# Supplementary Digital Content 1: Additional Methods

## Assumptions on which the mathematical model is based

1. The patient starts with a certain plasma volume, FII level and AT level (it is assumed that all circulating FII and AT is in the patient’s plasma).
2. Hemostatic agent (therapeutic plasma/PCC) is added one unit at a time until the specified amount of hemostatic agent is reached.
3. Volume resuscitation with crystalloid or colloid may be co-administered, particularly with PCC.
4. Immediately before adding each unit of hemostatic agent, the volume of the unit plus the volume of crystalloid or colloid, as whole blood, is removed from the patient’s circulation. (This is to avoid modelling an ever-increasing circulatory volume. Removal of volume simulates administration of hemostatic agent during ongoing bleeding; however, the model makes no assumptions regarding bleeding rate).
5. Upon adding each unit of hemostatic agent (which is all fluid) plus crystalloid or colloid, the patient’s plasma volume is increased by the volume of the unit – thus restoring the circulation to the ‘baseline’ volume.
6. After adding each unit of hemostatic agent, new values for FII level, AT level and FII:AT ratio are calculated. These are based on the new plasma volume (changed because of removal of whole blood and subsequent addition of hemostatic agent) and the new total quantities of FII and AT (changed because of removal of whole blood and addition of hemostatic agent with defined *in vivo* recovery).
7. As a result of whole blood removal and subsequent addition of hemostatic agent, hematocrit decreases with every unit of hemostatic agent that is added. If hematocrit decreases below a defined threshold, one unit red blood cells (RBC) is added to the simulation at the same time as the next unit of hemostatic agent, as follows: (i) whole blood removed (volume removed = volume of one unit RBC + volume of hemostatic agent + volume of crystalloid or colloid); (ii) RBC is added (assumption: RBC contains no fibrinogen); (iii) hemostatic agent plus crystalloid or colloid is added.
8. Hematocrit is calculated by subtracting plasma volume from the whole blood volume, and dividing the result by the whole blood volume. This approximation, which effectively ignores the volume of white blood cells and platelets, was used to avoid unnecessary complications.

## Default values for therapeutic plasma and PCC

Default values were needed to provide a starting point for the model, although they should not be considered as definitive because of variability, for example, between different PCC products. We searched the literature for data published on each parameter.

The volume per dosage unit of therapeutic plasma is 250 mL, and the mean concentration of both FII and AT is 0.97 IU/mL.1 For PCC, default values are based on labelled constituents of the four-factor PCC Beriplex P/N 500 (CSL Behring, Marburg, Germany). The volume per PCC dosage unit is 20 mL and the concentrations of FIX, FII and AT are 25 IU/mL, 34 IU/mL and 0.85 IU/mL, respectively (mid-points of the labelled ranges).2

## Initial development of the mathematical model

The patient’s blood volume and plasma volume are calculated from bodyweight and hematocrit as follows:3,4

$$BV=70×BW$$

$$PV=BV×\frac{100-HCT}{100}$$

*BV* = blood volume (mL); *BW* = patient’s bodyweight (kg); *HCT* = hematocrit (%); *PV* = plasma volume (mL).

Example (assuming bodyweight of 70 kg and hematocrit of 40%): BV = 70 × 70 = 4900 mL; PV= 70 × 70 × (60/100) = 2940 mL

Using this example, an arbitrary baseline plasma FII level of 1.0 IU/mL, and the assumptions listed above, the effects of adding therapeutic plasma on FII are represented in Table 1. Values for AT would be identical, with the same baseline level of 1.0 IU/mL; the FII:AT ratio would be 1.00 throughout.

**Table 1. Initial consideration of addition of therapeutic plasma to a patient’s blood and the resultant plasma FII level.**

Assumptions as follows: patient has a baseline plasma FII level of 1.0 IU/mL, a bodyweight of 70 kg (blood volume 4900 mL) and hematocrit of 40% (plasma volume 2940 mL). One unit of therapeutic plasma contains 242.5 IU of FII in 250 mL, the patient is not actively losing blood, and the patient’s plasma volume increases by the same volume as the amount of therapeutic plasma added.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Units of therapeutic plasma administered** | **Volume of therapeutic plasma administered (mL)** | **Patient’s plasma volume (mL)** | **FII added (IU)** | **FII in patient’s plasma (IU)** | **Patient’s plasma FII level (IU/mL)** |
| 0 [Baseline] | 0 | 2940 | 0 | 2940 | 1 |
| 1 | 250 | 3190 | 242.5 | 3182.5 | 0.998 |
| 2 | 500 | 3440 | 485 | 3425 | 0.996 |
| 3 | 750 | 3690 | 727.5 | 3667.5 | 0.994 |
| 4 | 1000 | 3940 | 970 | 3910 | 0.992 |
| 5 | 1250 | 4190 | 1212.5 | 4152.5 | 0.991 |
| 6 | 1500 | 4440 | 1455 | 4395 | 0.990 |
| 7 | 1750 | 4690 | 1697.5 | 4637.5 | 0.989 |
| 8 | 2000 | 4940 | 1940 | 4880 | 0.988 |
| 9 | 2250 | 5190 | 2182.5 | 5122.5 | 0.987 |
| 10 | 2500 | 5440 | 2425 | 5365 | 0.986 |

To enable FII and AT concentrations to be modelled with different parameters (e.g. different bodyweight, different baseline FII or AT level), the relationships between amount of hemostatic agent and plasma levels of FII and AT were programmed into Excel using the following formula:

$$rC=\frac{\left(Baseline x PV\right)+(No.of units x pC x DV) }{PV+(No.of units x DV)}$$

*Baseline* = patient’s baseline plasma level of FII or AT (IU/mL); *DV* = volume of one unit of the hemostatic agent (mL); *pC* = concentration of FII or AT in the hemostatic agent (IU/mL); *PV* = patient’s plasma volume at baseline (mL); *rC* = resultant plasma level of FII or AT (IU/mL).

A graphical user interface was constructed for the user to specify the following parameters: bodyweight, baseline hematocrit, baseline FII level, baseline AT level and the amount of hemostatic agent to be added.

Excel was programmed to display graphs showing the effects of each hemostatic agent on FII level, AT level and FII:AT ratio.

## Refinements of the mathematical model

*In vivo* recovery was added to the model because the increase in plasma levels of FII and AT may not correspond exactly with the quantities administered. *In vivo* recovery was defined as the actual increase in plasma level divided by the expected increase. Volume resuscitation, not included in the initial model the fibrinogen concentration simulator, was also added. This was principally to reflect the clinical possibility of administering colloids or crystalloids together with PCC and, for consistency, the facility was also added to therapeutic plasma.

In the initial version of the model, circulatory volume increased without limitation as hemostatic agents were added. This may be unrealistic, for example when several units of therapeutic plasma are added. The model was modified to keep circulatory volume constant: a volume of whole blood equivalent to the volume of the hemostatic agent plus the volume of colloid or crystalloid is removed from circulation immediately before adding the hemostatic agent and volume resuscitation. This prompted changing from a continuous to a discrete model, with significant mathematical alterations.

With the removal of whole blood and addition of therapeutic plasma or PCC (with or without additional volume resuscitation), hematocrit decreases. The addition of RBC when hematocrit falls below a defined threshold was added to the model. The default volume for one unit of RBC is 280 mL, of which 182 mL (65%) is assumed to be red blood cells.5 For administration of RBC, a threshold hematocrit level of 21% was chosen, which corresponds with a hemoglobin value of ~7 g/dL.6

Additional revisions were to change the units of FII and AT concentration (from IU/mL to percentage activity, with 1 IU/mL corresponding to 100% in both cases), and to change the units of the PCC amount (from units [vials] to international units of factor IX). Details of the mathematics associated with the refinements are presented in the supplementary material of the Collins et al. manuscript.4

# References

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