

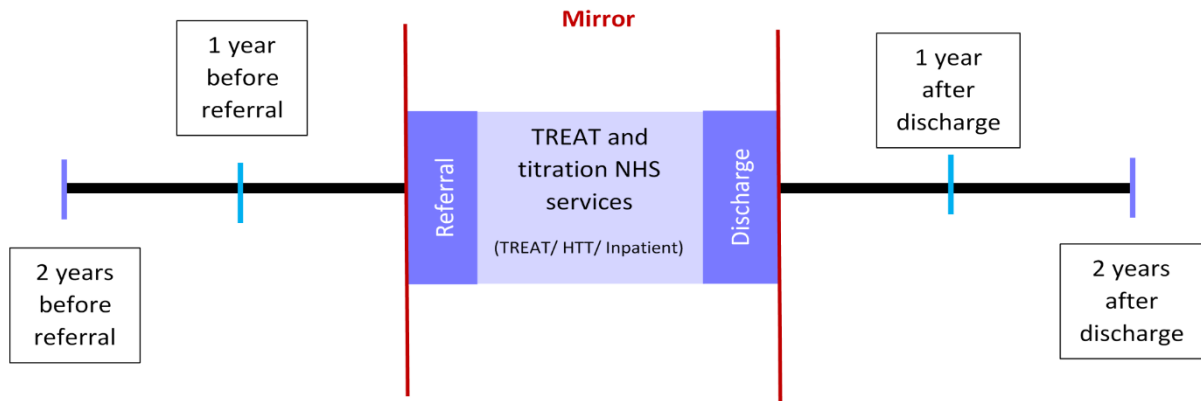
TREAT Clozapine Mirror- Supplementary

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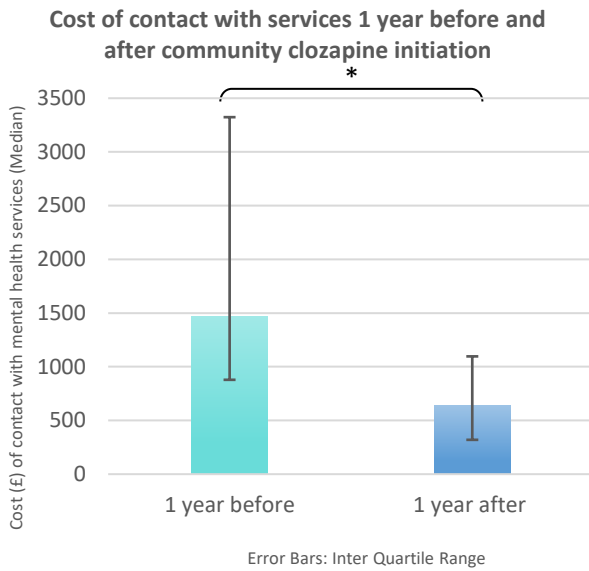
Supplementary Figure 1: Mirror Design



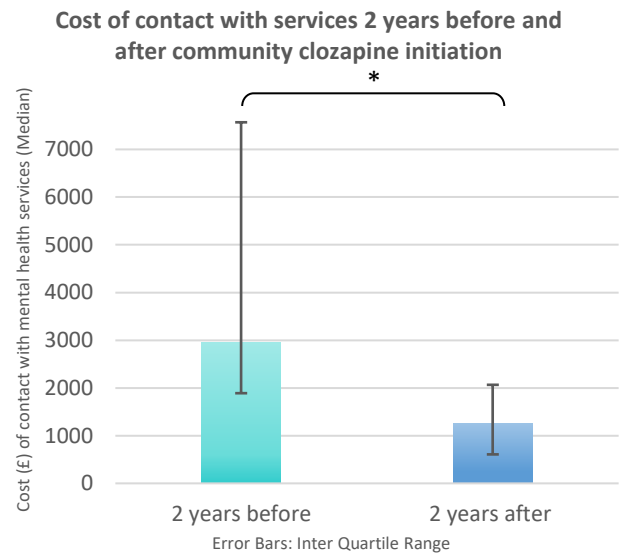
Supplementary Figure 1: Study Design - Clozapine Mirror Timeline

Supplementary Figure 2: Service Use and Cost-analysis for Community Clozapine Initiation

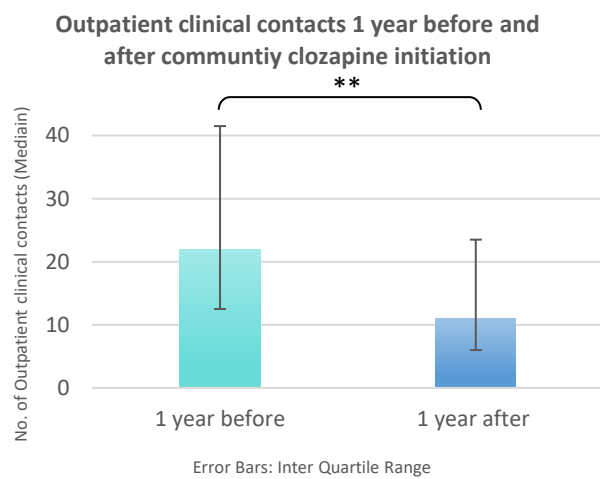
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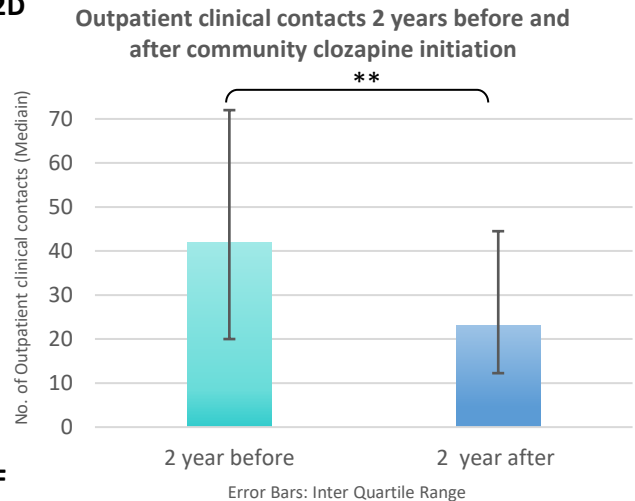
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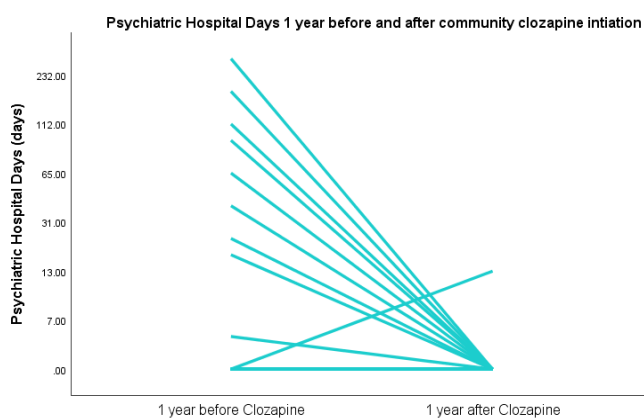
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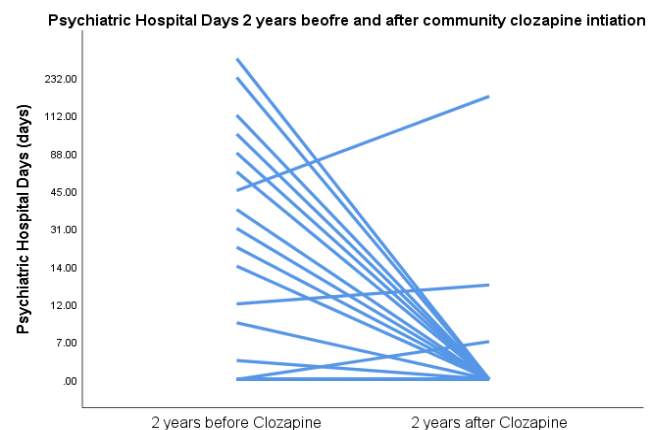
2D



2E



2F



Supplementary Figure 2: Service use data for community clozapine initiation showing a significant decrease in clinical contacts and healthcare costs in the 1 and 2 years following community clozapine initiation compared to the 1 and 2 years prior to clozapine. Error bars represent the inter-quartile range. Supplementary Figure 2A: Median Total cost of contact with mental health services for the 1 year before and after community clozapine titration (* $p=0.02$). Supplementary Figure 2B: Median Total cost of contact with mental health services for the 2 years before and after community clozapine initiation (* $p=0.01$). Supplementary Figure 2C: Median number of outpatient clinical contacts including psychiatrist, care-coordinators, nurses and psychologist visits, 1 year before and after community clozapine initiation (** $p=0.002$). Supplementary Figure 2D: Median number of outpatient clinical contacts including psychiatrist, care-coordinators, nurses and psychologist visits, 2 years before and after clozapine initiation in the community (** $p=0.005$). Supplementary Figure 2E: Patient level change in number of days spent in psychiatric hospital 1 year before and after clozapine titration in community setting, showing a significant reduction ($p<0.01$). Supplementary Figure 2F: Patient level change in number of days spent in psychiatric hospital in the 2 years before and after clozapine titration in community setting, showing a significant reduction ($p<0.01$).

Supplementary Tables

Supplementary Table 1: Community Titration Service Contra-indication Criteria

Criteria for HTT or Inpatient Titration rather than outpatient titration.

HTT	Inpatient
Inability to attend outpatient clinic due to:	
<ul style="list-style-type: none"> Mental or cognitive symptoms mean they are unable to reliably attend outpatient appointments or remember to take medication Physical health conditions mean they are unable to reliably attend outpatient appointments History of poor engagement or concordance that means they are unlikely to reliably adhere to treatment and/or monitoring 	<ul style="list-style-type: none"> Patient in active crisis (eg actively suicidal) requiring inpatient treatment Physical health condition that may be worsened by clozapine side-effects requiring close monitoring (eg poorly controlled diabetes) History of major adverse event(s) attributed to clozapine (eg agranulocytosis) requiring close monitoring

Supplementary Table 2: Frequency of Other Mental Health Associated Visits

Other visits were also recorded. Below is a table of the number of patients and cumulative frequency for each type of visit.

Supplementary Table 2: Observation frequencies of other mental health associated visits for 2 years pre and post clozapine intitation

	-2 Year		-1 Year		+1 Year		+2 Year	
	N	Frequency	N	Frequency	N	Frequency	N	Frequency
Psychology Group	2	14	3	14	6	36	2	32
Phlebotomy	2	32	5	30	32	500	25	300
Electro-convulsant Therapy	0	0	1	11	0	0	0	0
Social & Support Work	7	36	8	21	5	16	5	12
Liaison	4	4	1	1	3	5	2	3
Admin	0	0	1	4	0	0	0	0
Dietician	0	0	0	0	1	2	0	0
Speech and Language	0	0	0	0	1	1	0	0

Supplementary Table 3: Demographics

Supplementary Table 3: Demographics for Clozapine recommended sample

Demographics			
On recommendation	Mean Age (SD)	41(12.41)	
	Ethnicity		
	Black/African/Caribbean/Black British	60	38.0%
	White / European/ British	55	34.8%
	Asian / Asian British	8	5.1%
	Multiple ethnic groups	6	3.8%
	Other ethnic group	11	7.0%
	Not Stated	10	6.3%
Successful Titration	Mean Age (SD)	39 (12.5)	
	Ethnicity		
	Black/African/Caribbean/Black British	17	33.3%
	White / European/ British	21	41.2%
	Asian / Asian British	4	7.8%
	Multiple ethnic groups	4	7.8%
	Other ethnic group	2	3.9%
	Not Stated	8	15.7%
	Diagnosis		
	F20.0 Paranoid Schizophrenia	47	92.1%
	F20.0 Paranoid Schizophrenia + Learning Difficulty	1	1.96%
	F20.0 Paranoid Schizophrenia + Cerebral Palsy	1	1.96%
	F25.0 Schizoaffective Disorder	4	7.8%
	F31.0 Bipolar Disorder	1	1.96%
	F31.0 Bipolar + Post Traumatic Stress Disorder	1	1.96%
	F29 Unspecified Psychosis	1	1.96%
F42.8 Obsessive compulsive disorder + Intrusive Psychotic features	1	1.96%	
F33.3 Depression with Psychotic Features + Emotional Unstable Personality Disorder	1	1.96%	

Supplementary Table 4: Clinical Symptom and function scales across 2 year follow up

	Before Clozapine		Discharge on Clozapine		Change in Score (Wilcoxon test)		1 year follow up on Clozapine		2 year follow up on Clozapine	
	Median	IQR	Median	IQR	Z	P	Median	IQR	Median	IQR
All Clozapine Titrations										
PANSS Total	80.00	71.00-104.00	50.50	44.75-75.00	-5.01	<0.001	-	-	-	-
PANSS Positive	19.00	17.00-24.00	12.50	9.75-15.00	-5.02	<0.001	-	-	-	-
PANSS Negative	20.00	16.00-27.00	14.00	10.00-20.25	-4.32	<0.001	-	-	-	-
PANSS General	40.00	33.00-52.00	27.00	21.00-36.00	-4.80	<0.001	-	-	-	-
HONOS Total	13.00	9.00-15.00	10.00	7.00-14.00			9.00	6.00-13.00	8.00	3.00-13.00
Community Only Titrations										
PANSS Total	77.50	66.25-95.00	50.00	44.00-66.50	-4.62	<0.001	-	-	-	-
PANSS Positive	19.00	17.00-22.75	12.00	9.50-18.00	-4.63	<0.001	-	-	-	-
PANSS Negative	20.00	16.00-23.75	14.00	10.00-18.00	-3.84	<0.001	-	-	-	-
PANSS General	38.00	31.00-48.75	27.00	21.00-33.50	-4.46	<0.001	-	-	-	-
HONOS Total	12.00	8.25-14.00	10.50	6.00-13.75			9.00	5.00-13.00	7.00	2.00-12.00

Supplementary Table 5: Service Use Before and After Clozapine Titration

	1 year before Clozapine			1 year after Clozapine			Wilcoxon Rank Test 1-year Mirror Comparison				2 years before Clozapine			2 years after Clozapine			Wilcoxon Rank Test 2-year Mirror Comparison			
	Mean (SD)	Median	IQR	Mean (SD)	Median	IQR	N	Z	p	r	Mean (SD)	Median	IQR	Mean (SD)	Median	IQR	N	Z	p	r
	All Clozapine Titration																			
Total Cost of Contact (£)	10337.96 (22692.34)	1684.00	752.60-3323.60	1448.18 (2823.12)	721.80	330.00-1317.00	49	-3.790	<.001	0.54	13431.53 (25276.48)	2913.50	1213.50-10487.35	4248.95 (13920.07)	1315.40	652.00-2312.00	36	-3.930	<.001	0.66
Psychiatric Hospital Days	20.80 (54.66)	00.00	0.00-0.00	1.35 (6.30)	00.00	0.00-0.00	50	-2.480	.013	0.35	26.46 (59.07)	0.00	00.00-19.00	6.69 (33.21)	0.00	0.00-0.00	39	-2.49	.012	0.40
Psychiatric Admissions	0.37 (0.75)	00.00	0.00-0.00	0.06 (0.24)	00.00	0.00-0.00	49	-2.433	.015	0.35	0.7 (1.24)	0.00	00.00-1.00	0.21 (0.70)	0.00	0.00-0.00	37	-2.137	.033	0.35
HTT Visits	5.08 (11.73)	00.00	0.00-1.00	4.25 (15.4)	00.00	0.00-0.00	51	-0.828	.408	0.12	9.05 (19.40)	0.00	00.00-12.75	8.85 (22.68)	0.00	0.00-0.00	38	0.000	1.00	-
Outpatient Clinical Contact	27.71 (19.53)	24.00	14.00-41.00	16.80 (14.43)	13.00	5.00-24.00	51	-3.839	<.001	0.54	49.88 (33.05)	47.50	24.75-71.00	27.95 (23.89)	22.00	11.00-42.00	38	-3.712	<.001	0.60
Psychiatrist Visits	6.14 (9.00)	4.00	2.00-7.00	2.37 (2.38)	2.00	0.00-4.00	51	-4.432	<.001	0.62	10.78 (12.58)	8.00	3.00-13.00	4.10 (3.73)	3.00	1.00-7.00	38	-3.861	<.001	0.63
Nurse /CC Visits	15.39 (12.27)	14.00	6.00-24.00	10.04 (8.76)	7.00	3.00-17.00	51	-2.802	.005	0.39	30.93 (24.08)	25.00	11.00-50.00	16.59 (13.47)	16.00	3.00-26.00	38	-3.108	.002	0.50
Psychology 1:1	5.84 (8.63)	0.00	0.00-10.00	3.45 (7.55)	0.00	0.00-2.00	51	-1.938	.053	0.27	7.43 (11.26)	0.50	0.00-14.75	5.36 (9.75)	0.00	0.00-12.00	38	-0.959	.338	0.16
Psychology Groups	0.33 (1.19)	0.00	0.00-0.00	0.94	0.00	0.00-0.00	51	-1.091	.275	0.15	0.75 (2.39)	0.00	0.00-0.00	1.90 (7.41)	0.00	0.00-0.00	38	-0.432	.666	0.07
Occupation Health	2.61 (6.35)	0.00	0.00-1.00	2.00 (5.90)	0.00	0.00-0.00	51	-0.746	.456	0.10	4.6 (8.39)	0.00	0.00-6.50	3.90 (9.31)	0.00	0.00-1.00	38	-0.840	.401	0.14
Social Support	2.63 (6.35)	0.00	0.00-1.00	2.27 (6.12)	0.00	0.00-1.00	51	-1.311	.190	0.18	2.14 (5.41)	0.00	0.00-2.00	0.96 (2.15)	0.00	0.00-1.00	38	-1.736	.083	0.28
Community only titrations																				
Total Cost of Contact (£)	9772.82 (22981.66)	1466.40	588.00-3323.60	921.72 (1111.61)	639.00	319.50-1096.50	41	-3.784	<.001	0.59	10898.28 (21772.81)	2943.00	1053.00-7568.40	1940.74	1256.50	649.50-2065.25	29	-3.298	.001	0.61
Psychiatric Hospital Days	20.00 (56.147)	00.00	0.00-0.00	0.32 (2.03)	00.00	0.00-0.00	41	-2.599	.009	0.41	20.58 (52.35)	00.00	0.00-12.00	1.30 (4.27)	00.00	0.00-0.00	29	-2.667	.008	0.50
Psychiatric Admissions	0.29 (0.60)	00.00	0.00-0.00	0.03 (0.16)	00.00	0.00-0.00	40	-2.495	.013	0.39	0.42 (0.72)	00.00	0.00-1.00	0.10 (0.31)	00.00	0.00-0.00	28	-2.111	.035	0.39
HTT Visits	4.46 (9.63)	00.00	0.00-0.50	1.39 (5.20)	00.00	0.00-0.00	41	-1.824	.068	0.28	7.68 (13.51)	00.00	0.00-14.00	5.70 (16.24)	00.00	0.00-0.00	29	-0.392	.695	0.07
Outpatient Clinical Contact	27.22 (21.29)	22.00	9.50-41.50	16.68 (14.99)	11.00	5.00-23.50	41	-3.111	.002	0.49	48.19 (36.64)	42.00	22.00-72.00	28.70 (24.88)	23.00	10.75-44.50	29	-2.813	.005	0.52
Psychiatrist Visits	6.54 (9.78)	5.00	2.00-7.00	2.49 (2.41)	2.00	0.00-4.50	41	-4.200	<.001	0.66	11.32 (13.87)	8.00	3.00-13.00	4.33 (3.74)	3.00	1.00-7.00	29	-3.308	.001	0.61
Nurse /CC Visits	13.51 (12.44)	10.00	3.50-22.50	8.98 (8.27)	7.00	2.50-14.00	41	-1.990	.047	0.31	27.00 (24.25)	20.00	4.00-50.00	15.50 (13.29)	14.50	2.75-23.00	29	-2.198	.028	0.41
Psychology 1:1	6.83 (9.30)	0.00	0.00-13.00	4.07 (8.23)	00.00	0.00-4.50	41	-1.699	.089	0.27	9.00 (12.29)	1.00	0.00-19.00	6.57 (10.66)	00.00	0.00-13.25	29	-0.784	.433	0.15
Psychology Groups	0.34 (1.26)	00.00	0.00-0.00	1.90 (5.46)	00.00	0.00-0.00	41	-1.343	.179	0.21	0.87 (2.67)	00.00	0.00-0.00	1.15 (3.36)	00.00	0.00-0.00	29	-0.358	.721	0.07
Occupation Health	2.39 (6.43)	00.00	0.00-0.50	1.56 (5.31)	00.00	0.00-0.00	41	-0.997	.319	0.16	3.90 (7.25)	00.00	0.00-7.00	3.77 (9.65)	00.00	0.00-1.25	29	-0.691	.490	0.13
Social Support	1.34 (5.39)	00.00	0.00-0.50	0.46 (1.78)	00.00	0.00-0.00	41	-0.989	.323	0.15	1.90 (5.46)	00.00	0.00-1.50	1.024 (2.33)	00.00	0.00-1.00	29	-0.925	.323	0.17

Supplementary Appendices

Appendix 1: Treatment Resistance Assessment Criteria

Treatment resistance is defined here as inadequate response despite adequate treatment for the illness

Adequate treatment requires:

- Trials of at least two different antipsychotic drugs
- Each drug should have been given for at least six weeks at an adequate dose as defined in the TRIPP guidelines (1)
- Evidence of good adherence :
 - assured delivery such as a long-acting injectable formulation,
 - plasma antipsychotic levels within the expected range
- Antipsychotic levels for oral treatment to confirm that they were in the expected range as listed in the Maudsley Guidelines (2).

Inadequate therapeutic response was defined as contemporaneous clinical records documenting troubling and/or distressing on-going symptoms despite adequate treatment.

Appendix 2: Service Use Unit Cost Estimates

Cost estimates for service-use were calculated based on United Kingdom estimates for unit healthcare costs and via direct communication with South London and Maudsley NHS Foundation Trust

- Curtis & Burns (2017/2018) Unit Costs of Health & Social Care (3)
- McCrone et al (2009) Impact of crisis resolution team on service costs in the UK (4)
- NICE (2003) Guidance on the use of electroconvulsive therapy (5)
- NICE (2015) Preoperative tests (6)

Breakdown of costs

- One-day in psychiatric hospital: £410
- One Home Treatment Team visit: £49
- One Doctor/Nurse/Care Co-ordinator / Psychologist /Social Services visit: £39
- One Accident & Emergency Liaison Psychiatric Clinician Assessment: £196
- One Occupational Therapy / Dietician /Speech and Language Therapist: £35
- One Psychology group visit £7.80 (£39/5 – average group size)
- One Electro Convulsant Therapy session: £412.50
- One Phlebotomy visit (Full Blood Count): £6

Appendix 3: TREAT Clozapine initiation cost estimation

Costs were calculated from United Kingdom estimates for unit healthcare costs.

Baseline visit approximately 3 hours (including clinical review and electronic patient records review)
= 3 x £39

Bloods:

Full blood count (FBC)	£3.94
Renal profile & Urea	£1.57
Liver profile	£3.45
Thyroid	£3.45
B12 / folate	£8.67
ESR	£4.13
Autoantibodies	£11.50
Nt pro BNP	£7.58
Creatine kinase	£2.00
Typical antipsychotic plasma levels	£30.80
Olanzapine	£30.80
Risperidone	£30.80
Paliperidone	£19.25
Aripiprazole	£30.80
Amisulpride	£30.80

Bloods Total = **£77.09**

ECG = **£37**

MDT: cost for visit with doctor x2 + nurse + admin = **4 x £39**

Follow-up visit to explain plan = **1 x £39**

Repeat FBC pre-clozapine = **£3.94**

Titration and monitoring

Week 1: **5 x £39**

Week 2: **5 x £39**

Week 3: **3 x £39**

Week 4: **2 x £39**

Week 5: **1 x £39**

Week 6: **1 x £39**

Week 11: **1 x £39**

Discharge meeting: **1 x £39**

Bloods during titration:

FBC: **8 x £3.94**

Clozapine levels: **2 x £ 28.00**

Total TREAT Estimated Cost = £1,180.10

Appendix 4: Inpatient clozapine initiation cost estimation

Estimates based on a 4-week inpatient stay as recommended in the Maudsley guidelines.

Inpatient Bed Cost £404 x 28 = **£11,312**

Bloods:

Full blood count	£3.94
Renal profile & Urea	£1.57
Liver profile	£3.45
Thyroid	£3.45
B12 / folate	£8.67
ESR	£4.13
Autoantibodies	£11.50
NT pro BNP	£7.58
Creatine kinase	£2.00
Typical antipsychotic plasma levels	£30.80
Olanzapine	£30.80
Risperidone	£30.80
Paliperidone	£19.25
Aripiprazole	£30.80
Amisulpride	£30.80

Bloods Total = **£77.09**

ECG = **£37**

MDT: cost for visit with doctor x2 + nurse + admin = **4 x £39**

Follow-up visit to explain plan = **1 x £39**

Repeat FBC pre-clozapine = **£3.94**

Bloods during titration:

FBC: **4 x £3.94**

Clozapine levels: **2 x £ 28.00**

Total Inpatient Estimated Cost = £11,696.79

Appendix 5: Home Treatment Team (HTT) clozapine initiation cost estimation

Estimation provided by South London and Maudsley NHS Foundation Trust

Bloods:

Full blood count	£3.94
Renal profile & Urea	£1.57
Liver profile	£3.45
Thyroid	£3.45
B12 / folate	£8.67
ESR	£4.13
Autoantibodies	£11.50
NT pro BNP	£7.58
Creatine kinase	£2.00
Typical antipsychotic plasma levels	£30.80
Olanzapine	£30.80
Risperidone	£30.80
Paliperidone	£19.25
Aripiprazole	£30.80
Amisulpride	£30.80

Bloods Total = **£77.09**

ECG = **£37**

MDT: cost for visit with doctor x2 + nurse + admin = **4 x £39**

Follow-up visit to explain plan = **1 x £39**

Repeat FBC pre-clozapine = **£3.94**

£49 per HTT visit

2-weeks of 4x/day visit*

1-week of 3x/day visit

1-week of 2x/day visit

Bloods during titration:

FBC: **4 x £3.94**

Clozapine levels: **2 x £ 28.00**

Total Home Treatment Estimated Cost = £4843.79

**Please note Beck et al (2014) (7) paper describes 2 visits per day for administration and monitoring in first 4 weeks. In practice, the home treatment teams split up the administration and monitoring to avoid having to wait for the monitoring, and so make 4 visits per day*

Supplementary References

1. Howes OD, McCutcheon R, Agid O, De Bartolomeis A, Van Beveren NJM, Birnbaum ML, et al. Treatment-Resistant Schizophrenia: Treatment Response and Resistance in Psychosis (TRRIP) Working Group Consensus Guidelines on Diagnosis and Terminology. *Am J Psychiatry*. 2017 Mar 1;174(3):216–29.
2. Taylor D, Barnes TRE, Young AH (Allan H). *The Maudsley prescribing guidelines in psychiatry*. 13th ed. Wiley-Blackwell; 2018.
3. Curtis L, Burns A. Unit Costs of Health and Social Care 2017 [Internet]. Personal Social Services Research Unit. 2017. Available from: <https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2017/>
4. McCrone P, Johnson S, Nolan F, Sandor A, Houlton J, Pilling S, et al. Impact of a crisis resolution team on service costs in the UK. *Psychiatr Bull*. 2009;33(1):17–9.
5. NICE. Guidance on the use of electroconvulsive therapy - Guidance. In NICE; 2009. Available from: <https://www.nice.org.uk/guidance/ta59>
6. NICE. Routine preoperative tests for elective surgery - Guidance. In NICE; 2016. Available from: <https://www.nice.org.uk/guidance/ng45>
7. Beck K, McCutcheon R, Bloomfield MAP, Gaughran F, Reis Marques T, Maccabe J, et al. The practical management of refractory schizophrenia - the Maudsley Treatment Review and Assessment Team service approach. *Acta Psychiatr Scand*. 2014 Dec 1;130(6):427–38.