Combatting Bacterial Resistance in Europe – *Clostridium difficile* Infections (COMBACTE-CDI)

Statistical analysis plan

Version 1.1 04/06/2019

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Sponsor:
Innovative Medicines Initiative 2 (part of Horizon 2020).

Contents

1. Introduction

This statistical analysis plan (SAP) is to provide a description of the study design, study variables, and statistical analysis methods for the COMBACTE-CDI study, which aims to develop a detailed understanding of the epidemiology and clinical impact of CDI. More specifically, this project's objectives are to:

- Align and understand the unmet public health needs relating to CDI;
- Identify and quantify the direct and long-term burden of CDI on healthcare systems

The COMBACTE CDI case/control studyfollows a cohort of patients identified during the COMBACTE CDI sample collection study. The sample collection study involved 119 sites from 12 countries from Europe, with a national coordinator recruited for every country. National coordinators selected participating sites (PS) to cover all major geographical regions within every country. Participating sites were recruited at a rate of one per 3 million population in all study countries. Figure 1 shows the full study design.

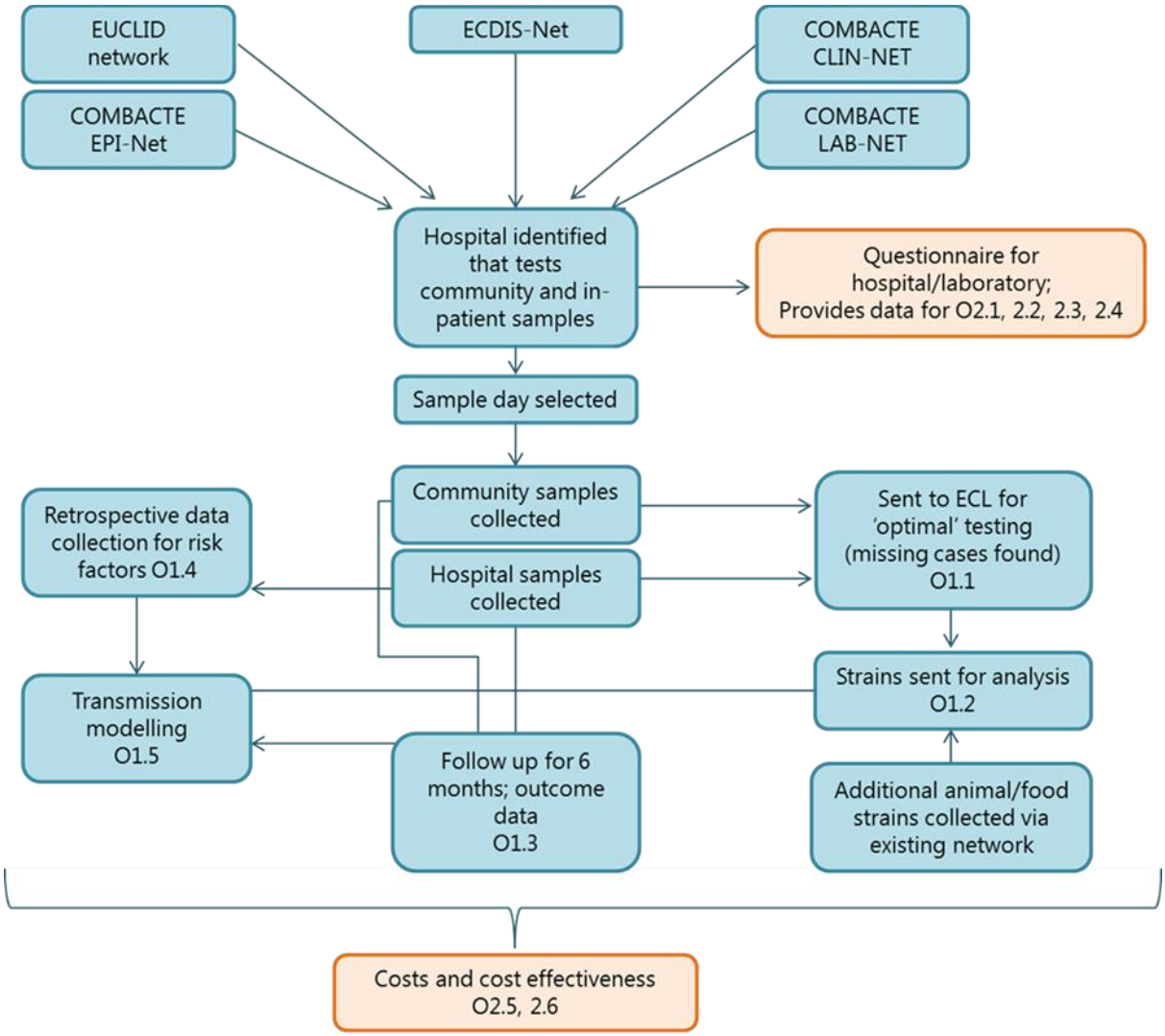

Figure 1. Schematic representation of study design (WP1 &WP2). A synergistic approach will enable completion of all the objectives from WP1 and WP2, with data created from a single, large complex study flowing into other objectives for further results analysis. Boxes in blue denote objectives in WP1, and those in orange denote for objectives in WP2. Due to the inter-related nature of the

objectives within both WP1 and WP2, the flow of work has been planned to ensure maximum outputs within the timeframe of the grant. The directions of the arrows indicates data flow and, therefore, also the timing of activities;. i.e. Strains cannot be analysed (1.2) until after they have been collected (1.1). This ambitious comprehensive project design takes influence from several existing, separate studies; the scope of producing all of these is data from one, well-designed and far-reaching study is novel and innovative.

During the COMBACTE-CDI sample collection study, cases and controls were identified;
Multiple diagnostic definitions of a case;

- Case defined as C. difficile toxin positive (gold standard method – CCNA) positive
- Case defined as C. difficile toxin positive (new novel method –SIMOA)
- Case defined as free toxin negative but positive for a cytotoxigenic strain (by culture or detection of toxin gene)
- Control defined as negative by all assays

This enriched case/control study will provide data on the difference in severity of CDI and the risks and outcomes for these different 'diagnostic types'. There are a paucity of data on these differences, particularly with regard to the new technology of the SIMOA assay. A retrospective CDI case-control study is proposed to determine the outcomes and risk factors for CDI, but different diagnostic criteria, for patients both within the hospital setting and in the community.

Ethical and regulatory approvals are in place for each site within the case/control study, as per the COMBACTE-CDI full study protocol.

2. Data source

Retrospective case note data is collected on paper case report forms (CRFs) before upload onto an electronic data management system by the European coordinator.

2.1 Selection of case and controls (total possible to be recruited)

		Location of participant at time of sample		
Diagnostic categories:		Hospital	Community	TOTAL
CDI positive cases	1. CCNA positive	83	20	103
	2. CCNA negative/Simoa positive	49	22	71
	3. CCNA and Simoa negative but CTC positive or bioFire pos	24	15	39
CDI negative controls	4. Negative control *	365	147	512
Total number selected for case/control study		521	204	**725**

Table1. The total number of samples selected for the case/control study (n=725). The table shows the number of CDI positive cases according to the indicated diagnostic categories (1-3, n=213) and by location of participant (Hospital n=156, Community n=57). Negative controls (4, n=512) were selected at a rate of 1:3 from matching participating sites (one case to three controls). As some participating sites had less than 3 controls per case, average rate was of 1:2.4 (one case to 2.4 controls) (*).

2.3 Data to be collected

A clinical report form will be completed for each patient following collection of the patient notes. For a full list of variables please see attached table in appendix 1.

2.4 Timeline

Sample collection period: Summer/Winter 2018
CRF collection period ends: June 2019
Data upload and verification: June 2019
Analysis and Write up: September 2019

2.5. Analysis objectives

The main objectives of the analyses are to;

1. Determine the outcomes of cases (of each classification) vs controls, and compare between countries and hospital vs community cases

2. Determine the risk factors for cases (of each classification) vs controls, and compare between countries and hospital vs community cases

3. Sample size

Based on a previous risk factor study using a similar study design (ORCHID) the following power calculations were made;

Age >65; previously found 65% in cases and 39% in controls. Comparing proportions for equivalence, a sample size of 20 cases and 60 controls would give 80% power to detect a difference of 23% between cases and controls with an α type one error rate of 5%.

At least one antibiotic; previously found 67% in cases and 45% in controls. Comparing proportions for equivalence, a sample size of 23 cases and 67 controls would give and 80% to detect a difference of 22% between cases and controls with an α type one error rate of 5%.

At least one antibiotic; alternative single centre cohort found 85% in cases and 75% in controls. Comparing proportions for equivalence, a sample size of 92 cases and 276 controls would give and 80% to detect a difference of 13% between cases and controls with an α type one error rate of 5%.

Previous surgery; previously found 26% in cases and 16% in controls. Comparing proportions for equivalence, a sample size of 156 cases and 469 controls would give and 80% to detect a difference of 10% between cases and controls with an α type one error rate of 5%.

Previous surgery; alternative single centre cohort previously found 41% in cases and 28% in controls. Comparing proportions for equivalence, a sample size of 88 cases and 351controls would give and 80% to detect a difference of 13% between cases and controls with an α type one error rate of 5%.

4. Study Design

This is case-control study with the cases and controls selected from the patients who had stool samples tested for CDI. The study will collect data on cases/controls (1:3 ratio) identified during the sample collection phase of COMBACTE-CDI.

For each case of confirmed CDI (or other diagnostic criteria), three controls will be randomly selected from the same participating site (i.e. if hospital case, controls will come from the same hospital, if community case, controls will come from the community). Thus initially the controls are only matched on location only, as the cohort is not large enough to enable closer matching. Subsequent further matching (e.g. by age) may be considered depending on final available sample size, but this would reduce the overall pool of controls substantially.

4.1 Inclusion-exclusion criteria

4.1.1 Inclusion criteria

1. A case is defined as a patient who;
    a. had a *C. difficile* toxin positive (gold standard method – CCNA) stool sample
    b. had a *C. difficile* toxin positive (new novel method –SIMOA) stool sample
    c. had a free toxin negative stool sample but was positive for a cytotoxigenic strain (by culture or detection of toxin gene)
2. A Control is defined as a patient who had a sample included int eh sample collection study but tested negative by all assays

4.1.2 Exclusion criteria

1. Patients outside of the COMBACTE-CDI sample collection study

2. Patients with a GDH positive/toxin negative sample during the sample collection study

4.1.5 Definition of controls

Patients with CDI positive samples within the 8 weeks previous or subsequent to the Index sample date will be excluded from the control cohort, after receipt of the CRF. The target case/control ratio is 1:3, though there may be variability in this ratio due to site sample size.

4.2 Analysis sets and subgroups

Data will be analysed to determine the outcomes and possible risk factors for CDI based on the different diagnostic criteria. Comparisons will be made between outcomes and risks for different countries and healthcare settings (hospital, community). Sample size will be too small to perform subgroup analysis within each country.

5. Handling of missing values and other data conventions

Where data is unknown, 'data unavailable' will be entered onto the data management system. Patterns of missing data will be described. Where an individual has a missing value for one of the study outcomes, they will be excluded from the analysis of that outcome. Sensitivity analysis can be used to determine the potential effect of missing data.

6. Outcome and key variables

6.1. Outcome

The outcome CDI is defined as either;

1. a diarrhoeal sample that is *C. difficile* toxin positive using the gold standard method – CCNA
2. a diarrhoeal sample that is *C. difficile* toxin positive using a new novel method (SIMOA)
3. a diarrhoeal sample that is positive for a toxigenic isolates of *C. difficile* (by either cytotoxigenic culture of toxin gene testing) AND is negative for free toxin

6.2. Key variables

The following is a partial list of variables that will be collected, measured and included as potential risk factors of the analysis.

- Demographic information including age, gender, etc.
- Laboratory testing for other enteric pathogens
- Medical conditions as independent variables and as a variable based on the Charleson comorbidity index (medical conditions included are listed in appendix 1)
- Medication used including antibiotics, proton pump inhibitors, drugs affecting the gastrointestinal tract, systemic steroids or immunosuppressive drugs
- Medical procedures including acute or elective surgery and GI interventions

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A detailed list of the variables and definition of the variables is attached as appendix 1.

6.3. Study period and important time points.

The study period is June 2018-June 2019.

The index date for the cases is defined as the date of the stool sample collection (either June/July 2018 or Oct/Nov 2019).

The index date for the controls is defined as the date of the stool sample collection either June/July 2018 or Oct/Nov 2019).

Queries within the CRF relate to that patients episode, with reference to the six months prior and six months subsequent to the index sample.

7. Statistical methodology and statistical analysis

7.1 Descriptive analysis

Distribution of demographic, concomitant pathogens, medical conditions, medical procedures, and medication used will be tabulated by case and controls. The analysis will also be stratified by age group (<18, 18-49 years, 50+ 50-64 years, 65 +, 65--84 years, and 85 + years).

Where data are continuous variables, means and standard deviations will be presented; where these data have a highly skewed distribution, medians, 25th and 75th percentiles will be presented. Where data are categorical variables, the number and percentage of participants within each category will be presented. The percentage of missing values will be reported for each variable (continuous or categorical).

7.2 Univariate analysis

Univariate analysis will be used to assess outcomes and risk factors; continuous variables will be compared between cases and controls by t-test; categorical variables will be compared between cases and controls by chi-squared (fishers exact where numbers are below 5). Risk ratios (Odds ratio if it is case control study) will be calculated for CDI cases with identified variables of interest. Univariate analysis will be used to assess consistency between countries and between different healthcare settings.

The variables to be included in the univariate analysis are shown in the table in appendix 1.

7.3 Regression analysis (or Multivariate analysis)

To evaluate risk factors considering confounding, unconditional logistic regression analysis will be perform with case/control as dependent variable, and all variables listed in the univariate analysis as independent variables.

To build the logistic regression model, we will apply a stepwise forward selection to identity risk factors. The process of the forward selection will be recorded to rank the risk factor.

The regression analysis will be performed separately for the three age groups (18-49,50-64 and 65+ years). If there is a reasonable sample size analysis will also be performed for the age group <18 years.

8. QC plans

All data will be double checked on the paper CRF by the receiving EC before upload into datbase. Data queries will be referred back to the originating hospital. Data will also be double checked as it is entered from the paper CRF onto the electronic data management system. Any further data queries generated upon data entry will be referred back to the originating hospital. Records of all data queries and responses will be held by the EC.

Appendix 1. Variable description table

Item Number	Data Item	Definition of variable	Analysis type	Time window
	Study ID			
1. Patient Demographics				
1.1	Age of patient at time of sample	Continuous	Univariate/multivariate	Patient admission when the sample was taken
1.2	Gender of patient	Binary	Univariate/multivariate	Patient admission when the sample was taken
1.3	Date of sample in COMBACTE	N/A		
1.4	Location of the patient at time of sample	Categorical	Univariate/multivariate	Patient admission when the sample was taken
2. Admission History				
2.1	If the sample was taken as a hospital inpatient Reason for admission	Categorical	Univariate/multivariate	Patient admission when the sample was taken
2.1.1	Date of admission	Number of days between admission and index sample is Continuous	Univariate/multivariate	Patient admission when the sample was taken
2.1.2	Admitting specialty	Categorical Patient admission when the sample was taken	Univariate/multivariate	Patient admission when the sample was taken
2.2	Did the patient move wards during their admission	Categorical	Univariate/multivariate	Patient admission when the sample was taken
2.2.1	If yes, please complete the table	Number of days between admission and movement is	Univariate/multivariate	Patient admission when the sample was taken

		Continuous		
2.3	If the sample was taken as a hospital inpatient Where was patient admitted from	Categorical	Univariate/multivariate	Patient admission when the sample was taken
2.4	If the sample was taken as a hospital inpatient Where was the patient discharged to	Categorical	Univariate/multivariate	Patient admission when the sample was taken
2.5	If the sample was taken in the community patient Reason for GP appointment	Categorical	Univariate/multivariate	Patient admission when the sample was taken
2.6	Did the patient have contact with a healthcare facility 6 months prior to the sample being taken?	Binary	Univariate/multivariate	Up to 6 months previous to sample
2.6.1	If yes and the visit was >24 hours, please complete the table below	Categorical	Univariate/multivariate	Up to 6 months previous to sample
2.6.2	If yes, because the patient had regular outpatient appointments, please complete the table below Frequency of visits - nature of visits	Categorical	Univariate/multivariate	Up to 6 months previous to sample
2.7	Did the patient receive any supportive measures/domestic help by friends or relatives during the presence of CDI?	Binary	Univariate/multivariate	Patient admission when the sample was taken

2.7.1	If yes, how many hours per day?	Continuous	Univariate/multivariate	Patient admission when the sample was taken
2.8	Did the patient receive any supportive measures/domestic help by professionals during the presence of CDI?	Binary	Univariate/multivariate	Patient admission when the sample was taken
2.8.1	If yes, how many hours per day?	Continuous	Univariate/multivariate	Patient admission when the sample was taken
2.9	Were any CDI related purchases necessary?	Binary	Univariate/multivariate	Patient admission when the sample was taken
2.9.1	If yes, please describe below	Categorical	Univariate/multivariate	Patient admission when the sample was taken
3. Laboratory Testing				
3.1	Did the patient have any test for other enteric pathogens up to 7 days before or up to 7 days after the EUCLID sample was taken	Binary	Univariate/multivariate	Patient admission when the sample was taken
3.1.1	If yes please indicate test results	Categorical	Univariate/multivariate	Patient admission when the sample was taken
3.2	What was the local policy for repeat testing of patients with CDI (at the time of the sample)	Binary (repeat or not repeat)	Univariate/multivariate	Patient admission when the sample was taken
4. CDI Testing				
4.1	Was the patient tested for CDI due to diarrhoea in the 6 months before the index sample	Binary	Univariate	Up to 6 months previous to the sample
4.1.1	If yes, date of sample and result of tests	Number of days between sample and	Univariate	Up to 6 months previous to the sample

		test is Continuous Result of test is Categorical		
4.2	Did the patient have a diarrhoea episode in the 6 months following the index sample	Binary	Univariate	Up to 6 months after the sample
4.3	Was the patient tested for CDI in the 6 months following the index sample	Binary	Univariate	Up to 6 months after the sample
4.3.1	If yes, date of sample and result of tests	Number of days between sample and test is Continuous Result of test is Categorical	Univariate	Up to 6 months after the sample
4.4	Was the *Clostridium difficile* sent for ribotyping?	Binary	Univariate	Patient admission when the sample was taken
4.5	Was the severity of CDI graded?	Binary	Univariate	Patient admission when the sample was taken
4.5.1	If yes, please record the severity of CDI	Categorical	Univariate/multivariate	Patient admission when the sample was taken
4.6	Has the patient **ever** had CDI	Binary	Univariate	Patient admission when the sample was taken
5. Clinical Information				
5.1	Temperature (highest reading +/- 3 days of the index sample)	Continuous	Univariate	Patient admission when the sample was taken
5.2	Serum creatinine (highest reading +/- 3 days of the index sample)	Continuous	Univariate	Patient admission when the sample was taken
5.3	White cell count	Continuous	Univariate	Patient admission

	(highest +/-3 days of the index sample)			when the sample was taken
5.4	Serum Albumin (lowest +/-3 days of the index sample)	Continuous	Univariate	Patient admission when the sample was taken
5.5	Primary diagnoses at time of index sample	Categorical	Univariate	Patient admission when the sample was taken
5.6	Does the patient have any significant illnesses	Binary	Univariate	Patient admission when the sample was taken
5.6.1	If yes, are the illnesses: Acute/chronic	Categorical	Univariate	Patient admission when the sample was taken
5.6.2	Please provide details of the significant illness	Categorical	Univariate	Patient admission when the sample was taken
5.7	**Co-morbidities**		**All of these could be Covariates**	
	Myocardial infarction	Binary	Univariate/multivariate	Patient admission when the sample was taken
	Congestive heart failure	Binary	Univariate/multivariate	Patient admission when the sample was taken
	Peripheral vascular disease	Binary	Univariate/multivariate	Patient admission when the sample was taken
	Cerebrovascular disease	Binary	Univariate/multivariate	Patient admission when the sample was taken
	Dementia	Binary	Univariate/multivariate	Patient admission when the sample was taken
	COPD	Binary	Univariate/multivariate	Patient admission when the sample was taken
	Peptic Ulcer disease	Binary	Univariate/multivariate	Patient admission when the sample was taken
	Cystic fibrosis	Binary	Univariate/multivariate	Patient admission when the sample was taken
	Diabetes without organ damage	Binary	Univariate/multivariate	Patient admission when the sample

				was taken
	Leukaemia within last 5 years	Binary	Univariate/multivariate	Patient admission when the sample was taken
	Solid tumour within last 5 years	Binary	Univariate/multivariate	Patient admission when the sample was taken
	Any other malignancy within last 5 years	Binary	Univariate/multivariate	Patient admission when the sample was taken
	AIDS (not just HIV positive)	Binary	Univariate/multivariate	Patient admission when the sample was taken
	Pneumonia	Binary	Univariate/multivariate	Patient admission when the sample was taken
	Cardiac arrest within 7 days of sample	Binary	Univariate/multivariate	Patient admission when the sample was taken
	Date of cardiac arrest	Number of days between cardiac arrest and sample is Continuous	Univariate/multivariate	Patient admission when the sample was taken
	HIV positive	Binary	Univariate/multivariate	Patient admission when the sample was taken
	Hemiplegia	Binary	Univariate/multivariate	Patient admission when the sample was taken
	Mental disorientation	Binary	Univariate/multivariate	Patient admission when the sample was taken
	Connective tissue disease	Binary	Univariate/multivariate	Patient admission when the sample was taken
	Mild liver disease	Binary	Univariate/multivariate	Patient admission when the sample was taken
	Diabetes with organ damage	Binary	Univariate/multivariate	Patient admission when the sample was taken
	Lymphoma within last 5 years	Binary	Univariate/multivariate	Patient admission when the sample was taken

	Chemotherapy in preceding 12 weeks to index sample	Binary	Univariate/multivariate	Patient admission when the sample was taken
	Renal replacement therapy (eg. Dialysis) within 7 days of sample	Binary	Univariate/multivariate	Patient admission when the sample was taken
	Chronic kidney disease	Binary	Univariate/multivariate	Patient admission when the sample was taken
	Radiotherapy in preceding 12 weeks to index sample	Binary	Univariate/multivariate	Patient admission when the sample was taken
	Moderate or severe liver disease	Binary	Univariate/multivariate	Patient admission when the sample was taken
	UTI	Binary	Univariate/multivariate	Patient admission when the sample was taken
	Transplant	Binary	Univariate/multivariate	Patient admission when the sample was taken
	Other	Binary	Univariate/multivariate	Patient admission when the sample was taken
5.8	Patient gastrointestinal symptoms at time of index sample	Categorical	Univariate	Patient admission when the sample was taken
5.9	Was there an alternative cause for the patients diarrhoea	Binary	Univariate	Patient admission when the sample was taken
5.9.1	If yes please give details	Categorical	Univariate	Patient admission when the sample was taken
5.10	Duration of diarrhoea before and after the index sample	Number of days of diarrhoea is Continuous	Univariate	Patient admission when the sample was taken
5.11	Did the patient undergo any diagnostic procedures for this episode of CDI?	Binary	Univariate	Patient admission when the sample was taken
5.11.1	If yes, please complete the table	Categorical	Univariate	Patient admission when the sample

				was taken
5.12	Evidence of colitis	Binary	Univariate	Patient admission when the sample was taken
5.12.1	If yes please give details	Categorical	Univariate	Patient admission when the sample was taken
5.13	Was the patient in contact with a diagnosed *Clostridium difficile* case in the preceding 3 months to the sample?	Binary	Univariate	Patient admission when the sample was taken
5.13.1	If yes please give the date	Categorical	Univariate	Patient admission when the sample was taken
5.14	Was the patient in kissing contact of an infant in the preceding 3 months to the sample?	Binary	Univariate	Patient admission when the sample was taken
5.14.1	If yes please give the date	Categorical	Univariate	Patient admission when the sample was taken
5.15	Did the patient receive mechanical ventilation	Binary	Univariate	Patient admission when the sample was taken
5.15.1	If yes, please give the duration of the ventilation in minutes	Continuous	Univariate	Patient admission when the sample was taken
5.16	Was the patient source isolated due to CDI	Binary	Univariate	Patient admission when the sample was taken
5.16.1	If yes, please give the duration of source isolation in days	Continuous	Univariate	Patient admission when the sample was taken
5.16.2	Did the patient in source isolation lead to the blocking of beds	Binary	Univariate	Patient admission when the sample was taken
5.16.3	If yes, how many beds were blocked during that time?	Continuous	Univariate	Patient admission when the sample was taken
6. Drug History				

6.1	Was the patient prescribed **treatment for CDI** at the time or after the sample	Binary	Univariate/multivariate	Patient admission when the sample was taken
6.1.1	If Yes please complete table	Class of antibiotic is Categorical Number of dates of treatment is Continuous Indication is Categorical Route is Categorical	Univariate/multivariate Univariate/multivariate Univariate/multivariate Univariate/multivariate	Patient admission when the sample was taken
6.2	Was the patient prescribed antibiotics for an infection **other than CDI (or for prophylaxis)** in the 12 weeks preceding the index sample	Binary	Univariate/multivariate	Up to 12 weeks previous to the sample
6.2.1	If Yes please complete table	Class of antibiotic is Categorical Number of dates of treatment is Continuous Indication is Categorical Route is Categorical	Univariate/multivariate Univariate/multivariate Univariate/multivariate Univariate/multivariate	Up to 12 weeks previous to the sample
6.3	Did the patient have proton pump inhibitors in the 12 weeks preceding the index sample	Binary	Univariate/multivariate	Up to 12 weeks previous to the sample
6.3.1	If yes please	Name of PPI	Univariate/multivariate	Up to 12 weeks

	complete the table	is Categorical Number of dates of treatment is Continuous Indication is Categorical Route is Categorical	Univariate/multivariate Univariate/multivariate Univariate/multivariate	previous to the sample
6.4	Has the patient had any drugs which affect the gastrointestinal tract in the 12 weeks preceding the index sample	Binary	Univariate/multivariate	Up to 12 weeks previous to the sample
6.4.1	If yes please complete the table	Name of drug is Categorical Number of dates of treatment is Continuous Indication is Categorical Route is Categorical	Univariate/multivariate Univariate/multivariate Univariate/multivariate Univariate/multivariate	Up to 12 weeks previous to the sample
6.5	Has the patient had systemic steroids or other systemic immunosuppressive drugs in the 12 weeks preceding the index sample	Binary	Univariate/multivariate	Up to 12 weeks previous to the sample
6.5.1	If yes please complete the table	Name of drug is Categorical Number of dates of	Univariate/multivariate Univariate/multivariate Univariate/multivariate	Up to 12 weeks previous to the sample

		treatment is Continuous Indication is Categorical Route is Categorical	Univariate/multivariate	
7. CDI treatment escalation				
7.1	Did the patient require change/escalation of CDI medication	Binary	Univariate/multivariate	Patient admission when the sample was taken
7.1.1	If yes please complete the table below	Name of drug is Categorical Number of dates of treatment is Continuous Indication is Categorical Route is Categorical	Univariate/multivariate Univariate/multivariate Univariate/multivariate Univariate/multivariate	Patient admission when the sample was taken
7.2	Did the patient require change/escalation of surgical management	Binary	Univariate/multivariate	Patient admission when the sample was taken
7.2.1	If yes please complete the table	Name of drug is Categorical Number of dates of treatment is Continuous Indication is Categorical Route is Categorical	Univariate/multivariate Univariate/multivariate Univariate/multivariate Univariate/multivariate	Patient admission when the sample was taken
8. Surgery				

8.1	Has the patient had any surgery in the 12 weeks preceding the index sample	Binary	Univariate/multivariate	Up to 12 weeks previous to the sample
8.1.1	If yes was it Elective or Acute	Binary	Univariate/multivariate	Up to 12 weeks previous to the sample
8.1.2	Please complete table	Type of surgery is Categorical Number of days between surgery and sample is Continuous	Univariate/multivariate Univariate/multivariate	Up to 12 weeks previous to the sample
9. GI Interventions				
9.1	Has the patient had any GI interventions or diagnoses in the 12 weeks preceding the index sample	Binary	Univariate/multivariate	Up to 12 weeks previous to the sample
9.1.1	If yes please complete the table	Type of intervention is Categorical Number of days between intervention and sample is Continuous	Univariate/multivariate Univariate/multivariate	Up to 12 weeks previous to the sample
10. Outcomes				
If the sample was taken as a hospital inpatient				
10.1	During the **30 days** after the sample was the patient, was the patient discharged	Binary Continuous (no. of days)	Univariate/multivariate Univariate/multivariate	Up to 30 days after the index sample
10.2	Was the patient re-admitted	Binary	Univariate/multivariate	Up to 30 days after the index

				sample
10.2.1	If yes, please give the dates of subsequent hospital admissions	Continuous (no. of days)	Univariate/multivariate	Up to 30 days after the index sample
10.3	If the sample was taken as a hospital inpatient, was the patient discharged **>30 days** after the sample	Binary Continuous (no. of days)	Univariate/multivariate Univariate/multivariate	Up to six months after the index sample
If the sample was taken as a community patient				
10.4	Was the patient admitted to hospital	Binary	Univariate/multivariate	Up to 30 days after the index sample
10.4.1	If yes, please give dates of the subsequent hospital admissions	Continuous (no. of days)	Univariate/multivariate	Up to 30 days after the index sample
If the sample was taken as a hospital inpatient or a community patient				
10.5	Did the patient die in the 30 days after the sample	Binary Continuous (no. of days)	Univariate/multivariate Univariate/multivariate	Up to 30 days after the index sample
10.5.1	If yes, was the death linked to CDI	Binary	Univariate/multivariate	Up to 30 days after the index sample
10.6	Was the patient admitted to hospital between 30 days and 6 months after the sample	Binary	Univariate/multivariate	Up to six months after the index sample
10.6.1	If yes, please give the dates of hospital admissions	Continuous (no. of days)	Univariate/multivariate	Up to six months after the index sample
10.7	Did the patient die between 30 days and 6 months after sample?	Binary Continuous (no. of days)	Univariate/multivariate Univariate/multivariate	Up to six months after the index sample
10.7.1	If yes, was the death linked to CDI	Binary	Univariate/multivariate	Up to six months after the index

				sample