REFERENCE MANUAL (USER GUIDE)

App for analysis of maintenance treatment practice in acute lymphoblastic leukaemia

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Abbreviations

6MP	6-mercaptopurine
ALL	Acute lymphoblastic leukaemia
allMT	Maintenance treatment phase of acute lymphoblastic leukaemia
ANC	Absolute neutrophil count
Hb	Haemoglobin
PLT	Platelet count
MTX	Methotrexate
WBC	White blood cell

Background

Treatment of acute lymphoblastic leukaemia (ALL) involves two distinct phases of treatment: an intensive phase and a maintenance phase. This app is designed for analysis of treatment practice during the maintenance treatment phase of ALL

ALL Maintenance treatment phase (allMT)

During the maintenance phase of ALL treatment (allMT), patients are treated using a combination of the oral antimetabolite drugs 6-mercaptopurine (6MP) and methotrexate (MTX). The duration of allMT is typically 24 months. The 24 months (or 96 weeks) of allMT are divided into eight cycles, each of 12 weeks' duration. Oral 6MP is typically administered every day and oral MTX is administered once a week.

Other treatments include intrathecal chemotherapy (administered usually every 12 weeks), infection prophylaxis with trimethoprim-sulphamethoxazole (two consecutive days in a week) and in some cases, additional chemotherapy medicines (vincristine-steroid pulses, imatinib)

Treatment principles in allMT

The central tenet in allMT is to treat to tolerance. This requires uninterrupted treatment and periodic dose increments of 6MP and MTX until the limits of clinical tolerance, over the course of allMT. Clinical tolerance is determined by monitoring blood counts serially and reviewing clinical features that indicate drug intolerance. The dose levels associated with clinical tolerance vary from patient to patient. Where clinical tolerance limits have been exceeded, drug doses are reduced or withheld until recovery – treatment is then resumed either at dose levels that were tolerated previously or at the same dose levels that were accompanied by toxicity (i.e., dose re-challenge). This practice is continued through the 96 weeks of allMT (refer **Appendix 1**)

App purpose

The purpose of the app is to examine the application of the 'treat to tolerance' principle in the management of allMT. This analysis may be carried out at three levels

(a) In individual patients
(b) In a cohort of patients
(c) Between two patient cohorts

Input allMT information

For each patient, the input data table will contain information on blood counts and prescribed doses and dose intensities of 6MP and MTX at each clinic visit through the duration of allMT (**Appendix 1**)

(a) Blood counts include haemoglobin (Hb, in g/dL), absolute neutrophil count (ANC) and platelet count (PLT)

Note: ANC of $0{\cdot}8 \times 10^9$/L & PLT of 115×10^9/L may be recorded in different ways as below

If the laboratory unit is	ANC is recorded as	PLT is recorded as
/ mm^3	800	115,000
/ µL	800	115,000
× 10^3 / µL	0·8	115
× 10^6 / mL	0·8	115
× 10^9 / L	0·8	115
ANC, absolute neutrophil count; PLT, platelet count		

It is important to maintain consistent laboratory units when recording blood count values

(b) Doses of 6MP and MTX are recorded as weekly doses in milligrams
e.g., a daily 6MP dose of 50 mg is recorded as 350 mg/week

(c) Doses of 6MP and MTX are also recorded as dose intensities, i.e. prescribed drug dose as a proportion of the protocol-recommended start dose
e.g., for a patient with body surface area of 0·8 m^2, the protocol-recommended weekly start dose of 6MP (60mg/m^2/day or 420 mg/m^2/week) is 336 mg. If the patient is prescribed a weekly 6MP dose of 350 mg (i.e., 50 mg 6MP daily), the estimated 6MP dose intensity would be 1·04 or 104% (i.e., 350 mg ÷ 336 mg)

Derived allMT variables

These include weighted means of ANC, 6MP and MTX dose intensities, and the antimetabolite dose intensity.

(a) Weighted mean ANC refers to the mean of serial ANCs, weighted by the duration (in weeks) over which individual counts were recorded.
(b) Weighted mean 6MP and MTX dose intensities refer to the mean dose intensities of 6MP and MTX, weighted by the duration (in weeks) over which individual dose intensities were recorded.
(c) Weighted mean antimetabolite dose intensity refers to the product of the weighted mean dose intensities of 6MP and MTX.

allMT analysis outputs

Analysis outputs include graphs and tables.
Longitudinal line plots in individual patients include

(a) visualisation of serial ANC values against corresponding weekly doses of 6MP and MTX (in mg/week): the "**Longitudinal Progression**" function; and
(b) monitoring serial weighted mean antimetabolite dose intensities (i.e., product of weighted mean dose intensities of 6MP and MTX) against weighted mean neutrophil count in each 12-week cycle over the course of allMT: the "**Serial Treatment Intensity**" function

Scatter plots represent summary allMT treatment intensity in individual patients, calculated by mapping weighted mean antimetabolite dose intensity against weighted mean ANC over the duration of allMT treatment for each patient. This may be done in one of two ways:
(a) within a cohort: the "**Cohort Summary Treatment Intensity**" function;
(b) between patient cohorts: the "**Compare Cohort Summary Treatment Intensities**" function

Compliance of practitioners with allMT protocol rules for drug dose titration is determined by analysing concordance of dose decisions with blood count thresholds for
(a) dose reduction
"**Assess dose decisions – Reduce dose decisions**" function
(b) dose suspension
"**Assess dose decisions - Stop dose decisions*"*** function
(c) dose increase
"**Assess dose decisions – Increase dose decisions**" function
[Note: Dose increase is based both on blood count values and uninterrupted duration of treatment at a given dose level]

A cumulative incidence function curve allows analysis of compliance with the 'treat to tolerance' principle both in individual patients and in patient cohorts by plotting the time to the first prescribed dose increase of 6MP over the course of allMT: the "**Assess time to dose escalation**" function

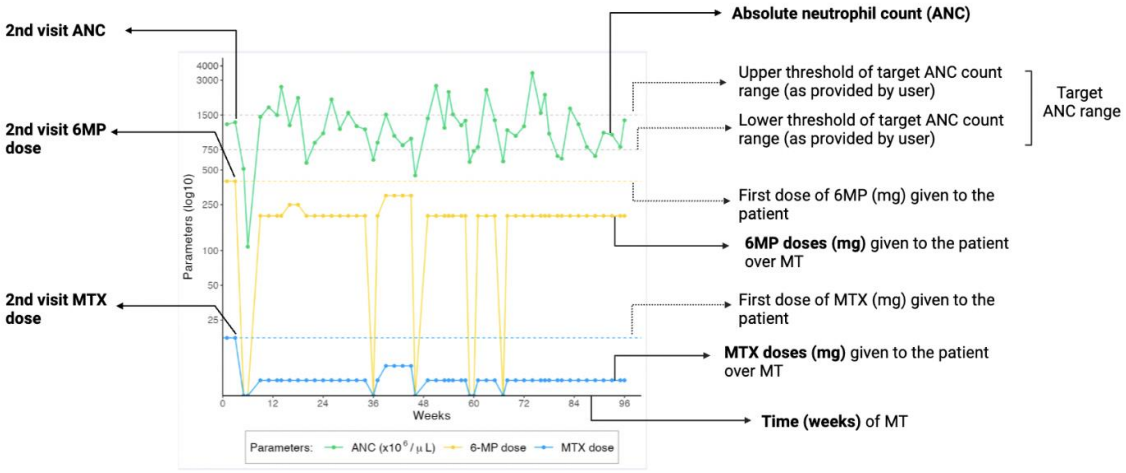
Treatment-related toxicity is determined by examining the frequency of low blood count values (neutropenia, anaemia, thrombocytopenia) that warranted treatment suspension during allMT. This is assessed in individual patients and in patient cohorts
(a) individual patients
"**Neutropenia_Individual**"; "**Thrombocytopenia_Individual**"; "**Anaemia_Individual**"
(b) patient cohorts
"**Neutropenia_Cohort**"; "**Thrombocytopenia_Cohort**"; "**Anaemia_Cohort**"

Exemplar: Analysis of allMT practice in individual patients

The **Longitudinal Progression** function

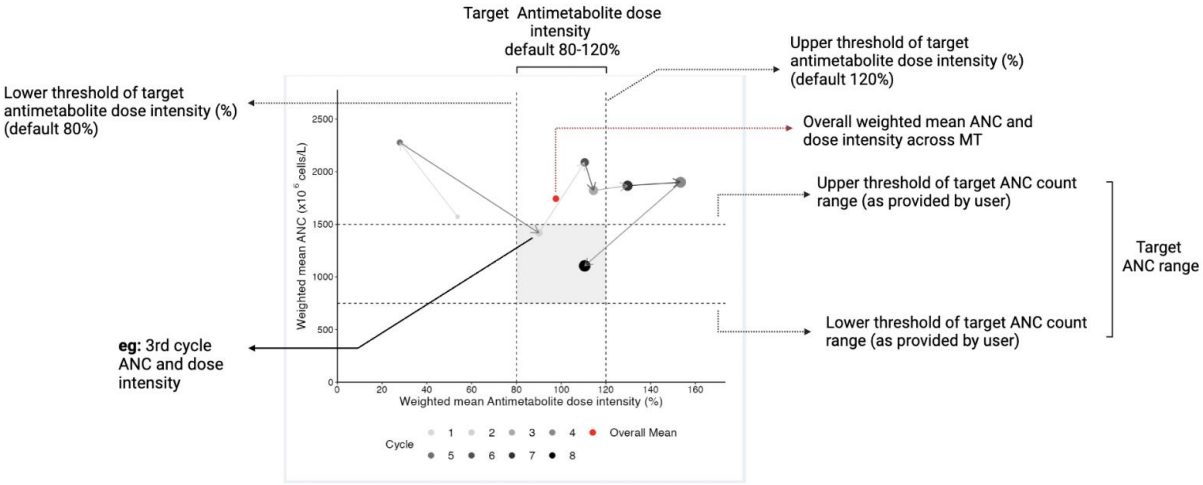
The purpose is to visualise the application of the 'treat to tolerance' principle

Line plot representation of serial absolute neutrophil counts (ANC, green) and corresponding 6MP (yellow) and MTX (blue) doses (in mg/week) over the course of allMT



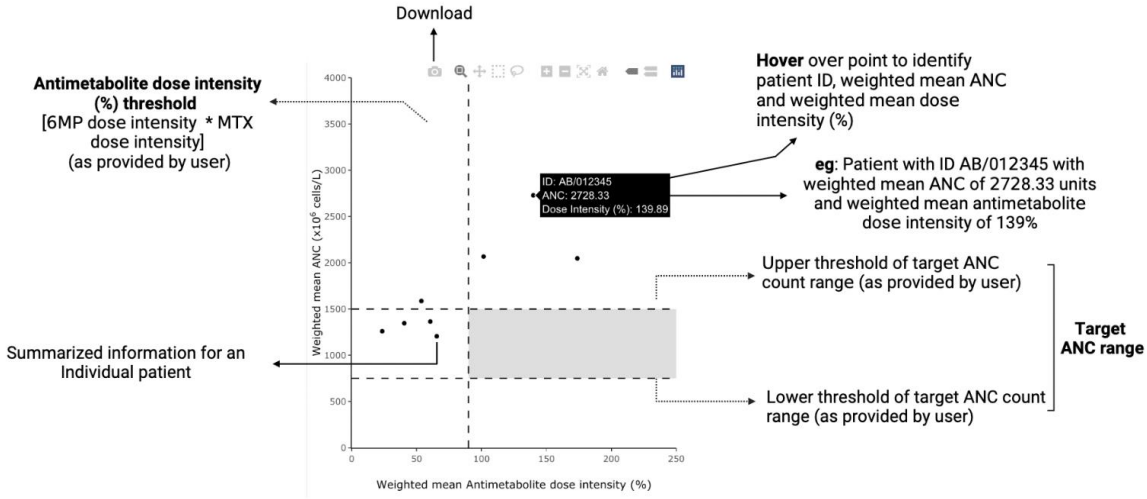
The **Serial Treatment Intensity** function

Line graph representation of weighted mean neutrophil counts plotted against weighted mean antimetabolite dose intensities (product of weighted mean dose intensities of 6MP and MTX) in each of the eight 12-week cycles of allMT



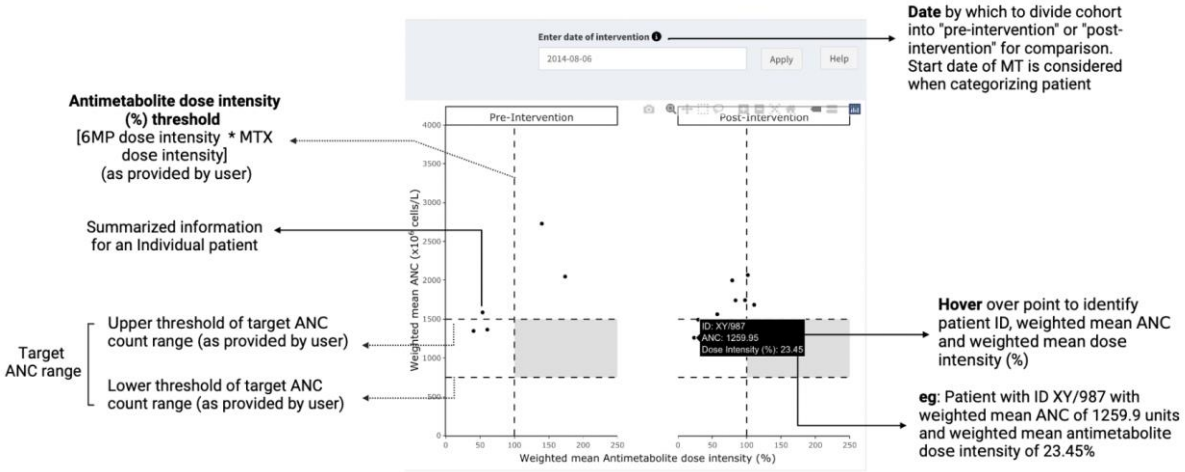
Exemplar: Analysis of allMT practice in patient cohorts

The **Cohort Summary Treatment Intensity** function



Scatter plot representation of weighted mean ANC plotted against weighted mean antimetabolite dose intensity over the course of allMT in individual patients from a cohort

The **Compare Cohort Summary Treatment Intensities** function



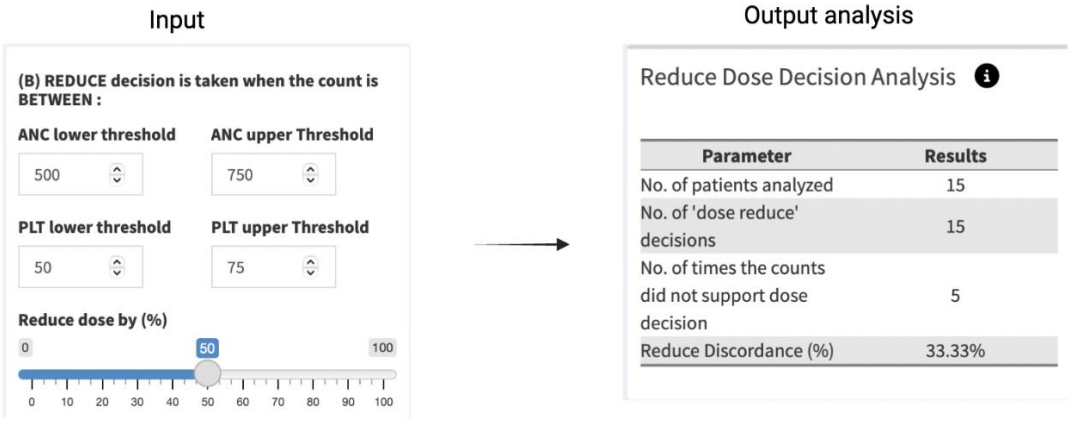
Scatter plot summary representation comparing allMT practice between patient cohorts.

Note: Each point in the scatterplot represents an individual patient and is annotated with the unique patient identifier and weighted means of ANC and antimetabolite dose intensities (obtained by hovering over each point).

Exemplar: Analysis of practitioner compliance with protocol rules for dose modifications in allMT

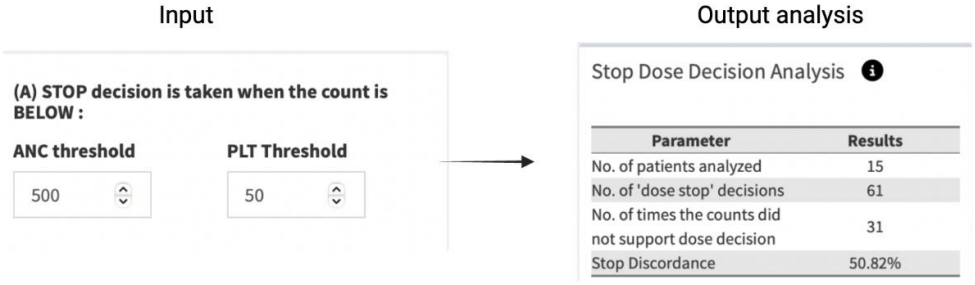
Assessing practitioner compliance with pre-specified rules for drug dose reduction, dose suspension and dose increase based on blood count thresholds (Hb, ANC, PLT) and additionally in the case of dose increase decisions, duration of treatment at a given dose level of 6MP and MTX

The **Assess dose decisions – Reduce dose decisions** function



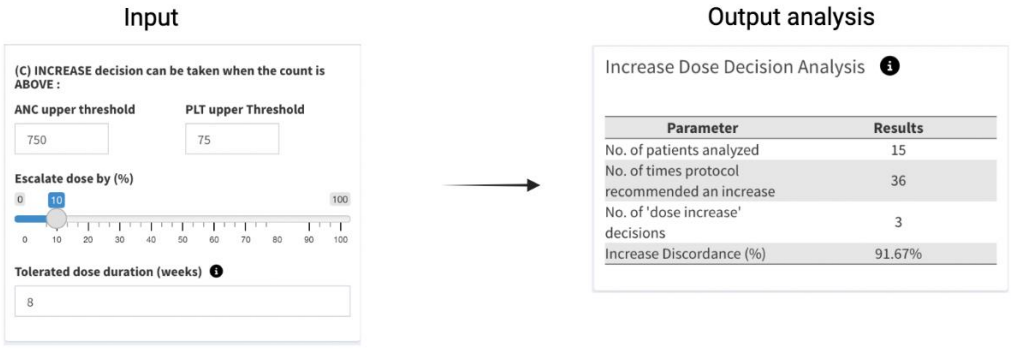
In the example below, the allMT protocol requires that the doses of 6MP and MTX be each decreased by 50% when blood counts are low, specifically when the ANC is between 500/μL and 750/μL, and/or the platelet count is between 50 × 10^9/L and 75 × 10^9/L (left panel). Compliance with this rule is assessed by reviewing the output analysis (right panel). In the example, output analysis in 15 patients (right panel) indicated that 5 of 15 (33%) 'reduce dose' decisions were not supported by blood count values, suggesting non-compliance with protocol-specified rules

The **Assess dose decisions - Stop dose decisions** function



In the example below, the allMT protocol requires that the doses of 6MP and MTX be stopped when blood counts are low, specifically when the ANC is below 500/μL, and/or the platelet count is below 50 × 10^9/L (left panel). Compliance with this rule is assessed by reviewing the output analysis (right panel). In the example, output analysis in 15 patients (right panel) indicated that 31 of 61 (51%) 'stop dose' decisions were not supported by blood count values, suggesting non-compliance with protocol-specified rules

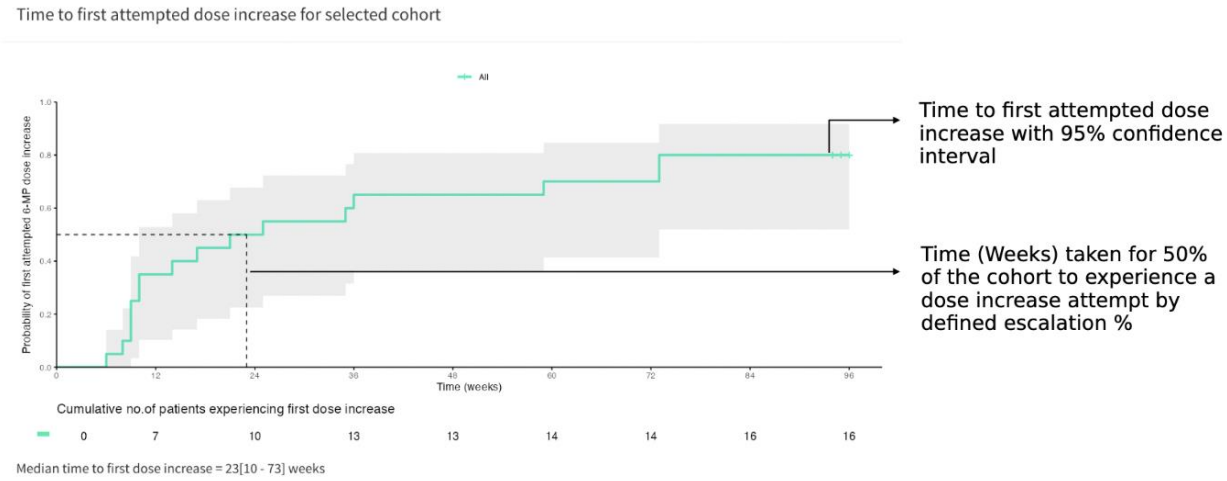
The **Assess dose decisions – Increase dose decisions** function



In the example below, the allMT protocol requires that doses of 6MP and MTX be increased by 10% above a given dose level [left panel, 'Escalate dose by (%)'] when treatment at the given dose level proceeds without interruption for eight consecutive weeks [left panel, 'Tolerated dose duration (weeks)'] and when blood counts at the dose increase decision timepoint are satisfactory [left panel, ANC and PLT thresholds; in this example, ANC ≥ 750/μL and PLT ≥ 75 × 10^9/L]. In the example, output analysis in 15 patients (right panel) indicated that 36 situations (or opportunities) were available for drug dose increase as dictated by protocol, but dose increase was prescribed in only 3 situations, indicating a 92% discordance between practitioner dosing practice and protocol-specified rules for dose increase.

Exemplar: The **Assess time to dose escalation** function
Cumulative incidence function plot to represent the estimated probability (with 95% confidence intervals) of time (in weeks) to the first attempt at drug dose increase in a patient cohort during allMT.

In the example, the estimated median time to first dose increase in the cohort was 23 weeks (95% confidence interval, 10 – 73 weeks)

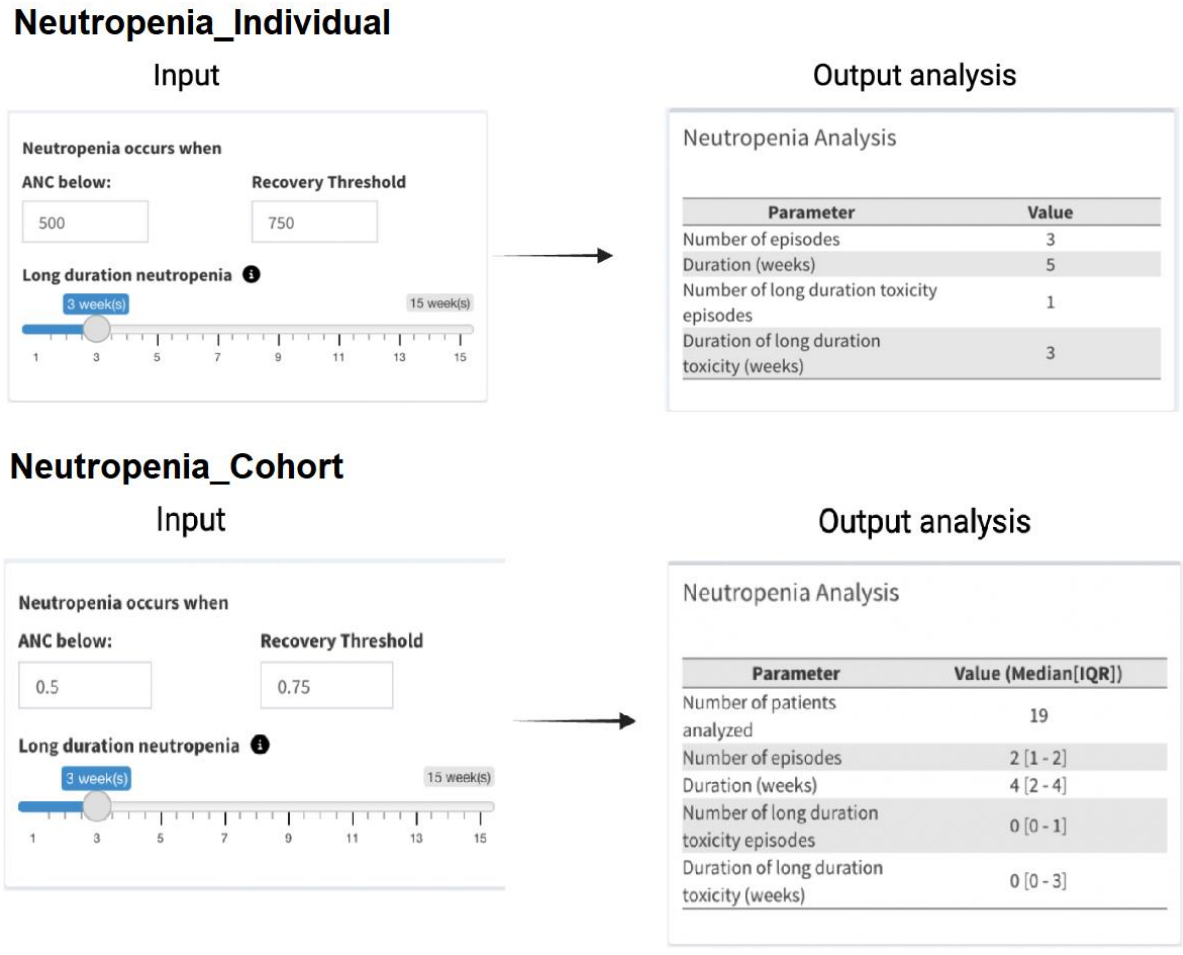


Exemplar: Evaluation of treatment-related toxicity in allMT by examining the frequency (and cumulative duration) of visits with low blood count values, requiring suspension of drug treatment with the antimetabolite drugs 6MP and MTX.

The **Neutropenia_Individual** (upper panel) and **Neutropenia_Cohort** (lower panel) functions report the number of episodes of neutropenia in allMT that required suspension of antimetabolite drug treatment.

In the upper panel example, analysis in an individual patient indicated 3 distinct episodes of neutropenia (ANC below 500/mm^3) during the course of allMT, requiring halt in antimetabolite drug treatment for a cumulative 5 weeks. One of the neutropenia episodes was of long duration (long duration in this example, ≥ 3 weeks; 'long duration toxicity episode'). The ANC threshold for resumption of drug treatment ('Recovery Threshold') in this example was 750/mm^3

In the lower panel example, analysis in a 19-patient cohort indicated a median 2 episodes of neutropenia (interquartile range, 1-2) during the course of allMT, requiring halt in antimetabolite drug treatment for a median cumulative 4 weeks (interquartile range, 2-4 weeks). The median number of long duration toxicity episodes (consequent to 'Long duration neutropenia' ≥ 3 weeks) in this cohort was 0 (interquartile range, 0-1) and the cumulative median duration (in weeks) of 'long duration toxicity episodes' was 0 (interquartile range, 0-3



weeks). In this example, drug treatment was halted when ANC was below $0{\cdot}5 \times 10^9$/L and resumed when ANC was ≥ $0{\cdot}75 \times 10^9$/L

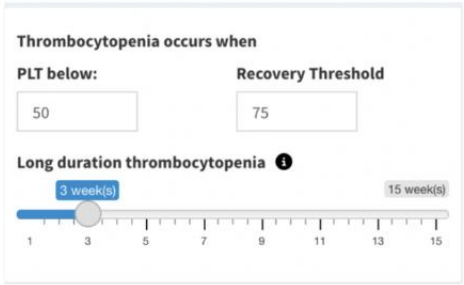
The **Thrombocytopenia_Individual** (upper panel) and **Thrombocytopenia_Cohort** (lower panel) functions report the number of episodes of thrombocytopenia in allMT that required suspension of antimetabolite drug treatment.

In the upper panel example, analysis in an individual patient indicated 3 distinct episodes of thrombocytopenia (PLT below 50×10^9/L) during the course of allMT, requiring halt in antimetabolite drug treatment for a cumulative 5 weeks. None of the thrombocytopenia episodes was of long duration (long duration in this example, ≥ 3 weeks; 'long duration toxicity episode'). The PLT threshold for resumption of drug treatment ('Recovery Threshold') in this example was 75×10^9/L

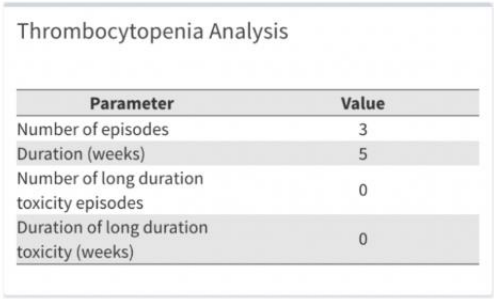
In the lower panel example, drug treatment was halted when PLT was below 50×10^9/L and treatment resumed when PLT was ≥ 75×10^9/L. Analysis in a 19-patient cohort in this example indicated that the median number (in brackets, interquartile range) of thrombocytopenia episodes that required halt of antimetabolite drug treatment was 0.

Thrombocytopenia_Individual

Input



Output analysis

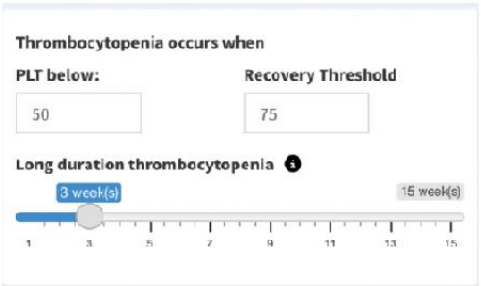


Thrombocytopenia Analysis

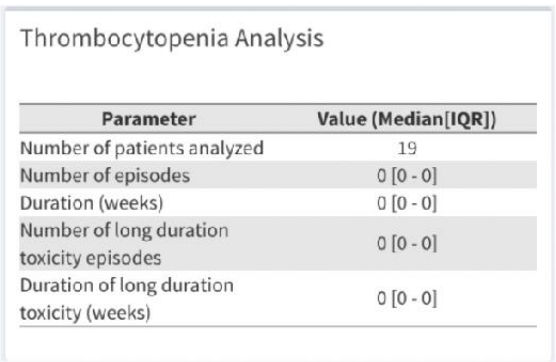
Parameter	Value
Number of episodes	3
Duration (weeks)	5
Number of long duration toxicity episodes	0
Duration of long duration toxicity (weeks)	0

Thrombocytopenia_Cohort

Input



Output analysis



Thrombocytopenia Analysis

Parameter	Value (Median[IQR])
Number of patients analyzed	19
Number of episodes	0 [0 - 0]
Duration (weeks)	0 [0 - 0]
Number of long duration toxicity episodes	0 [0 - 0]
Duration of long duration toxicity (weeks)	0 [0 - 0]

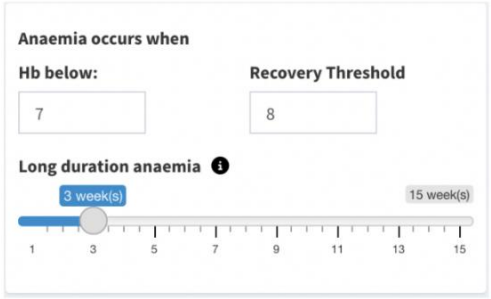
The **Anaemia_Individual** (upper panel) and **Anaemia_Cohort** (lower panel) functions report the number of episodes of anaemia in allMT that required suspension of antimetabolite drug treatment.

In the upper panel example, analysis in an individual patient indicated one episode of anaemia (Hb below 7 g/dL) during the course of allMT, requiring halt in antimetabolite drug treatment for a cumulative 3 weeks. The episode of anaemia in this example was of long duration (≥ 3 weeks; 'long duration toxicity episode'). The Hb threshold for resumption of drug treatment ('Recovery Threshold') in this example was 8 g/dL

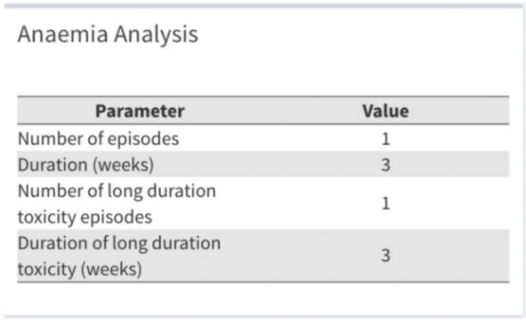
In the lower panel example, drug treatment was halted when Hb was below 8 g/dL and treatment resumed when Hb was ≥ 9g/dL. In this example, analysis of episodes of anaemia that warranted suspension of antimetabolite drug treatment in a 19-patient cohort indicated a median 0 episodes (interquartile range, 0-1), over a cumulative median duration of 0 weeks (interquartile range, 0-2 weeks). The median number and cumulative median duration (in weeks) of long toxicity episodes (i.e., anaemia duration ≥ 3 weeks) in this cohort were both 0.

Anaemia_Individual

Input

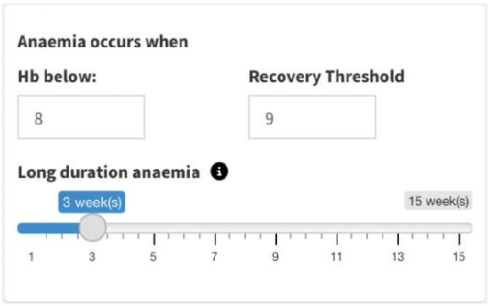


Output analysis

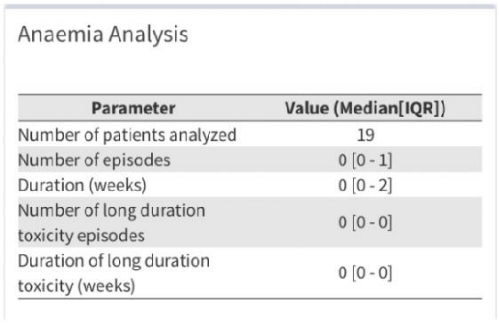


Anaemia_Cohort

Input



Output analysis



Appendix 1: Exemplar record of serial dose titration of 6-mercaptopurine and oral methotrexate doses using blood count endpoints (tested every 2 weeks) over 96 weeks (i.e., eight 12-week cycles) of ALL maintenance treatment.

Age		5	years
Weight		18	kg
Height		105	cm
BSA		0.72	m^2
Oral 6MP	100%	302.4	mg/week (60 mg/m^2/day)
Oral MTX	100%	14.4	mg/week (20 mg/m^2/week)

Cycle	Dates	Weeks	ANC	PLT	Hb	MP[a]	MP_adj[b]	MTX[c]	MTX_adj[d]
1	13/05/2014	1	2.09	135	11.8	300	100	15	100
1	27/05/2014	3	1.71	122	10.8	300	100	15	100
1	10/06/2014	5	1.21	148	10.8	300	100	15	100
1	24/06/2014	7	1.44	281	9.1	300	100	15	100
1	08/07/2014	9	1.01	111	8.5	300	100	15	100
1	22/07/2014	11	1.15	215	8.8	350	117	15	100
2	05/08/2014	13	0.89	301	9.2	350	117	15	100
2	19/08/2014	15	1.52	220	8.6	350	117	17·5	117
2	02/09/2014	17	2.03	250	7.9	350	117	17·5	117
2	16/09/2014	19	0.67	71	8.1	175	50	7.5	43
2	30/09/2014	21	0.44	78	7.6	0	0	0	0
2	14/10/2014	23	0.63	101	8.2	0	0	0	0
3	28/10/2014	25	2.12	287	8.4	300	100	15	100
3	11/11/2014	27	1.93	300	9.3	300	100	15	100
3	25/11/2014	29	1.91	199	9.1	300	100	15	100
3	09/12/2014	31	1.61	91	9.5	300	100	15	100
3	23/12/2014	33	1.22	265	8.8	300	100	15	100
3	06/01/2015	35	0.99	192	9.3	350	117	15	100
4	20/01/2015	37	1.03	113	8.8	350	117	15	100
4	03/02/2015	39	1.02	272	8.3	350	117	17.5	117
4	17/02/2015	41	1.07	236	10.3	350	117	17.5	117
4	03/03/2015	43	0.95	201	9.7	350	117	17.5	117
4	17/03/2015	45	0.89	79	9.5	350	117	17·5	117
4	31/03/2015	47	1.12	197	8.7	350	117	17.5	117
5	14/04/2015	49	0.85	112	8.7	350	117	17.5	117
5	28/04/2015	51	0.51	110	8.2	0	0	0	0
5	12/05/2015	53	0.56	97	7.9	0	0	0	0
5	26/05/2015	55	0.93	211	8.3	350	117	17.5	117
5	09/06/2015	57	1.15	201	10.1	350	117	17·5	117
5	23/06/2015	59	1.44	284	9.8	350	117	17.5	117
6	07/07/2015	61	1.24	218	8.5	350	117	17.5	117
6	21/07/2015	63	0.97	176	9.7	350	117	17.5	117
6	04/08/2015	65	1.34	161	8.8	400	133	17.5	117
6	18/08/2015	67	1.13	170	9.1	400	133	17·5	117
6	01/09/2015	69	0.96	145	8.9	400	133	17.5	117
6	15/09/2015	71	1.01	133	8.4	400	133	20	133
7	29/09/2015	73	1.17	273	9.3	400	133	20	133
7	13/10/2015	75	0.81	201	8.1	400	133	20	133
7	27/10/2015	77	0.87	118	8.8	400	133	20	133
7	10/11/2015	79	0.95	146	8.3	400	133	20	133
7	24/11/2015	81	1.11	126	8.9	400	133	20	133
7	08/12/2015	83	0.35	80	8.7	0	0	0	0
8	22/12/2015	85	0.46	101	9.1	0	0	0	0
8	05/01/2016	87	0.77	123	7.3	0	0	0	0
8	19/01/2016	89	1.15	186	8.2	400	133	20	133
8	02/02/2016	91	0.87	171	8.7	400	133	20	133
8	16/02/2016	93	0.82	89	8.1	400	133	20	133
8	01/03/2016	95	1.03	121	8.5	400	133	20	133

BSA, body surface area; ANC, absolute neutrophil count, $\times 10^9$/L; PLT, platelet count, $\times 10^9$/L; Hb, haemoglobin, g/dL

[a]Column 'MP' refers to weekly 6-mercaptopurine dose (mg/week)

[b]Column 'MP_adj' refers to corresponding weekly 6-mercaptopurine dose intensity [(prescribed dose/protocol dose) × 100; %]

[c]Column 'MTX' refers to weekly methotrexate dose (mg/week)

[d]Column 'MTX_adj' refers to corresponding weekly methotrexate dose intensity [(prescribed dose/protocol dose) × 100; %]

In this table, intrathecal methotrexate treatment weeks have been recorded as continuation of (oral) methotrexate treatment