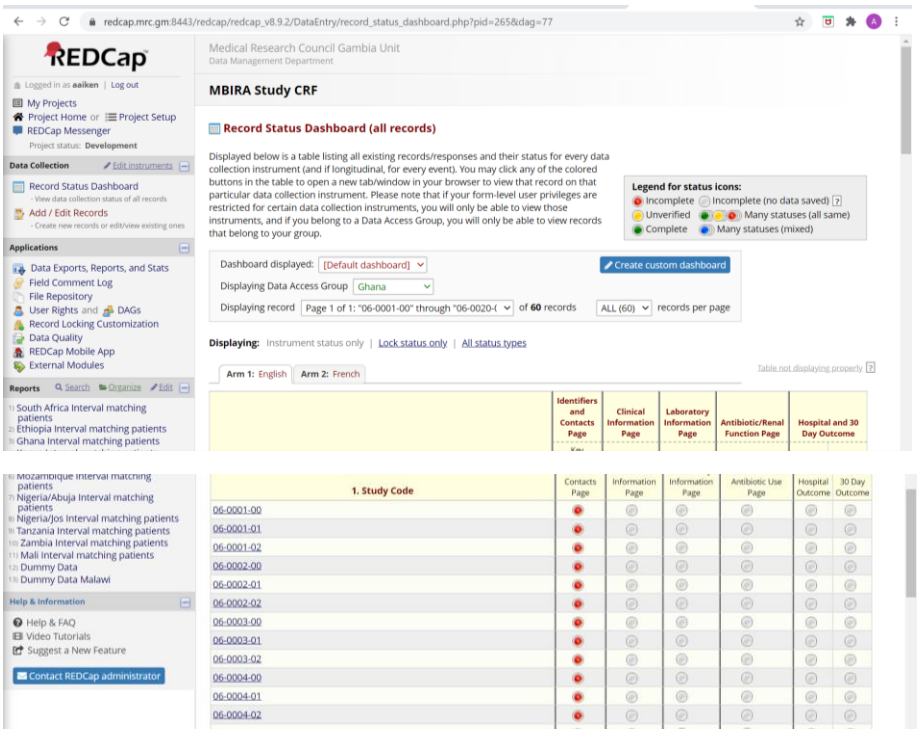
10. Training exercise 3 – practical CRF data entry into Redcap

This training exercise requires you to have a completed CRF for at least one patient, either a "mock" patient from Section 8 (above) or a real patient record from your own hospital that you wish to enter. When you are learning to use this database, it is good to enter data for both a "bacteraemia" patient and also a "matching" patient, as some of the sections of the database work differently for these types of patient. We suggest doing data entry using the "Development" database, currently running on the MRC Gambia server – so you cannot cause problems with damaging / losing data.

To start, you should already be able to access a home screen in Redcap that looks similar to this



Click on the project titled "MBIRA study CRF". Then from the next screen, click on the "Record Status Dashboard" under "Data Collection" in the bar at the left side of the page. You will then see this:



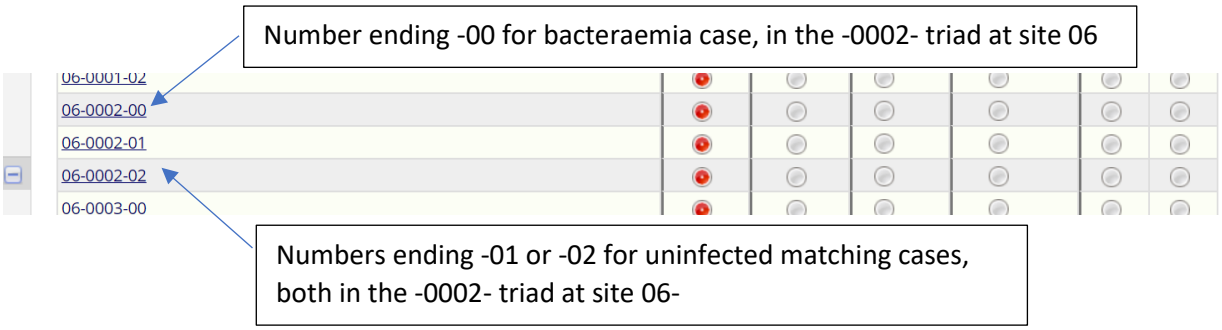
In the CRF database, we have already created the records for 20 bacteraemia cases and 40 controls at each site, following the study numbering system (see Section 3) above. These records are (mostly) currently "empty" – a few have been entered with "mock" data as we test the system out. When we create the "Production" database, similarly, the study numbers will be created in advance as empty records. It is possible to create extra records, if needed, via the "Add/Edit Records" option.

For the purposes of data entry, CRF for each record is divided into six sections, represented by the row of six dots for each number. When a dot in the Redcap record dashboard is red or grey, this means the record is

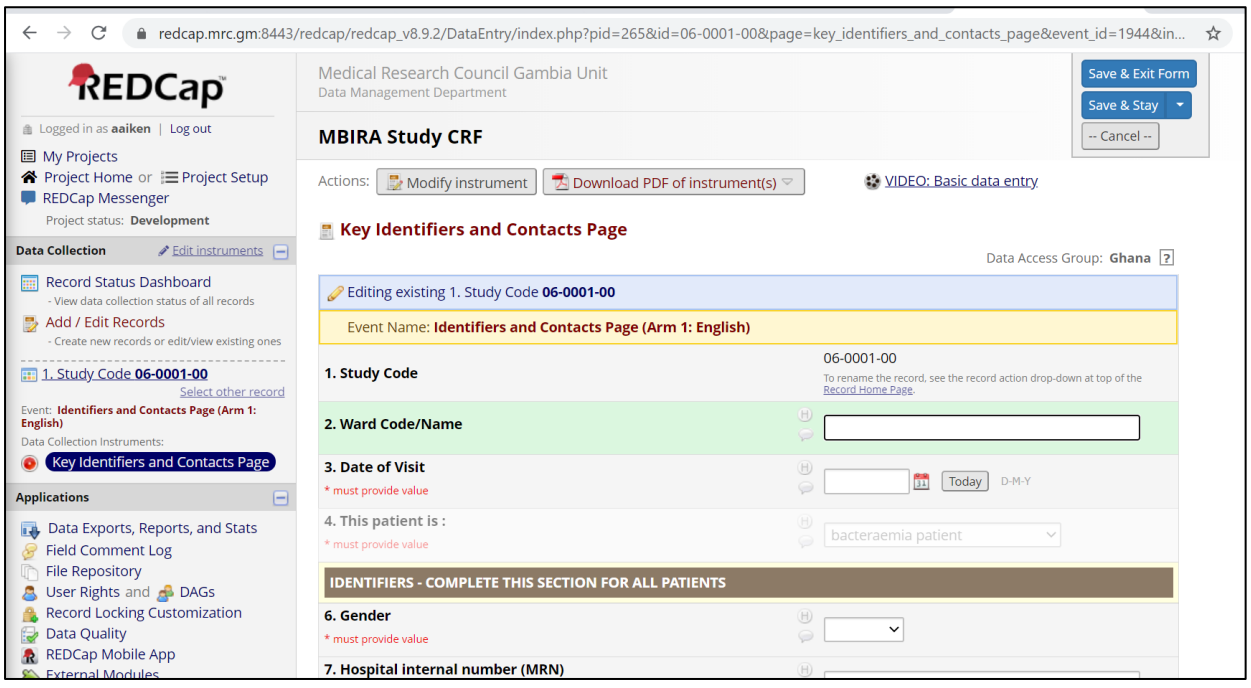
incomplete, yellow means some data has been entered but the page has been marked as “unverified” and green means it has been marked as being “completed”.

For the paper-based CRF that you have, you are now going to enter these data. You need to pick a study number that is relevant for the type of patient that you have (-00 at the end for bacteraemia patient; -01 or -02 for a non-infected patient). There should only be records visible to you that correspond to your study site number (see section 3) because you are limited within a Data Access Group – if you are able to see records from any other sites, please contact the study administrators.

Activity: using the Record Status Dashboard, find an MBIRA study number for your site that corresponds to the type of form you wish to enter (either bacteraemia case or non-infected patient) which has not yet had any information filled in – empty records have a red dot in the first column followed by grey dots. Always enter a bacteraemia case first and then the information for the relevant matching patients.



Click on the red dot in the first row for the number you have selected. This will bring you to the first page for entering data, which should look like this.



Activity: enter the information from the paper CRF that you have collected on this first page.

Note that there is no space in the database for entering the patient’s name – this is deliberate.

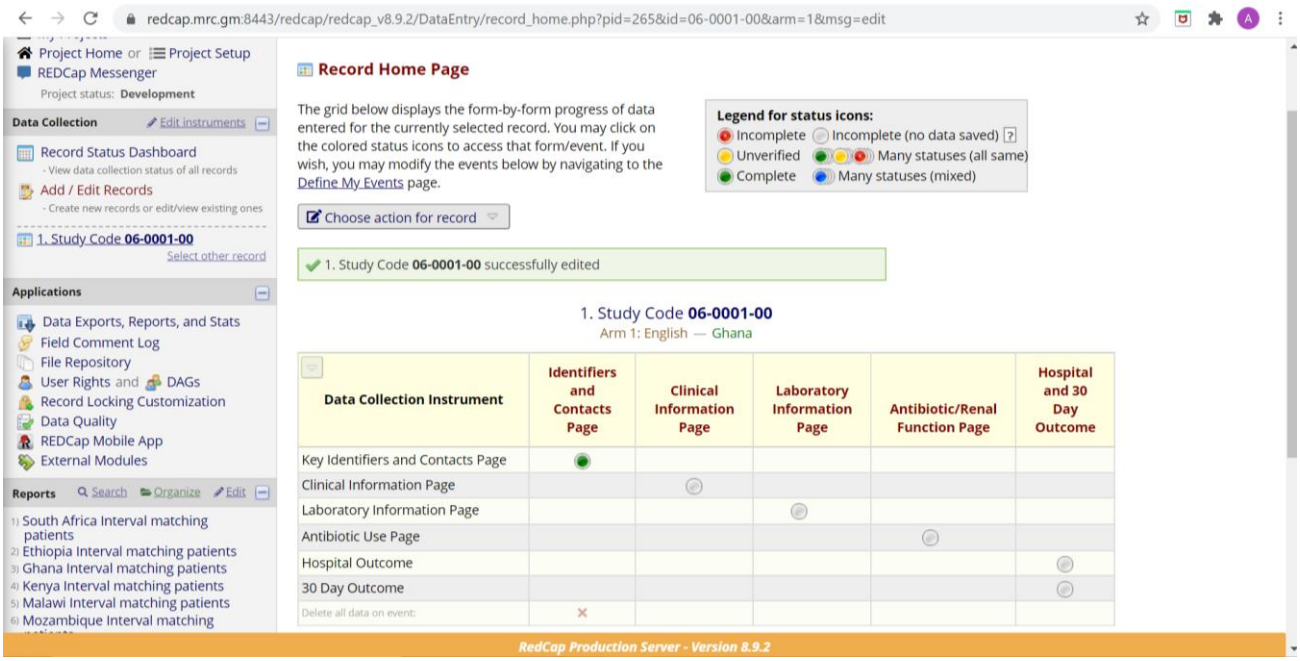
The status of the patient (Q4. on this page) is already filled in – this is based on the type of study number (ending in -00 or -01 / -02 etc) that you have selected – Redcap automatically determines the type of patient,

based on this number. You will not be able to enter all the relevant data for a bacteraemia patient if you try to enter this under a "non-infected match" number.

Where there is a " * must provide value ", this means the field is "required", so Redcap will give you an alert if you try to save the record without filling in a value here. You can choose to ignore this, but these required fields are vital pieces of information for the study.

In some boxes, when you click on a particular response, this will "expand" further areas for data entry.

When you have completed all the information on this table, change the "Form Status" to "Complete" and then click "Save & Exit Form". You will now return to the Record Home Page, which should now look like this:



Note that the dot for the "Identifier and Contacts Page" has now changed from red to green to indicate that it is completed.

Activity: now click on the green dot and go back and change one detail in the form and save it. Go out of the record and back in to check that your change has been saved. Try saving a record where you have not filled in a "required" value – what message do you get?

Now click on the empty grey dot for the "clinical information page". This will bring you into the data entry screen for this part of the CRF

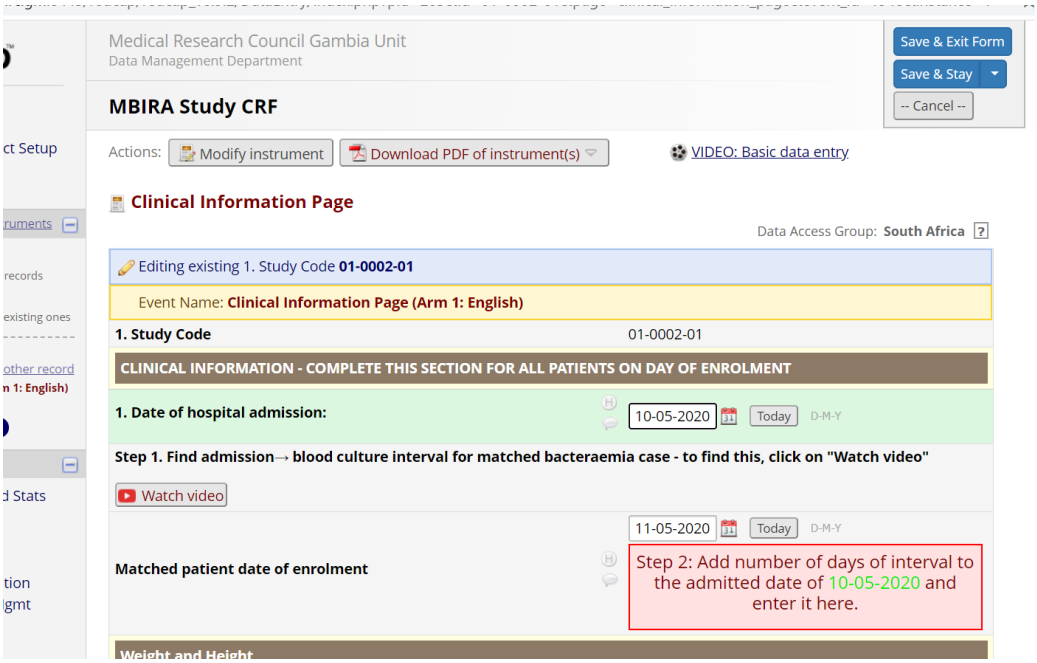
Activity: now fill in all the data that you have collected for the Clinical Information part of the CRF. Note that some of the boxes will change or be invisible, based on the type of the patient (age group, bacteraemia v uninfected).

This Clinical Information section includes the "Date of Enrolment" in the MBIRA study. As described in section 7c) above, this date is **a calculated date relating to the matching process** – it is not the same as the "Date of visit" or Date of admission". For a bacteraemic patient, "Date of Enrolment" is simply the "Date of blood culture collection". For a matching patient, the "Date of enrolment" is a more complex date to calculate, as you have practiced in the section 7c) above.

To try to help you with the calculation of the "Date of Enrolment" in the database, we have created a small reporting function within the Redcap database to try to help correct calculation of the "Date of Enrolment" – this function works for matching patients only.

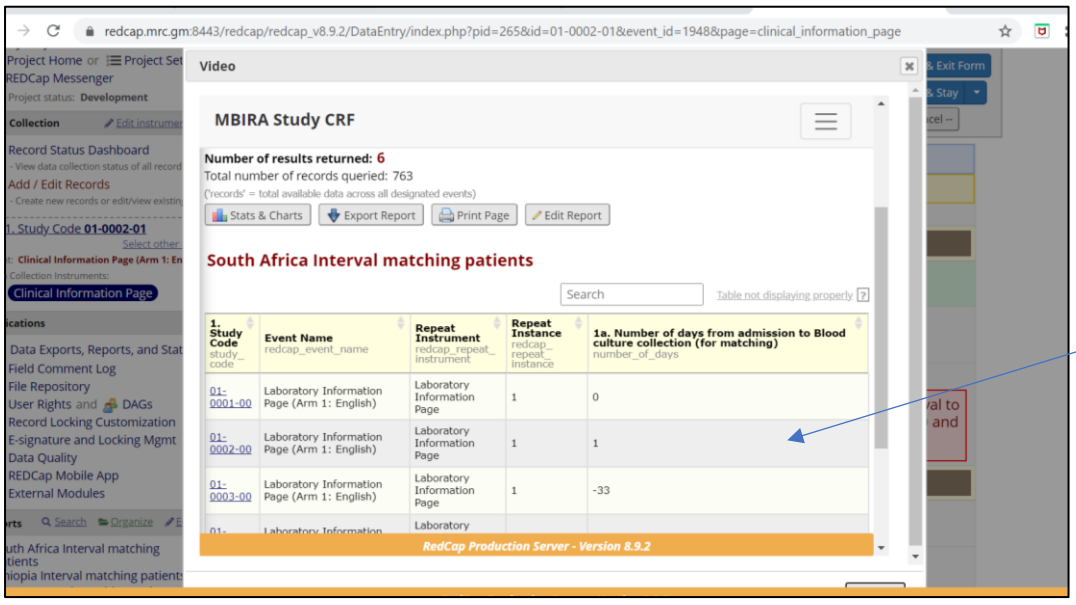
This shows how to use this reporting function for a matching patient. This only works if relevant dates have already been entered for the bacteraemia case within the same "triad".

This shows the clinical information screen for individual with study code 01-0002-01. As the number ends with an "-01", we know this should be a "matching patient" who is within the triad "-0002-".



Step 1. To find the relevant "interval" for the bacteraemia patient in this triad, click on the button that says "Watch video" underneath where "Step 1. Find admission → blood culture interval …" is written.

When you click this button, a new pop-up box should then appear in a few seconds, like this



This is the relevant bacteraemia case – it has same triad number "-0002-" as the matching patient

In this new box, you need to find the relevant bacteraemia case for this matching patient – this will be the bacteraemia case with the same "triad" number – here "-0002-". In the final column of this table, the calculated "Number of days" is shown – this is the "Interval".

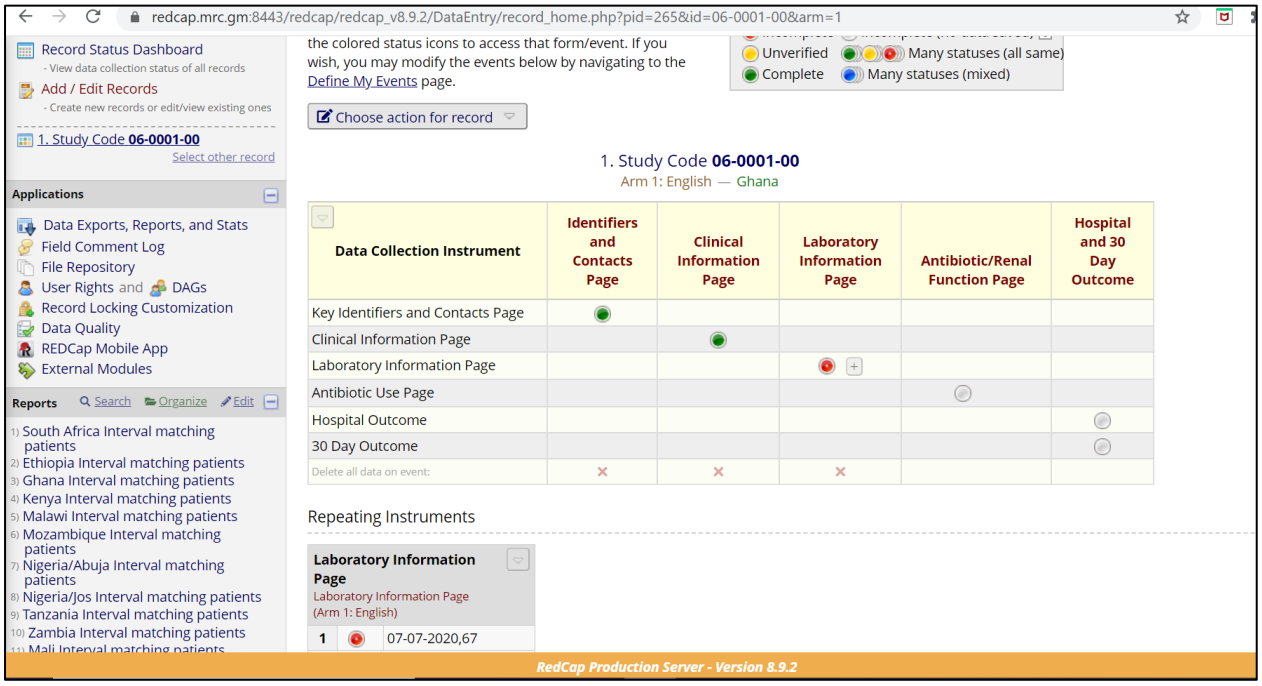
Step 2. Once you have established the right "interval" for this triad, either by using the pop-up box as above, or by another method, you then have to add this number of days (working it our yourself, or with a

calendar) to the admission date of the matching patient. For example, if you calculated the "interval" as being 10 days and the matching patient was admitted on the 12th July 2020, then you should then record the "Matched patient date of enrolment" as 22nd July 2020. If the "interval" was 0 days, then the "Matched patient date of enrolment" will be the same as the date of admission. Redcap cannot calculate this for you !

Activity: if you are entering data for a matching patient, try out the steps above. Is this helpful ?

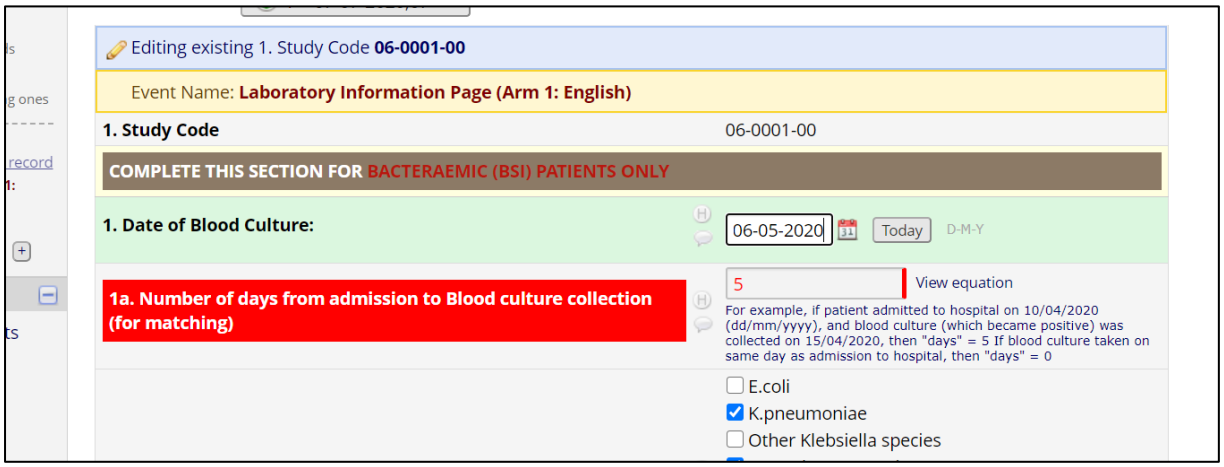
When you have entered all the Clinical Information part of the CRF, save and exit when you are finished. Clinical information "dot" should now have changed from red to green. If this has not happened, you need to go back and try to complete whatever information is missing.

If you are entering a record for a bacteraemic patient, you will now need to enter details for the laboratory identification of the bacteria causing the infection. If you are entering a record for a non-infected patient, you need to open this section of the form, change the status of the form to "complete" and then immediately save and close it.



Activity: now enter the laboratory information for the CRF that you have collected.

Note that after you have entered the date of a blood culture for a bacteraemia patient, Redcap automatically calculates the interval (in number of days) from "Date of admission" to "Date of blood culture" in the red box as shown below – this is a key number (the "interval" as above) needed for when you are matching to uninfected patients. You do not need to do anything with this information – it is just to help you.



When you have finished entering all the laboratory information available, click “Save & Exit form”.

If you click “Save & create new instance”, this will create an empty copy of the laboratory form – this is not needed, unless there are two or more Enterobacteria isolates in the same blood culture for the patient.

If you are entering information for a bacteraemia patient, you will now need to record the information about the use of antibiotics for this patient. This uses the section called “Antibiotic use”. For this section, you will need to create one “instance” (=copy) of the form for each drug on each day. This corresponds to the rows of the paper-based form – so if three drugs are given for five days, this will require 3 “instances” of the form for each day = 3 x 5 = 15 “instances” of the form. Each “instance” of the form is quite quick to fill in !

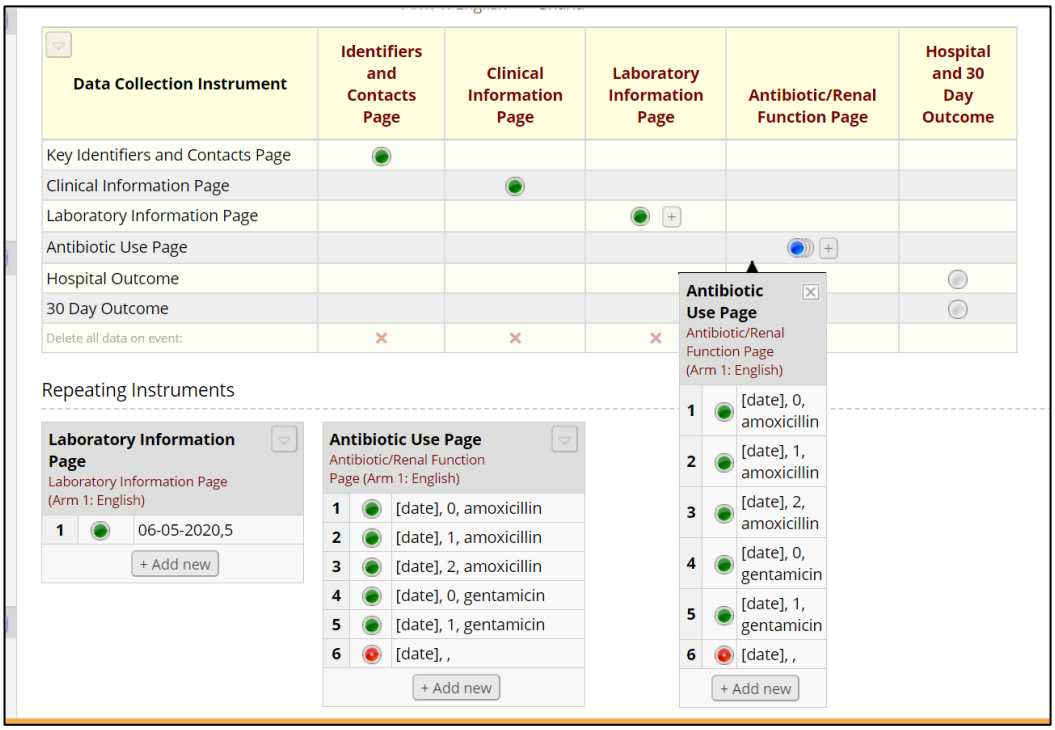
If you are completing information for an uninfected patient, you do not need to fill in data here – just open the form, the change the status to “complete” and close.

Activity: for a bacteraemia patient with data recorded about the use of antibiotics on the CRF, fill in the antibiotic use section of the form, creating new “instances” of the form for each drug on each day, by pressing “Save & Add New Instance” when you have completed each drug on each day.

Note – Redcap helps you by calculating which “day” of treatment of bacteraemia each date corresponds to. The day that the blood culture was taken = day 0, the day after the blood culture = day 1 etc.

Note – there is a question on this form about “appropriate-ness” of antibiotics, which does not feature on the CRF – just answer “no” to this question at this point regardless of your role in the project – completing this information is covered in the next sections.

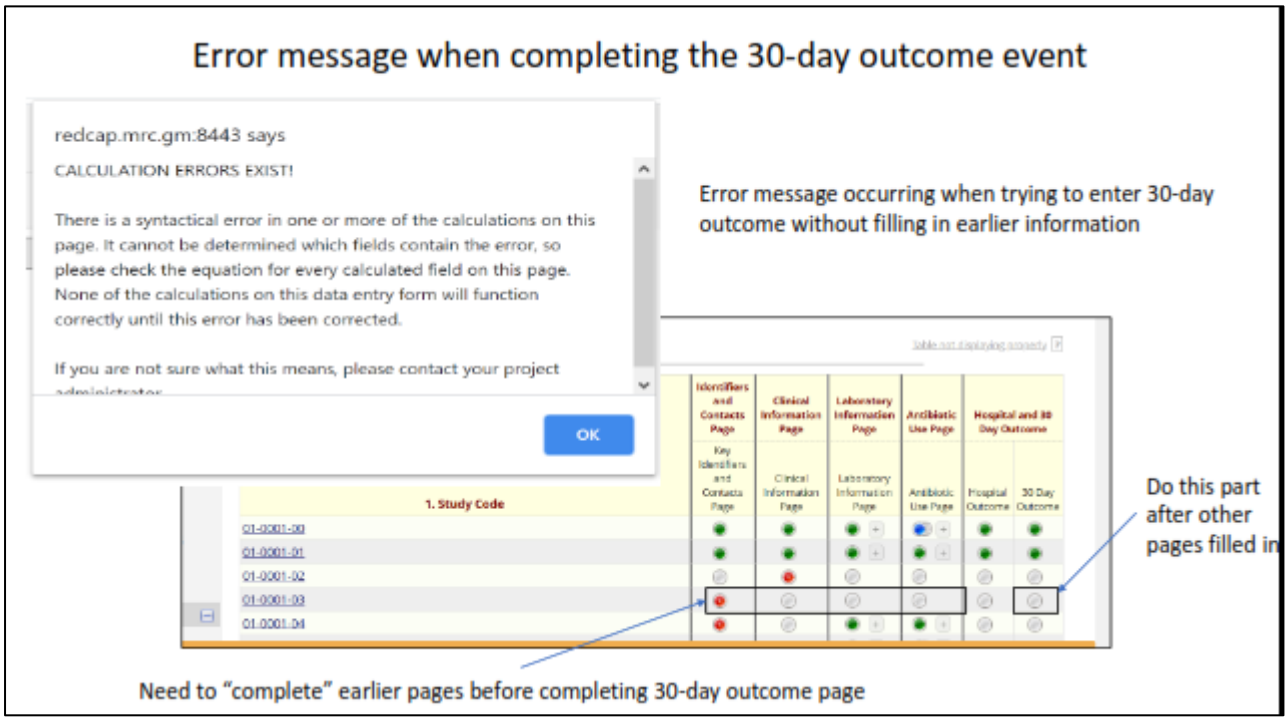
When you have entered all the information about all the drug on all the day, return to the Record Status dashboard. The Column with the Antibiotic use will now show multiple “dots”. If the status of all the dots is “green”, then the dot at the front will be “green”. If there are a mixture of “green” and “red” dots (because one is not completed), then the dot at the front will be “blue” – see below.



.

Activity: check that all your records for antibiotic use are correctly entered and are saved with "green" status – see one of the records above still has a "red" (incomplete) status. If necessary, go back and edit any records that need further information added.

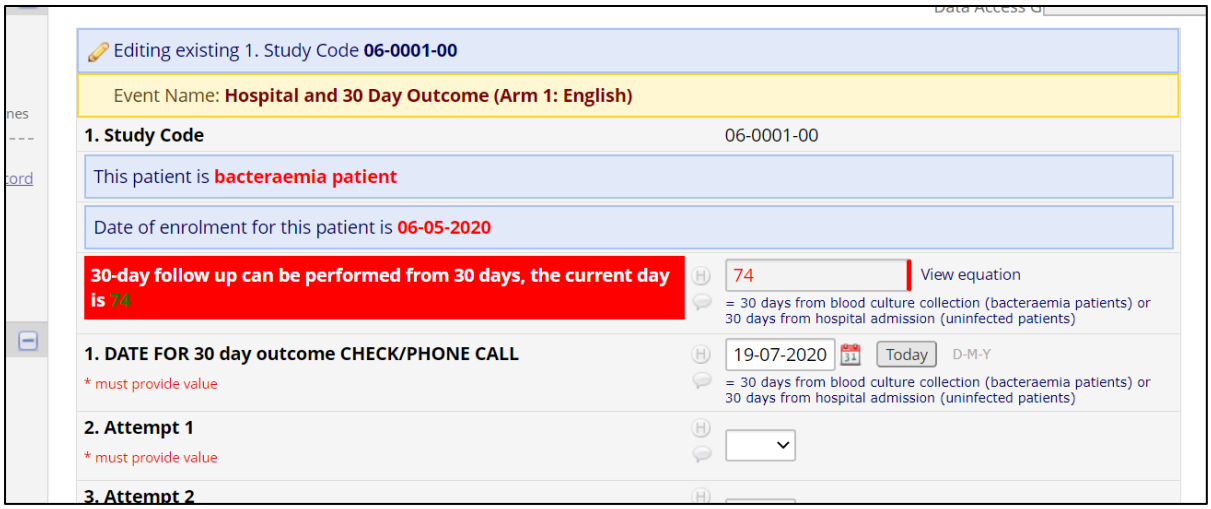
** Note that if you do not mark the "laboratory" and "antibiotic use" pages as "complete" in Redcap, then the system will give you an error message when you come to complete the 30-day outcomes. This is a minor glitch in the database, we were attempting to make sure that the all parts of the form were filled in order.



Now you can enter the final pieces of information for the individual in the study – the hospital outcome and the 30-day outcome.

Activity: enter the hospital outcome for the CRF that you have and save this. Then enter the 30-day outcome under the next section of the form.

A 30-day outcome is 30 days after the "Date of enrolment" which is a calculated date in the study, rather than the actual date that the patient actually gave permission to participate. This "date of enrolment" is described in sections above. Obviously, a 30-day outcome cannot be determined until at least 30 days have elapsed from the "Date of enrolment", so there is no point making phone calls to contact patients before this time. Redcap helps to calculate which date is appropriate to start attempting to contact the patient – this is shown in the red box as below:

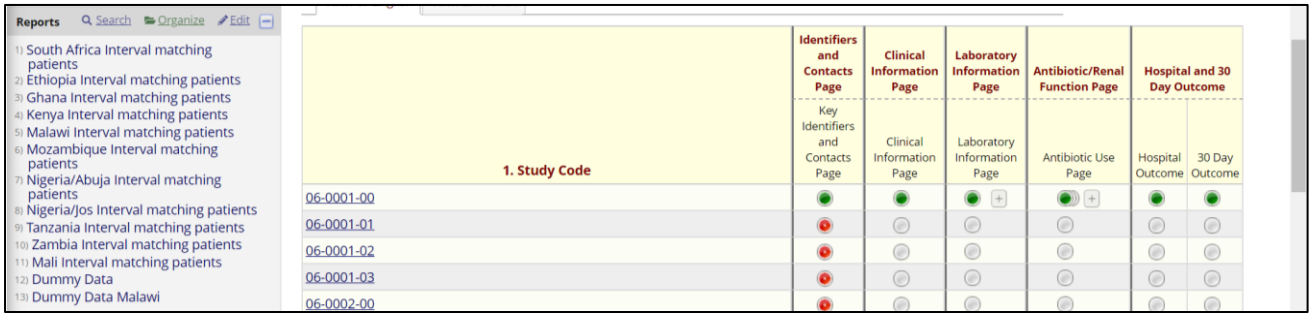


So long as the red number is more than 30 days, it is reasonable for the phone calls to take place. A phone call does not have to take place exactly on "day 30" – a few days later is reasonable to allow for the working week. This number of days will automatically update according to today's date.

Note: if a patient has died in hospital, obviously there is no need to make a further phone call to family members to determine their status at 30 days – this can be entered directly without phone calls. You do have to physically record the "30-day outcome" in Redcap separately from the "hospital outcome", even if it is obvious that the 30-day outcome is "died" – the database does not move this information across.

You should now have completed all the fields for entering data for this CRF.

Activity: navigate back to the main "Record Status Dashboard (all records)" and find the CRF record you were entering. Check that all the fields are now "green" – see below. If any are any other colours for any of the dots, click on that dot to go back to complete any further information needed.



Activity: if you were entering information for a bacteraemia patient, now you need to go back to the start of this exercise and enter information for one matching patient, which has some differences.

11. Data entry in the MBIRA study – timeline and accuracy checking

In general terms for any research study, the sooner data can be entered, the better - this minimizes risks of accidental loss. Also, data entry may prompt the data collector to notice missing or impossible values in the data collected, requiring re-visiting the original sources of the information – the sooner a mistake is corrected, the easier to find the relevant information. However, these are balanced against convenience and practicality – it may be quicker to enter all the information for a CRF at one sitting once the 30-day outcome has been collected.

In the MBIRA study, as far as possible, we leave it in the hand of the site-leads to determine appropriate timelines for data-entry and choice of methods to ensure that data collection and entry is accurate, or as accurate as possible given the limitations of data available. We do not expect double entry of data or double checking of every single record, but intermittent review of records by the site lead would probably be a good practice.

** Note that we will also be regularly performing data quality checks for key items of information in the MBIRA study during the period of live data collection and giving regular feedback on these via emails to the study leads. If you discover that there is a mistake in information that has been entered, you should go back and change the relevant data.

12. Introduction to appropriate-ness of antibiotic use in MBIRA

One of the main research questions of the MBIRA study is to examine how the appropriate-ness of use of antibiotics, in terms of antibiotic drug being used, relates to outcomes for the patient.

There are many different aspects of whether antibiotic use is appropriate, including

1. Suitable antibiotic drug for empirical treatment of an infection "syndrome" in a certain age group
2. Suitable antibiotic drug for an identified bacterial pathogen, based on antibiotic resistance tests
3. Suitable dosing of antibiotic drug for this patient, based on their weight, renal function, other factors
4. Suitable route of administration of antibiotic drug – intra-venous versus oral versus other
5. Suitable timing of the first (and subsequent) doses of antibiotics from onset of illness
6. Suitable duration of antibiotic use, in terms of overall number of days of (effective) therapy
7. Suitable choice of agent, based on local availability, costs, antibiotic usage guidelines/policies

And probably there are several other factors too! We are not able to assess all of these in this study, but we are going to focus on aspects "2", with some attention also to aspects "3", "6" and "7". We are therefore particularly looking at just the question of whether the antibiotic agent being used would be expected to be active against the specific bacteria identified from the positive blood culture.

In order to do this, one or two experienced people* (→ see below) in each site need to assess each antibiotic used for each patient with bacteraemia to say whether or not, in terms of the local antibiotic susceptibility testing results, this antibiotic would be expected to be active against this particular bacteria.

This is obviously a very narrow interpretation of the "appropriate-ness" of antibiotic use – patients might receive an "appropriate" choice of drug agent, but at an inadequate (or excessive) dose or via an inappropriate route or at an excessive cost to the hospital or patient. Drugs might have passed their expiry date or not be administered appropriately. The patient might miss some doses of an appropriate antibiotic due to limited availability or oversight by treating staff. Also, there may be some antibiotic drugs used where there is no local testing information available to determine whether or not the agent is likely to be effective. Furthermore, for some types of antibiotic resistance (eg resistance mediated by ESBL enzymes), there are differences of opinion amongst microbiologists over whether or not particular antibiotic agents are "appropriate" to use, though current versions of major antibiotic susceptibility testing guidelines (EUCAST and CLSI) now make broad recommendations on interpretation of test results in most situations.

For the purposes of this study, we are just going to focus on this narrow question relating to aspect number "2" above – **does this particular drug potentially have therapeutic activity against this particular bacteria?** This will mean each drug will typically need a "yes" or "no" answer each day to say whether the relevant person/people considers this to be an appropriate drug to use. We will also allow options for "unable to determine" and "Yes, but at inadequate dosing" to be used. All of these choices will be based on the professional opinion of the relevant person. The next section describes how to enter this information.

* In each site, an appropriate person with extensive clinical and microbiological experience should be making this assessment for "appropriate-ness" of antibiotic drug choice all the patients in the study – this assessment should not be performed by a study research nurse in isolation. Typically, this person will be the site lead or another clinical microbiologist and will participate in further relevant study trainings. The choice of who who will perform this part of the study should be agreed in advance with the study co-ordinators.

Activity: identify who in your research site is the local person/people who will perform this "appropriate-ness of antibiotic use" determination. Ideally this person/people should have both clinical and microbiological training and extensive experience in the management of antibiotic use for Gram-negative bacterial infections. If you are the site lead, please communicate this choice to the study coordinators.

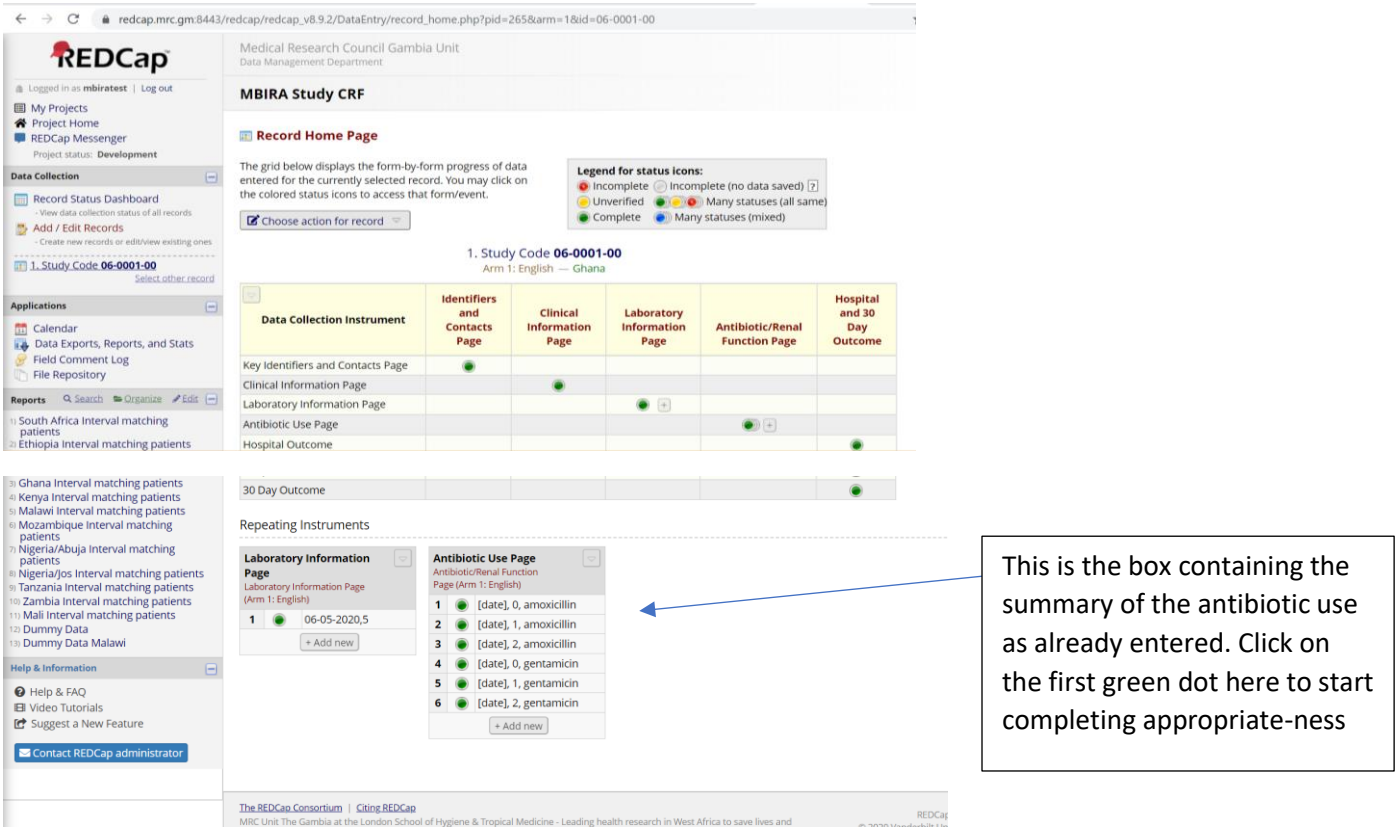
13. Training exercise 4 – coding appropriate-ness of antibiotic use

To enter data on the appropriate-ness of antibiotic use in participating patients in the study, you must be an identified person at a participating site qualified to do this. If you are not sure if this is you, please discuss with your local site leader.

To complete this training exercise, you need to have access to the Redcap database with entered data on at least one bacteraemia case within your Data Access Group (DAG). You will need to be able to locate this "mock" patient in the Redcap database and it will be useful to have the paper CRF record containing written details of antibiotic resistance (as tested in the laboratory) and antibiotic use (as recorded from the ward).

In routine practice in the study, this part of data entry may be best performed after the patient has been discharged from hospital, so the appropriate-ness of the whole treatment course can be determined in one session. There is no time-dependency of entering these data, but the earliest possible opportunity is advisable.

Activity: log onto the Redcap database, go into the "MBIRA study CRF" project and locate the patient record that you are going to determine the appropriate-ness of antibiotic treatment for. You will need to use the study ID number to locate the relevant patient. When you reach the Record Home Page, the screen should look similar to this:

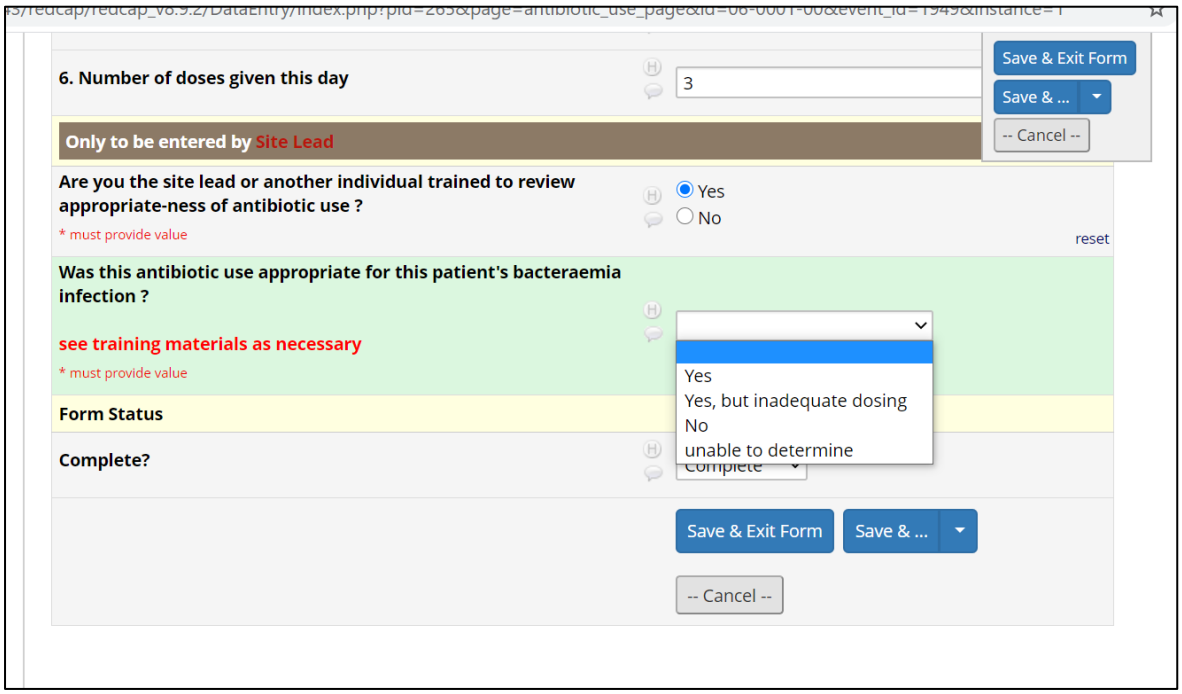


This is the box containing the summary of the antibiotic use as already entered. Click on the first green dot here to start completing appropriate-ness

Note that the column for "Antibiotic use" should show multiple dots and these should all be green (as shown above - as the dot at the front of the group is green). At the bottom of the screen, you can see a separate box with a brief summary of the antibiotic agents given and on which day of the bacteraemia (here day 0, day 1, day 2 only).

Activity: click on the green dot for the first antibiotic use box recorded to start to enter appropriate-ness

On the following page, scroll down and change the value of the question "Are you the site lead or another individual trained to review …" from "No" to "Yes". A further question should now appear, with options for response as shown below.



Activity: using the antibiotic resistance testing this patient's laboratory information (may be easiest to refer to the paper CRF, or copy down results from the "Laboratory information" page of the CRF), make your judgement on whether you consider the antibiotic dose described on this page to be potentially appropriate to treat this patient's bacteraemia. Ideally, we are seeking a "Yes" or "No" answer.

As discussed in section 12 above, this is a "narrow" and purely microbiological interpretation of antibiotic appropriate-ness and takes no account of several other important pharmacological and logistical factors. However, given the importance of the correct dosing of antibiotic drugs, you can also opt to record **"Yes, but inadequate dosing"** if the amount of drug given was (in your opinion) potentially inadequate for this patient (based on patient age/weight, number of doses given this day, route of administration).

If there is substantial uncertainty about the potential effectiveness of the antibiotic agent (eg. if no susceptibility testing performed for this agent) for whatever reason, it is also possible to record **"unable to determine"**. Any patient or drug where this option is recorded should be discussed with the study coordinators to see if the status can be clarified.

Activity: now press "Save & go to next instance" and repeat the steps above for each antibiotic-day recorded. You need to record an "appropriate-ness" status for each antibiotic-day of treatment. When you have done this, the data collection for this patient is complete and no further action is needed.

**** For more extensive discussion and description of how to conduct this "antibiotic appropriate-ness" part of the MBIRA study, please see the longer document "MBIRA study: Guide to scoring appropriate-ness of antibiotic use, v1.1", which is now included as Appendix 2 of this Training Manual. All study leads should be familiar the details of this document.**

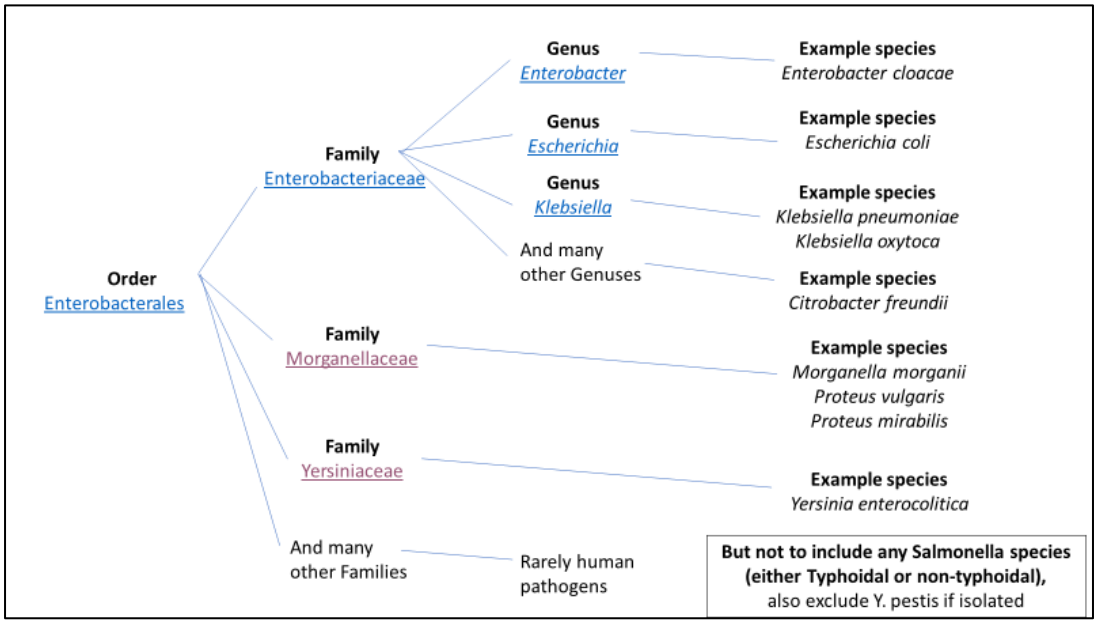
14. Introduction to microbiology work in MBIRA

Clinical microbiology work in African hospitals is difficult. There are relatively few trained specialists in this area and the resources available are often very limited and supplies of consumables can be erratic. Clinicians working in African hospitals often have a poor understanding of how best to use the microbiology services available and hence samples are often sent inappropriately, leading to high rates of contamination and low rates of identification of true pathogens. Laboratory experience in performing antibiotic susceptibility testing can be very variable, such that susceptibility results can sometimes be unreliable. Systems for disseminating important microbiology results often have substantial shortcomings and hence it can be difficult for a positive result to be communicated to the relevant treating clinicians. However, in recent years, many governments and external funders are recognizing the importance of microbiology laboratories in tackling the impending crisis of antibiotic resistance across the continent. New investment and activity are now taking place in many African hospitals to augment the microbiological capacity and skills for rapid and appropriate identification of microbial pathogens.

In the MBIRA study, we recognize the challenges faced in many African hospital microbiology laboratories. We seek to work with our collaborating laboratories to make the best of their current situation, within the budget and timeframe of the study. The study is focused on the performance of blood cultures, specifically looking at the Enteric bacteria as pathogens in the study. We have purposefully selected collaborating hospitals and institutions with a wide range of microbiology expertise – some are "high-performing" research institutions with decades of blood culturing experience, others are hospital laboratories newly in receipt of support from the Fleming Fund (or otherwise) to augment their blood culturing capacity.

In the study, we will follow the methods of identification (to bacterial species level) and Antibiotic Susceptibility Testing already routinely performed in the participating laboratories – we do not seek to make any changes to laboratory methods used, unless we identify major areas of concern in review of the local SOPs (see next section).

The bacterial species of interest for this study are all bacteria identified from clinical blood cultures within the order Enterobacterales. Typically, the most common bacterial species in this order are *E.coli* and *K.pneumoniae* (in the Enterobacteriaceae family), but other bacteria that are in this category are other species of Klebsiella, Proteus species, Enterobacter species, Citrobacter species, Morganella species and various other less common organisms. The classification hierarchy is shown below



As an important piece of standardization of the study across all the participating hospital laboratories, we aim to transport all the bacterial isolates identified from blood cultures for patients in the study to our study Reference Laboratory in the Department of Medical Microbiology, Stellenbosch University, South Africa (affiliated to Tygerberg Hospital). This will be done at the end of the data collection period in the MBIRA study, so likely to be in January - February 2022. These bacterial isolates from all sites will be double-checked for both their species-level identification and their antibiotic susceptibility testing profile. The purpose of this double-testing is to ensure a standard quality for bacterial identification across all sites – some sites are much more experienced than others. Any discrepancies between local and reference laboratory identification of bacteria will be given as feedback to the local laboratories.

In order for the bacterial isolates identified in the study to be available for transportation to South Africa in late 2021, **it is critical that bacterial isolates are stored appropriately between time of isolation and time of shipping**. We will therefore be asking quite detailed information about the normal practices for storing bacterial isolates in freezers and providing any suggestions as necessary.

The collection of bacterial isolates at Stellenbosch University will represent an important cross-sectional collection of pathogenic bacteria from across the African continent. There are no funds in this project for further investigation of this collection, but there are now plans being developed for whole genome sequencing of this collection of bacteria, to be led by MBIRA collaborators at Kilimanjaro Clinical Research Institute (KCRI) in Tanzania, one of the participating sites in the study – further information to follow. .

15. Laboratory baseline information at start of study

As part of the preparation for the study, we need to gather various pieces of information about the current working of the Microbiology laboratory in your hospital/institution, to help us understand the identification and storage processes and quality control mechanisms you already have in place. This is so that we can identify which laboratories in the study may need additional support in the study, so that all laboratories are working to more-or-less equivalent standards and methods. Given the challenges of COVID-19 and the number of sites involved, it will be impossible for us to visit all the laboratories in person before the start of the study, so this baseline information will help guide us to which sites need most attention and support. We will not to interfere with your existing laboratory processes unless we identify issues that will threaten the work of the study !

Activity: if you are the site lead for the MBIRA study in the study, please complete the following activities:

- Please find the Laboratory Scoping Questionnaire in the Dropbox folder. We are also seeking electronic copies of your local laboratory SOPs for
    - Blood culturing
    - Antibiotic susceptibility testing
    - Quality Control
    - Storage of isolates in Freezer (either -20C or -80C)

- Complete the Laboratory Scoping Questionnaire (4 pages) and sent it to Prof Andrew Whitelaw (awhitelaw@sun.ac.za) and Alex Aiken (alexander.aiken@lshtm.ac.uk) along with the local laboratory SOPs documents requested, as above.

**** Please send the completed questionnaire and SOPs by 14th August 2020 **** You will receive feedback on whether there are any particular queries or concerns about current activity in the following weeks.

16. Training exercise 5 – mock laboratory monitoring data

As part of the monitoring of progress during the study, we are asking all the sites to submit a monthly simple report on the amount of blood culturing work being done in the hospital laboratory, and the outcomes of these blood cultures. This will inform us about the quantity and quality of blood culture performance in the hospital, and help us know how many relevant bacteraemia cases can be expected in the site.

Activity: find the Laboratory Monitoring Form, either a version printed out earlier or download from the study Dropbox folder

This is a simple form with just 3 main questions – we hope this will be straightforwards for laboratory staff to complete every month. It should use blood cultures from the 1st day to the last day of each month (eg. 1st to 31st of July), though we recommend that the data are collected at approximately the middle of the following month (eg from approx. 14th day of month onwards) to allow completion of laboratory work-up of cultures from the last day of the previous month. There is also an optional 4th question in the form to allow feedback on particular "quality control issues" in blood culture work in the past month – this is to encourage communication of new quality issues that may be relevant to the study.

The main challenge of this form is to separate blood culture isolates into "pathogens" and "contaminants". For some bacteria (eg. *E. coli*, *K. pneumoniae*), their presence in a blood culture is almost always pathogenic while some others are usually contaminants (eg. Coagulase-negative staphylococci, Bacillus spp, Micrococcus spp, coryneform bacteria) – but there are always exceptions to any rule in microbiology. We just need broad local judgements of most likely pathogen v contaminant status – there is no need for individual investigation of every single organism isolated, though unusual organisms may need looking into.

A useful starting point for determining whether organism isolated is a pathogen or contaminant is the following table from Ombelet, "Best Practices of Blood Cultures in Low and Middle Income Countries", 2019.

TABLE 1 | Examples of common bacterial species grown in blood cultures.

	Gram-positive		Gram-negative		Yeast
	Pathogen	**Contaminant**	**Pathogen**	**Contaminant**	**Pathogen**
Aerobic		*Bacillus* species	*Pseudomonas aeruginosa* *Burkholderia pseudomallei* *Acinetobacter* species	*Stenotrophomonas maltophilia** *Pseudomonas* species (non-aeruginosa)*	*Cryptococcus neoformans*
Anaerobic	*Clostridium* species	*Cutibacterium acnes*	*Bacteroides* species		
Facultative /aero-tolerant	*Streptococcus pneumoniae* *Staphylococcus aureus*	Coagulase-negative *Staphylococcus* spp. *Micrococcus* species	*Escherichia coli* *Klebsiella pneumoniae* Non-typhoidal *Salmonella* *Salmonella* Typhi		*Candida albicans* *Candida glabrata*

*Uncertainty of interpretation according to current literature.

Beyond this, we recommend that you seek the advice from an experienced clinical microbiologist in your site to determine Pathogen v Contaminant status for any further or unusual organisms.

Activity: using the laboratory monitoring form, work with your local hospital microbiology laboratory to complete the 3 monitoring questions for a recent past month (eg. June 2020), plus any feedback in Q4.

To return the data from the laboratory monitoring form, there is a Redcap "project" (=data entry section) relating to this form (currently in production, should complete soon). This is a very simple form to enter.

Activity: Access Redcap in the normal way and select "MBIRA Laboratory monitoring form" at the first menu. Enter your responses to the questions as above.

17. Introduction to Hospital form

The local hospital context is important to understand local patterns of treatment of patients, extent of antibiotic resistance and use of different antibiotic treatments. African hospitals face unique challenges through burden of disease, shortage of staff with appropriate expertise, availability of ICU beds and financial resources – this makes them a very different context for treating patients to hospitals in high-income countries. We are therefore collecting descriptive information about hospitals participating in the study, though using this "Hospital form" (described here), and also about antibiotic agent availability, through the Pharmacy Form (described in subsequent sections).

Activity: find the Hospital Form, either a version printed out earlier or download from the study Dropbox folder.

There are also two supplementary documents (as pdf files) that are needed for completing this form – first a "WHO Infection Prevention and Control Assessment Framework at the Facility Level" (15 pages) and second a section from the "WHO Antimicrobial Stewardship Programmes in Health-care Facilities in Low and Middle-Income Countries – A WHO Practical Toolkit" (section = 4 pages). The full document for the "WHO Stewardship Toolkit" document is 88 pages – this is also available in the Dropbox folder.

Activity: make sure you have also downloaded all these additional WHO documents, and it is probably useful to print out the two shorter documents. The full "Stewardship Toolkit" document is for reference.

We are using these two WHO materials as standard ways of assessing Infection Prevention and Control (IPC) and antibiotic stewardship activities at the hospitals participating in MBIRA, so that any results from the hospitals can be easily compared to results from large WHO-led surveys that have been conducted in recent years (but results not yet published, as far as we know). Both WHO materials are quite long to complete, but the whole Hospital form is only completed twice in the study – once at the beginning (between Nov 2020 and March 2021) and once at the end (between Oct 2021 and January 2022). We are repeating the collection of the form to determine if there is any evidence of change in relevant hospital practices over the course of the study.

In the MBIRA study, there is no requirement or expectation that any changes to IPC or Antimicrobial Stewardship activities are made during the course of the study – this is outside the scope of the research. However, the study may draw attention to issues around treatment of antibiotic resistant infections within the participating hospitals, so changes may occur as an indirect effect of the study. As the MBIRA study is purely observational, it does not matter either way for the study, but we hope to capture any evidence of change through the Hospital (and Pharmacy) Forms.

Activity: read through the MBIRA Hospital form and the two supplementary WHO documents. Are there any questions on these forms that you think you personally will not be able to give answers for? If so, who will you approach in your local hospital administration, IPC committee and Antibiotic Management Group (or similar) to help find answers for these?

18. Training exercise 6 – completion+entry of mock Hospital form

For the MBIRA hospital form, completing the whole form will take several days work and involve discussion with various people across various different sections of the hospital. We therefore do not expect you to make a "rehearsal" of this, as it would be too time consuming. However, to understand the form and the data entry method, it is useful to complete the form with some "imaginary" data which you think is approximately correct for your hospital. Practicing in this way will make it easier when you come to conduct the actual data collection work and entry in the study.

Activity: fill in the first page of the Hospital form, including numbers of beds and number of bed-days in 2019, using numbers that are your own personal estimates.

Note that there are specific descriptions of different types of Intensive Care Beds (Level 1 / Level 2 / Level 3)– try to match what you know of your hospital situation to the description of these different levels in the table from the publication "What is an intensive care unit? A report of the task force of the World Federation of Societies of Intensive and Critical Care Medicine" Marshal JC et al, J Crit Care Med, 2017 (on p2) of form.

Laboratory characteristics page – note that some of this information is a repetition of information about number of blood cultures that you may have collected previously for the "Laboratory scoping form" in the preparatory phase of the study.

Activity: for the next part of the Hospital Form, you need the print out of the "WHO Infection Prevention and Control Assessment Framework at the Facility Level" document, specifically the pages 3 to 14, which contain extensive questions about IPC activities in your hospital. Fill in some "imaginary" answers for at least the first page of the questions and add up the sub-total score (/100) for any pages you complete.

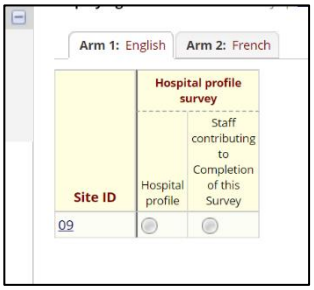
In practice, answering these questions will need to be done in conjunction with IPC staff from your hospital. Many of the questions have some degree of interpretation – you must use your best judgement for what is a fair representation of the situation in your hospital.

Activity: for the final part of the Hospital Form, you need the print out of the "WHO Antimicrobial Stewardship Programmes in Health-care Facilities in Low and Middle-Income Countries" document, with questions on pages 2 to 4. Again, fill in some "imaginary" answers for at least the first page of this. Add up your score for the different sections you have completed – 1 point for "yes", 0 points for "no". The score for section "1. Leadership and commitment" has a maximum of 3 as there are 3 questions in this section.

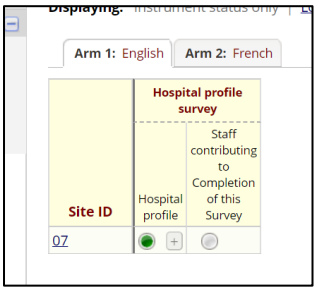
Again – note that these questions are, to some extent, open to interpretation. These questions were not designed in the MBIRA study, but it does make sense to use them, as it will allow easy comparison with any other hospitals that have used the same WHO tools.

Activity: open the Redcap database and log in. You should see a project called "MBIRA Hospital" on the project home page, then click on "Record Status Dashboard".

When you are on this page, you should see a table showing your site ID (see section 3 in this manual) in a Table with "Hospital profile" at the top of the first column. Click on the grey dot to create a first record.

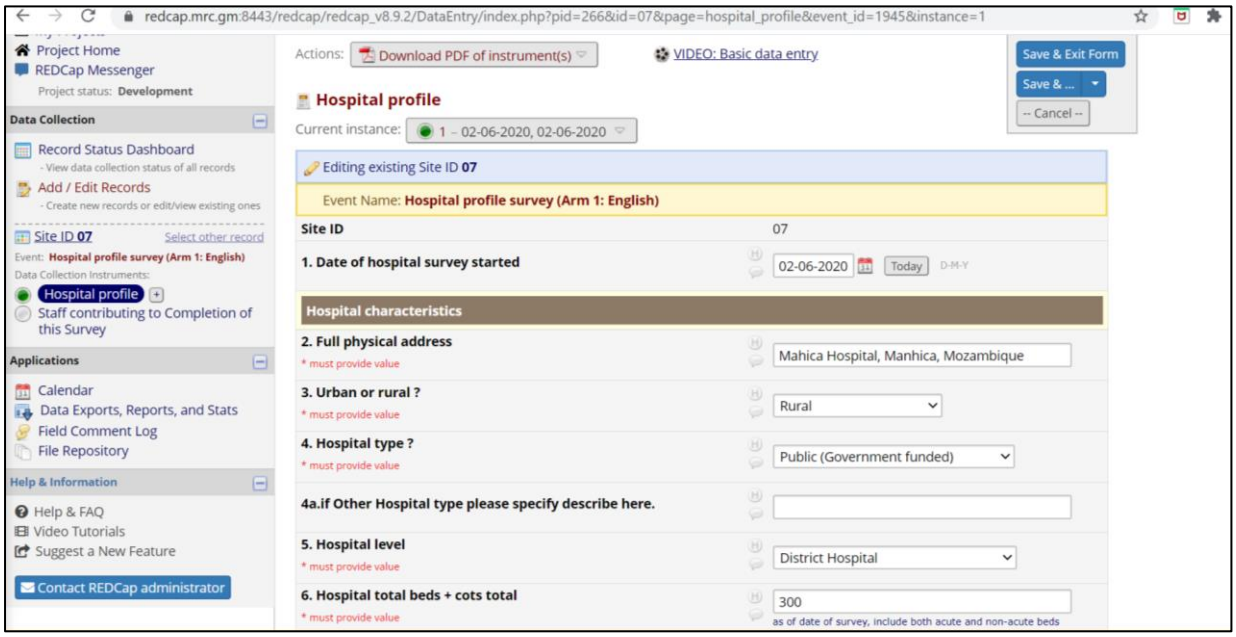


If someone at has previously created a record for your site, the "dot" will be red (incomplete) or green (complete) – in this case, you can start a new instance (copy) of the form by pressing the + button.



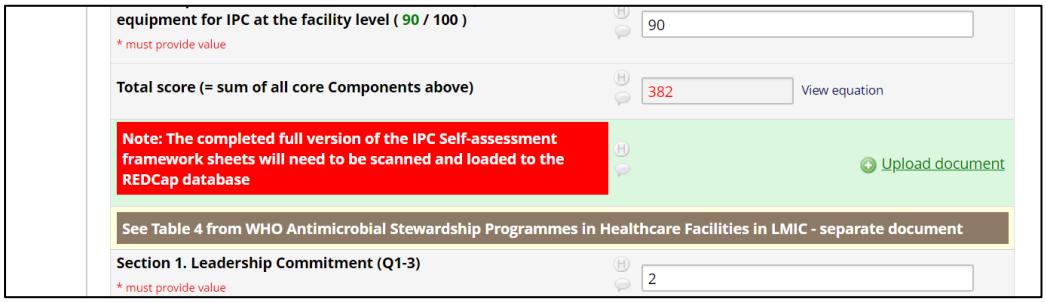
Activity: using the imaginary data that you wrote previously, start to complete the Hospital form.

The start of the form should look like this, after you have entered some data:



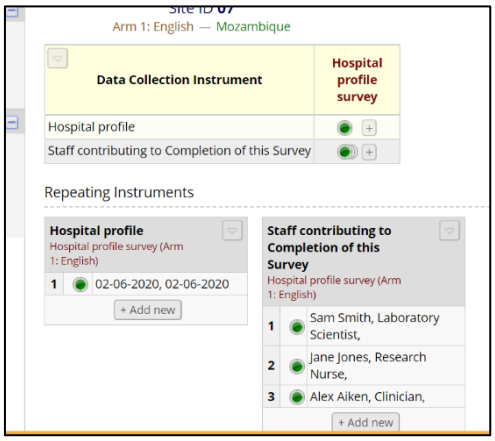
Activity: when you reach the sections about the two different WHO sets of questions, you only need to fill in the sub-total scores for each section – scores /100 for the parts of IPC questionnaire and scores out of other smaller totals for the Stewardship questions. Fill in your "imaginary" scores for each section that you have completed.

Finally, and just for future reference, you will need to scan both of the full WHO questionnaires to create a two .pdf files (or other format such as .doc) of all the scanned pages – one for each questionnaire. There are two separate places for the two separate WHO questionnaires. The scans are uploaded into Redcap by clicking on the "Upload document" shown below, and then following the instructions.



Activity: upload a pdf file (any file will do!) to one of the places in the MBIRA database from your computer. Once you have seen that the file has uploaded (the time depends on size + your connection speed), you can then delete it. Then you can "Save & Exit" this part of the form.

When you have completed the first part of the hospital form, you then also need to record the people who helped gather these data, as per the top of the paper copy of the Hospital Form. Go into the second section of the Hospital form, titled "Staff contributing to completion of this survey". You need to create one "instance" (=copy) of this form to record the name and role of each person who helped. Create new instances by clicking on the + button in the relevant row or press "Add new" below the names you have entered.



Activity: fill in some names and roles for "imaginary" people who might have helped you complete the Hospital form.

19. Introduction to Pharmacy form

One of the challenges of treating antibiotic resistant infections in African hospitals is the limited access to antibiotic agents for treating resistant infections – hospital pharmacies in African rarely stock advanced agents such as carbapenems (eg. meropenem, ertapenem), 4th or 5th generation cephalosporins (eg. cefipime, ceftaroline), newer β-lactam-β-lactam-inhibitor (BLBI) agents (eg. ceftazidime-avibactam) or polymyxins (eg. colistin). This means that when extensively antibiotic resistant infections occur, it can be very difficult, or even impossible, for a hospital to supply a suitable agent for treatment. Patient's relatives may be instructed to purchase suitable agents from independent retailers, but it is then hard to be certain of the quality of production and storage of such drugs. Additionally, many African hospitals experience unreliable supply chains for more basic antibiotics, so even agents considered "routine" or "essential" may occasionally be "out of stock".

In order to better understand this challenging aspect of treating antibiotic-resistant infections in the MBIRA study, we aim to collect monthly data on the local hospital pharmacy availability of antibiotic agents during the 12 month course of the study. By performing repeated in-person monthly measurements of the drug availability, we will be able to determine if drug-available is variable over the course of the study. We aim to survey the quantities of relevant antibiotic in the internal hospital pharmacy only, we are not looking at the supply from private or external providers.

Activity: find the Pharmacy Form, either a version printed out earlier or download from the study Dropbox folder.

As described on the form, the most useful person to complete this form with is a Registered Hospital Pharmacist, or equivalent professional group. This study only requires very broad information about drug availability, so the level of detail on the actual stock of particular agents if very low – this is to make the data simple to collect. We are interested in the **current availability of these drugs only** in the survey, not past or future estimations. We need in-person confirmation of approximate quantities available of these drugs and that the drugs are within their expiry date.

This data collection form makes use of the concept of Defined Daily Doses – this is a standardized quantity of a drug, according to WHO definitions, to make comparisons of quantities easier.

Optional activity: to look up a DDD quantity for an antibiotic (or any other drug), go to the website https://www.whocc.no/atc_ddd_index/ . In the Search query box, enter the name of an antibiotic that is typically used for treating E. coli bacteraemia infections in your hospital (eg "Ceftriaxone". Select an entry with a code beginning with a J and find the relevant DDD for this drug. Compare this value with the DDD written on the 2nd page of the Pharmacy Form

20. Training exercise 7 – completion+entry of mock Pharmacy form

Collection of data for the Pharmacy Form needs to be done on a monthly basis in the MBIRA study, ideally at roughly the same time each month. We suggest performing the data collection on the 1st Tuesday of the month every month, though this is a local choice in the project - the important principle is that the form should be performed on a similar day in each month. The data collection should always be performed by an MBIRA study staff member in conjunction with a Pharmacist the hospital.

This form is intended for surveying quantities of the antibiotics suitable for treating Gram-negative bacterial infections in the internal hospital Pharmacy only. Some antimicrobial agents are only suitable for Gram-positive infections or are for anti-TB, anti-viral or anti-parasitic uses primarily – these are not included in the survey.

In the training period of the MBIRA study, we need at least one "real" collection and entry of actual data for the Pharmacy form in the study preparation period, to make sure that the form is appropriately written. If this has already been done, it is reasonable to enter "mock" data (but not save it) for practice purposes only.

Activity: discuss with your local study lead about who will enter "real" data for this form for your site, and if it has already been done. If you are collecting "real" data, continue to follow the steps below. If you are entering "mock" data, you can create some imaginary values and follow the data entry steps later on.

Data collection in Pharmacy Form.

The key for this stage is to identify a local Pharmacist, ideally someone with interest in treatment of infections, to assist you with this task. Finding a suitable time is always a challenge! In-person completion of the form will take two people approximately 1 hour. A paper copy of the form will help for moving around.

Section 1.

An in-person verification of antibiotic-agent supply can normally be started by referring to local drug quantity records, whose format will vary between Pharmacies, for initial understanding of availability.
We additionally ask that, for each drug in each survey, the MBIRA investigator should physically verify the presence of the boxes of antibiotic agent "by eye" (ie looking to see the actual box exists in the Pharmacy), and check the expiry date of at least one container of the relevant drug to ensure that this has not already passed. This will require walking around relevant Pharmacy storage room(s).

Activity: working with a local Pharmacist, go through all the antibiotics in Section 1 of the Pharmacy form and estimate their availability, at present time in the Hospital Pharmacy, according to categories shown.

Note that we are estimating the quantities according to the DDD quantities as described on the form. The antibiotic will probably be supplied in some different quantity to the DDD. For example, a box of medicines may contain 1000 doses of the antibiotic Amoxicillin, supplied in 1g vials for intravenous injection. The DDD for iv amoxicillin is 3g. Therefore, this box contains 1000 / 3 = 333 DDD for amoxicillin. If this box was the only supply of amoxicillin in the Pharmacy, and the amoxicillin was "in date" (based on checking at least one date), then the total supply would be in the range "100-1000 doses", so tick this box on the form. A total availability across both oral and intravenous routes (where applicable) is fine.

It is not necessary to physically count all the doses of every antibiotic in the survey, nor to check the expiry date of every single dose of the antibiotics. Brand names of drugs are not important. We do not have resources in this study to investigate the quantity of drug agent within pharmaceutical products.

Section 2.

For this section of the form, we are looking at the availability of "specialist" agents for treating antibiotic-resistant infections. We think most of these are probably not routinely available in most hospitals in the MBIRA study, but we would like to investigate this, and also to see if the availability of these "specialist" antibiotic agents changes at all from month-to-month.

Activity: continuing with a Pharmacist, go through the antibiotic agents in Section 2 of the Pharmacy Form.

For these drugs, if they are available in the Hospital pharmacy, you do not need to enter the quantity, just confirm if at least one dose of the drug available by checking in person as above. Ensure that the scientific name of the drug, not the local trade name, is written down on the form.

For the final question, if you are uncertain whether an antibiotic agent is suitable to use for antibiotic-resistance Gram-negative infections, discuss with your local site lead. We are specifically interested in treatment of bloodstream infections, so this will typically involve intravenous or oral agents only.

Data entry for Pharmacy Form.

When you have a completed version of the Pharmacy form, either with "real" or "mock" data, you need to enter this to the Redcap database.

Activity: log into the Redcap database in the normal way and access the "MBIRA Pharma" project, and click on "Record Status Dashboard". Click on the dot or plus in the "Antibiotic availability" column to begin entering a new record.

Fill in the information you have collected in the for Sections 1 and 2. Check that you are entering the information in the correct row for each antibiotic – some antibiotic rows may have been added/removed in the Redcap database or the order or rows may be different from the paper version of the form.

When you reach the end of completing this Form, only Save the record if you are entering "real" data for your site. If you are entering "mock" data, do not save the record.

After you have completed the main part of the Pharmacy Form, you also need to record the names of the people that have worked on collection of these data, this month. As many people as needed can be recorded – this is done in the same way as for the Hospital form – see end of section 18 above.

21. Internal project reporting to LSHTM in MBIRA study

For project management and financial purposes, we need two different types of regular reports submitted in the MBIRA study – Financial Reports (quarterly) and Narrative Reports (annual).

Financial reports are to be submitted quarterly to lee.white@lshtm.ac.uk, based on the timelines in the table below. LSHTM's financial reporting template can be found in the MBIRA Dropbox folder. Please use this template for all reporting and be sure to keep the following guidance in mind:

- Budget variance is acceptable up to +/- 10% of each budget heading.
    - If you anticipate variance outside of the acceptable range, please contact Lee and Alex to discuss the feasibility of an amendment to your budget.
- Exchange rates and their source should be clearly listed.
- Reports must be stamped and signed by an authorised signatory.

Quarterly Financial Reporting	
Period	**Report due:**
Start of agreement – 31 October 2020	30 November 2020
1 November 2020 – 31 January 2021	28 February 2021
1 February – 30 April 2021	31 May 2021
1 May – 31 July 2021	31 August 2021
1 August – 31 October 2021	30 November 2021
1 November 2021 – 31 January 2022	28 February 2022
1 Feb 2022 – End of grant	30 April 2022

In addition to quarterly financial reporting, we also need to provide **narrative progress reports** to BMGF annually. At least one month in advance of the deadlines below, we will share a brief (1-2 page) template for you to complete with information on the following matters, at minimum:

- Progress toward deliverables
    - Updates on any remedial actions, if necessary
- Personnel updates
- Challenges and/or lessons learned
- Explanation of how project expenditure may have differed from agreed budget

Annual Narrative Progress Reporting	
Period	**Report due:**
Start of agreement – 31 October 2020	30 November 2020
1 November 2020 – 31 October 2021	30 November 2021
1 Nov 2021 – End of grant	30 April 2022

Invoices should be submitted to lee.white@lshtm.ac.uk and collaborations@lshtm.ac.uk and include the following details:

- LSHTM's full address:
  London School of Hygiene & Tropical Medicine
  Keppel Street
  London WC1E 7HT
  UK
- Unique invoice number and date
- Description of the goods/services
  - e.g. *For MBIRA project activities to [date], upon submission of financial report*
- Currency (USD) and amount clearly stated
- Marked as 'final'

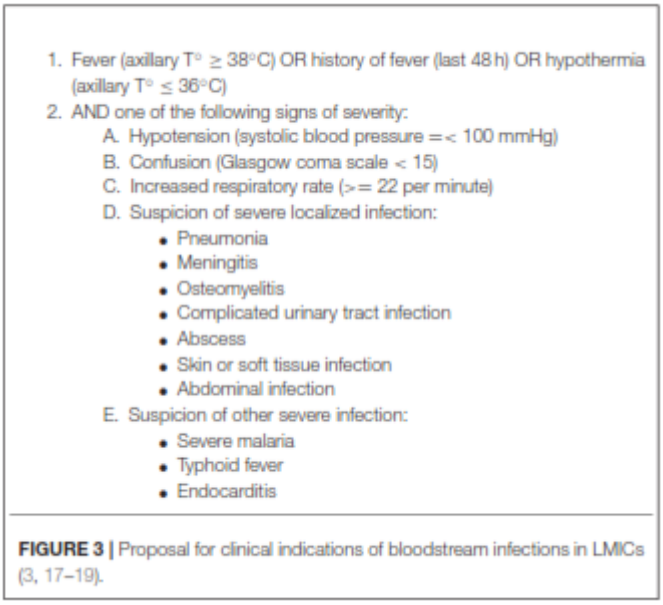
Payment schedules and amounts should be clearly listed in Schedule 3 of your agreement with LSHTM.

22. Ensuring appropriate collection of blood cultures

The MBIRA study relies on detection of bacteraemia cases, which relies on the performance of blood culture tests for appropriate patients in the hospitals. There are many challenges in ensuring the performance of blood cultures is done appropriately in clinical settings – the consumable materials for blood cultures are expensive, so ensuring that clinicians choose appropriate patients to have blood cultures performed is an important part of supporting the activity of the study.

Activity: locate the paper "Best practices for blood cultures in Low- and Middle-income countries", Ombelet S et al, Frontiers in Medicine, 2019. This paper is included at the end of this manual as Appendix 1 and a separate pdf copy is also in the Dropbox folder. Read the section of this paper titled "Indications for Blood Culture", on p2 and see also Figures 2 and 3.

Figure 3 from this paper is reproduced here – this is relevant for adults, children and infants. Neonates are more difficult – they may not manifest overt signs of infection in the same way.



1. Fever (axillary T° ≥ 38°C) OR history of fever (last 48 h) OR hypothermia (axillary T° ≤ 36°C)
2. AND one of the following signs of severity:
   - A. Hypotension (systolic blood pressure =< 100 mmHg)
   - B. Confusion (Glasgow coma scale < 15)
   - C. Increased respiratory rate (>= 22 per minute)
   - D. Suspicion of severe localized infection:
     - Pneumonia
     - Meningitis
     - Osteomyelitis
     - Complicated urinary tract infection
     - Abscess
     - Skin or soft tissue infection
     - Abdominal infection
   - E. Suspicion of other severe infection:
     - Severe malaria
     - Typhoid fever
     - Endocarditis

FIGURE 3 | Proposal for clinical indications of bloodstream infections in LMICs (3, 17–19).

In very simple terms, the single most important parameter suggesting the need for a blood culture is presence of a fever (T ≥ 38^{o}C) – this should be coupled with clinical suspicion of infection in some way.

Activity: think about the performance of blood cultures in the MBIRA hospital that you are working in. On a day-to-day basis, who makes the decision to collect a blood culture for an individual patient? On what basis do they make this decision? What could be done to improve this decision-making process?

In the few months approaching the start of the MBIRA study, we will prepare further materials for site leads to use to train local clinicians about the appropriate selection of patients for blood cultures. Training clinicians to use blood cultures wisely will be an important part of the work of the MBIRA study for all staff involved in the study, as appropriate. The need for this training will continue throughout the whole period of data collection. Turnover of staff in hospitals is so high that "refreshers" are needed periodically.

23. Minimizing contamination rates of blood cultures

A major challenge for any hospital performing blood cultures is to control the rate of contamination of blood cultures. Contamination of blood cultures normally occurs at the time of blood culture collection with bacteria from the skin of the patient (or the person collecting the sample) being accidentally inoculated into the culture media. Contamination of blood cultures is a problem for two main reasons. First, any growth of a contaminant in a blood culture requires use of laboratory time and consumables to identify, but adds no clinical information – this is wasteful. Second, growth of contaminants in blood cultures makes it harder to identify true pathogens – these may be missed by a laboratory if contaminants are also present.

A standard target for blood culture contamination rates is <3%.

Activity: using the paper in Appendix 1, ("Best practices for blood cultures in Low- and Middle-income countries", Ombelet S et al, Frontiers in Medicine, 2019), read the section on "Preventing Contamination of Blood cultures" beginning on page 10 through to page 13.

We expect that the contamination rates of blood cultures in many of the hospitals in the MBIRA study may be very high (eg 10% or more) at the start of the study – we will support sites to try to minimize this rate.

Activity: think about the practical collection of blood cultures in the MBIRA hospital that you are working in. On a day-to-day basis, who collects the blood cultures for individual patients ? How are they trained in collection of blood cultures ? Do they know if their personal collection of blood cultures has a high rate of contamination ? What could be done to improve this collection process?

In some hospitals in the UK, staff performing blood cultures are observed by a second person, to ensure that they do not deviate from appropriate collection methods. This is time-consuming, but helps to ensure good practices. Some hospitals create a local "checklist" to be completed with each blood culture.

Activity: look at the form "Blood culture checklist_MBIRA", which can be found in the Dropbox folder. How do the steps described in this checklist reflect what should ideally happen in your hospital and what actually happens in day-to-day practice?

In the few months approaching the start of the MBIRA study, we will prepare further materials for site leads to use to train local blood culture collectors about the appropriate methods for collection of blood cultures. Training hospital staff to use blood cultures appropriately will be an important part of the work of the MBIRA study for all staff involved in the study. The need for this training will continue throughout the whole period of data collection – many reminders and repeat trainings will be needed.

24. Other expected challenges in MBIRA study

We expect there to be many challenges in conducting the MBIRA study in participating sites – this is an ambitious clinical study spread across a large number of hospitals across many countries, many of which are institutions with very limited financial resources.

In general terms, there are challenges that we expect to face and challenges that are unexpected.

For some expected challenges, these are as follows

a) Getting enough positive blood cultures

The study relies upon positive blood cultures of particular bacterial species – we aim for a total of 120 of these in each site, over the course of 12 months. This is a challenging target to achieve, particularly for smaller hospitals and hospitals with limitation on the numbers of blood cultures performed monthly.

This is not an easy problem to solve and we have some flexibility in the project over the total number of positive cultures per site – 120 is an "aspirational" target for some hospitals. We want hospitals in MBIRA to make the best possible use of the blood culturing resources available to them, through the study or otherwise.

The important steps for maximizing the number of pathogens recovered from blood cultures are

1) Performance of a large total number of blood cultures – this should be **as large as possible given the existing local resources and constraints**. Local decisions about resource allocation and prioritization are primarily in the hands of the MBIRA Site lead and relevant colleagues across the institution.
2) Ensuring the right types of patients have blood cultures collected – see section 22 above
3) Ensuring minimization of blood culture contamination rates – see section 23 above.

We will gain information on numbers of positive (pathogenic) blood cultures each month via the Laboratory Monitoring Form and give feedback to site leads on this. If the number of positive blood cultures for pathogens is too low, we will ask site leads to address the issues above to try to increase recovery rates. We will support this as we can with advice and training materials, but the practical work must be done locally.

b) Death of patients before recruitment

Bacteraemia is a condition with high risk of death, especially in the early period of infection. We anticipate overall mortality rates of >10% of participating bacteraemia patients, which will require sensitive handling from all study staff.

One problem we expect is that bacteraemia patients will sometimes die in the interval between collection of a blood culture and identification of the pathogen in the laboratory (typically a 48-72 hour interval). This may make it difficult to collect all of the necessary information for the CRF – the relatives of the patient may have already left the hospital or be reluctant to share such information for a deceased patient.

This situation is best handled on a case-by-case basis by local MBIRA staff. Where-ever possible, we will try to include all patients with the relevant species of bacteraemia in the study, even if some information is not possible to recover in the study.

** One useful insight is that it may help to seek out bacteraemia patients on the day that the blood culture initially becomes positive, before the full ID of the bacterial species. A laboratory will typically perform a Gram stain for every positive blood culture on the first day it is identified as having bacterial growth. If this Gram stain shows "Gram-negative rods" or "Gram negative bacilli" (=rod-shaped bacteria), then these might be later identified as Enterobacteria species, typically 24 hours later. It is thus helpful for the laboratory to notify staff performing data collection on wards when a blood culture bottle has "Gram negative rods" seen.

c) Matching patients developing bacteraemia

Occasionally, a patient who is recruited into the study as a "matching patient" will develop bacteraemia with a pathogenic bacteria after recruitment into the study and before discharge from hospital. In this situation, the matching patient is no longer eligible to be a matching patient in the study, so will need to be excluded from the study. If this occurs, please ensure that the site lead is informed – they will need to communicate the matching patient's study ID number to the study co-ordinators so that the matching patient can be excluded from the study.

Development of any other type of infection (eg. hospital acquired pneumonia, suspected sepsis) or a positive blood culture with a contaminant is not grounds for exclusion of a matching patient.

If a matching patient subsequently develops a bacteraemia is a bacteria suitable for inclusion in the MBIRA study as a bacteraemia patient, prior inclusion as a "matching patient" is not a basis for exclusion.

d) Refusal to consent to participate in MBIRA study

The MBIRA study is a research exercise, governed by the normal rules of research activity. Therefore is a patient or their guardian does not wish to be part of the study, that is their independent choice. However, the MBIRA study has been designed to be a very "light touch" research exercise – there is very little additional "burden" on the patient / their family beyond the normal activities of hospital admission. There are no additional samples being collected or extra visits to hospital. We therefore hope that, if properly explained to patients, the rate of acceptance to participate in the study will be very high – we hope >90%.

Unexpected challenges in this study are, obviously, much harder to anticipate – but there will be many of these. Please always discuss with your local site lead in the first instance and then communicate with central study co-ordinators if unable to solve locally.

25. Feedback

This second version of the MBIRA study manual was written in May 2021, while the study was in-progress across the 8 remaining study sites. We apologize again for any errors of content or sections that are (still) confusingly written. We would highly appreciate any further corrections, clarifications or requests for more information/detail on any aspects of the study, either now or at any time in the course of the study work.

Please write to alexander.aiken@lshtm.ac.uk for issues on the majority of sections in the manual.

Please additionally write to Andrew Whitelaw awhitelaw@sun.ac.za for issues relating to Microbiological aspects of the manual.

Please write to Lee.white@lshtm.ac.uk for issues relating to section 21 on reporting in the MBIRA study.

Appendix 1. "Best practices of Blood Cultures in Low- and Middle- Income Countries" 2019 paper

Appendix 2 "MBIRA study: Guide to scoring appropriate-ness of antibiotic use, v1.1"