AnTIC Primary Outcome Assessment Procedure

1. Purpose

The purpose of this document is to set out the method used to verify the reports of symptomatic antibiotic treated UTI (primary outcome) by participants and local research staff. The data reviewers were unaware of the allocated arm (blinded).

2. Definitions

Primary outcome

The primary outcome for the study is defined as "symptomatic, antibiotic treated UTI". This includes description of at least one symptom and indication that a course of antibiotic active against common uropathogens was taken.

Episodes of UTI

The end of a single UTI has been defined as 14 days after the end of the final treatment course. If a further course of antibiotics was prescribed before the end of 14 days, this was not counted as a separate episode.

3. Hierarchy of Data Sources

Data Source	**Identification on UTI summary sheet (see Appendix 1)**
1. Participant UTI Record returned by participant to central trial office	Participant UTI Log – participant led primary outcome attribution
2. Contact with each participant at least every three months by local trial staff and recording of participant reported symptomatic, antibiotic treated UTI in the study database	One month researcher led attribution of primary outcome Three month researcher led attribution of primary outcome
3. Review of hospital and primary care record every three months by local trial staff and recording of any antibiotic treated UTI in the study database	3 monthly healthcare record review
4. Participant completed questionnaires at 3, 6, 9, and 12 months asking for details of episodes of antibiotic treated UTI.	Participant Questionnaire
5. Review of central and local lab data to confirm if reported episodes of UTI are also microbiologically confirmed (secondary outcome).	Central lab data

4. Process

Step 1 – Review of UTI summary sheets

Data from all data sources were extracted and combined on a UTI summary sheet for each participant (Appendix 1).

The summary sheets were reviewed and individual episodes of UTI identified. Each identified episode was marked on the sheet with a number from 1 upwards. If a UTI was reported in more than one data source it was given the same number to avoid double counting. If there were less than 14 days between UTI episodes these were counted as the same episode and also given the same number. Occurrence of secondary UTI outcomes were concurrently checked.

For ease of matching duplicate UTI episodes the number of days from randomisation to antibiotic start date, or date sample received in the central lab, was calculated and added to the summary sheet.

Step 2 – Transfer of UTI data to Primary/Secondary Outcomes Data Sheet

Data from the completed UTI summary sheet was transferred to the Primary/Secondary Outcomes Data Sheet (Appendix 2). Each episode, whether a primary outcome, secondary outcome or both, was entered in numerical order with one episode per line as follows:

Heading	**Heading Detail**
Number	Episode number
UTI_Start	Symptoms start date
AB_Start	Date antibiotic course started
AB_End	Date antibiotic course ended
AB_Days	Total number of days on antibiotics for this episode
AB_Name	Antibiotic Name. Enter code for all antibiotics taken for this episode
Primary	Does this episode meet primary outcome criteria (Yes/No)
If no, reason episode does not meet primary outcome (mark all that apply) (Yes/No):	
No_AB	No antibiotics recorded
No_Symp	No symptoms recorded
No_Epi	Not a separate episode
No_Oth	Other reason
Details	Details of other reason
Data source (mark all that apply) (Yes/No):	
Src_UTI	Participant UTI Log

Heading	Heading Detail
Src_CRF	One month or three monthly eCRF
Src_HCRev	Three monthly healthcare record review
Src_Qu	Participant Questionnaire
Src_Lab	Central Lab data
Does episode fulfil any secondary outcome criteria (Yes/No):	
Sec_Fever	Secondary outcome, febrile UTI
Sec_Hosp	Secondary outcome, hospitalisation for UTI
Sec_Micro	Secondary outcome, microbiologically confirmed symptomatic UTI
Sec_Presc	Secondary outcome, antibiotic prescription for asymptomatic bacteriuria
Sec_Asym	Secondary outcome, asymptomatic bacteriuria

Step 3 – Data entry of Primary/Secondary Outcomes Data Sheet into study eCRF (MACRO)

Data was entered into the Primary/Secondary Outcomes form in the study database. The fields were the same as those in the Primary/Secondary Outcomes Data sheet.

5. Special Notes

Primary outcome = yes

UTI log received **OR** participant reported UTI in 3 monthly contact **OR** Participant reported UTI in 3 monthly questionnaire.

Symptoms and antibiotic details should be present in one or more of the above sources.

Primary outcome = no

Primary outcome is **no** if data appears only in the healthcare record and/or the central lab data.

Central lab data

For asymptomatic UTI, start date is entered as date sample received at lab on the Outcome Data Sheet.

Total time on antibiotics

If UTI log states a 7 day course, those dates to be taken.

If there is more than one report of an episode and dates are inconsistent the dates in the healthcare record should be used.

Start and end date of antibiotic may not equal no. of days on antibiotics (if more than one antibiotic taken there may be a gap of a few days between antibiotics), only count the number of days on each antibiotic. If days overlap only count that day once.

6. Secondary outcomes

Febrile UTI

If health care record review states fever recorded for a symptomatic antibiotic treated UTI, 'Sec_Fev' on data sheet will be "yes". Local site staff are asked to record fever if 38^{o}C or over.

Hospitalisation due to UTI

Defined as an unplanned visit to hospital for treatment of a UTI which required at least one overnight stay in hospital. This information is not included in the Primary/Secondary Outcome Summary Sheet and will be assessed separately and then added to the Primary/Secondary Outcome eCRF.

Microbiologically-confirmed symptomatic UTI

Primary outcome measure combined with a positive urine culture from the central (or local site) laboratory. If primary outcome is 'yes' and Health care record review and/or central lab data show growth and isolate 'Sec_Micro' will be 'yes'.

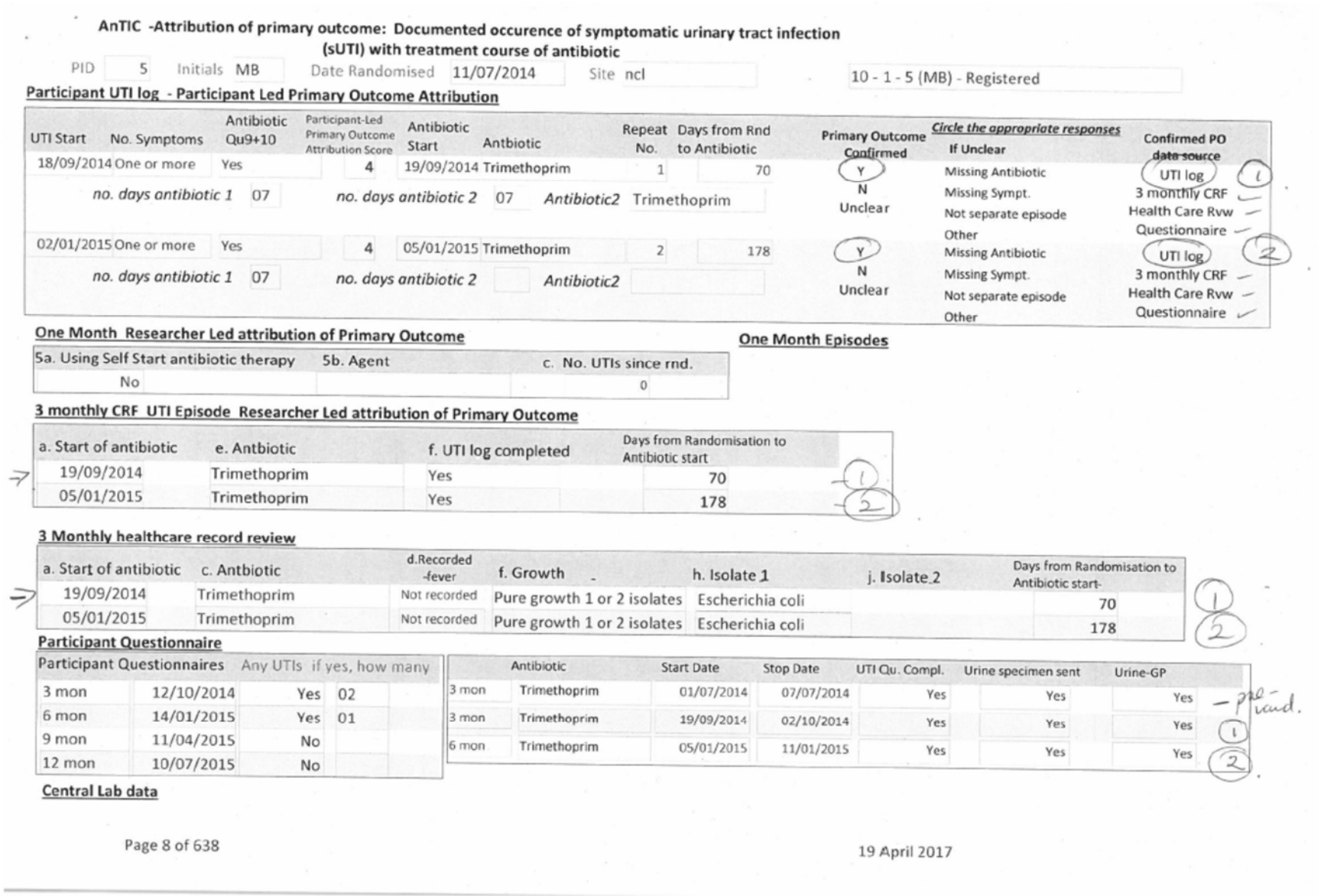
Antibiotic prescription for asymptomatic UTI

Antibiotic prescription given for UTI without a participant or clinician recorded symptomatic UTI, i.e. antibiotic recorded in health care record review only, combined with positive urine culture. In this case 'Sec_Presc' will be 'yes'

Asymptomatic bacteriuria

Positive urine culture from either the central or local site lab but no report of UTI by the participant or local site. In this case 'Sec_Asym' will be 'yes'.

Appendix 1: Example of completed UTI Summary Sheet



AnTIC -Attribution of primary outcome: Documented occurence of symptomatic urinary tract infection (sUTI) with treatment course of antibiotic

PID 5 Initials MB Date Randomised 11/07/2014 Site ncl 10 - 1 - 5 (MB) - Registered

Participant UTI log - Participant Led Primary Outcome Attribution

UTI Start	No. Symptoms	Antibiotic Qu9+10	Participant-Led Primary Outcome Attribution Score	Antibiotic Start	Antbiotic	Repeat No.	Days from Rnd to Antibiotic	Primary Outcome Confirmed	Circle the appropriate responses: If Unclear	Confirmed PO date source
18/09/2014	One or more	Yes	4	19/09/2014	Trimethoprim	1	70	Y	Missing Antibiotic	UTI log (1)
	no. days antibiotic 1 07		*no. days antibiotic 2* 07	*Antibiotic2*	Trimethoprim			N	Missing Sympt.	3 monthly CRF
								Unclear	Not separate episode	Health Care Rvw
									Other	Questionnaire
02/01/2015	One or more	Yes	4	05/01/2015	Trimethoprim	2	178	Y	Missing Antibiotic	UTI log (2)
	no. days antibiotic 1 07		*no. days antibiotic 2*	*Antibiotic2*				N	Missing Sympt.	3 monthly CRF
								Unclear	Not separate episode	Health Care Rvw
									Other	Questionnaire

One Month Researcher Led attribution of Primary Outcome

5a. Using Self Start antibiotic therapy	5b. Agent	c. No. UTIs since rnd.
No		0

One Month Episodes

3 monthly CRF UTI Episode Researcher Led attribution of Primary Outcome

a. Start of antibiotic	e. Antbiotic	f. UTI log completed	Days from Randomisation to Antibiotic start	
19/09/2014	Trimethoprim	Yes	70	(1)
05/01/2015	Trimethoprim	Yes	178	(2)

3 Monthly healthcare record review

a. Start of antibiotic	c. Antbiotic	d.Recorded -fever	f. Growth	h. Isolate 1	j. Isolate 2	Days from Randomisation to Antibiotic start	
19/09/2014	Trimethoprim	Not recorded	Pure growth 1 or 2 isolates	Escherichia coli		70	(1)
05/01/2015	Trimethoprim	Not recorded	Pure growth 1 or 2 isolates	Escherichia coli		178	(2)

Participant Questionnaire

Participant Questionnaires		Any UTIs	if yes, how many
3 mon	12/10/2014	Yes	02
6 mon	14/01/2015	Yes	01
9 mon	11/04/2015	No	
12 mon	10/07/2015	No	

	Antibiotic	Start Date	Stop Date	UTI Qu. Compl.	Urine specimen sent	Urine-GP	
3 mon	Trimethoprim	01/07/2014	07/07/2014	Yes	Yes	Yes	– pre-rand.
3 mon	Trimethoprim	19/09/2014	02/10/2014	Yes	Yes	Yes	(1)
6 mon	Trimethoprim	05/01/2015	11/01/2015	Yes	Yes	Yes	(2)

Central Lab data

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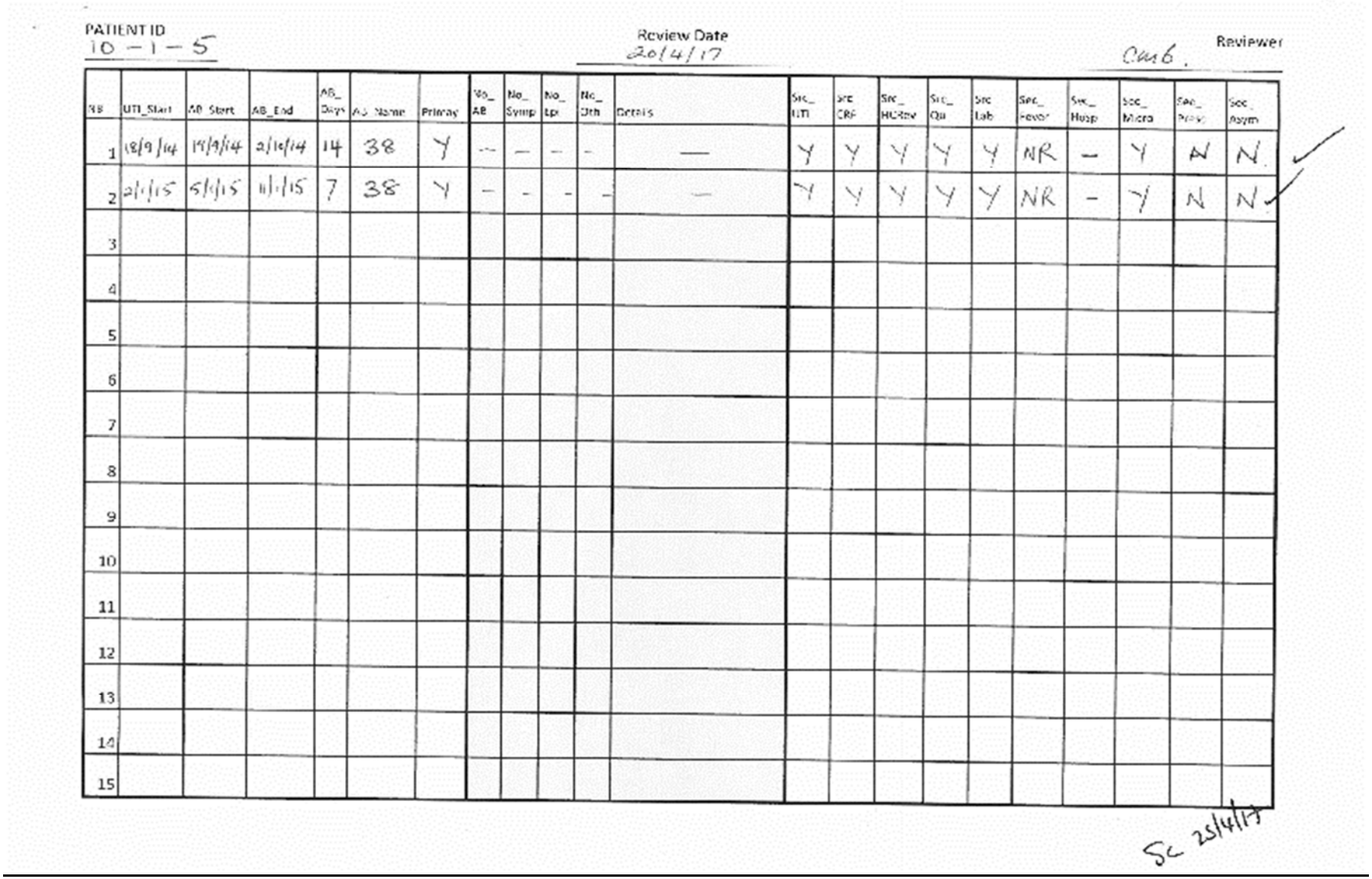
AnTIC -Attribution of primary outcome: Documented occurence of symptomatic urinary tract infection (sUTI) with treatment course of antibiotic

PID 5 Initials MB Date Randomised 11/07/2014 Site ncl 10 - 1 - 5 (MB) - Registered

Sample Collection	Growth	Isolate	Repeat No.	Days from Randomisation to sample collctn.	
11/07/2014	No Growth		2	0	
22/09/2014	Pure growth 1 or 2 isolates	Escherichia coli	3	73	(1)
06/01/2015	Pure growth 1 or 2 isolates	Escherichia coli	6	179	(2)
09/02/2015	No Growth		7	213	
13/07/2015	No Growth		8	367	

PID 5 Initials MB Date Randomised 11/07/2014 Site ncl 10 - 1 - 5 (MB) - Registered

Appendix 2: Example of completed Primary/Secondary Outcome Data Sheet



PATIENT ID: 10 – 1 – 5

Review Date: 20/4/17

Reviewer: Cm6.

AB	UTI_Start	AB Start	AB_End	AB_Days	AB Name	Primary	No_AB	No_Symp	No_Epi	No_Oth	Details	Src_UTI	Src CRF	Src_HCRev	Src_Qu	Src Lab	Src_Fever	Src_Hosp	Src_Micro	Src_Prov	Src_Asym
1	18/9/14	19/9/14	2/10/14	14	38	Y	--	–	–	–	—	Y	Y	Y	Y	Y	NR	–	Y	N	N
2	2/1/15	5/1/15	11/1/15	7	38	Y	–	-	-	–	—	Y	Y	Y	Y	Y	NR	-	Y	N	N
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