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Multi-dimension Comparison
using SAS: In the Context of
Counting Hemophilia Bleeding
Episode

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Chivia Qianyun Zou, SPAR, Sanofi, Cambridge, USA

Wenruo Hu , EGDS, Sanofi, Beijing, China

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Hemophilia Studies

*Collect
bleeds*

Rules for
bleeding
episode

Why bleeding episode
is important?

*Derive
bleeding
episodes*

**Traditional Approach
vs
Matrix Approach**

Annualized
Bleeding
Rate

$$\frac{\text{total number of qualifying bleeding episodes}}{\text{total number of days in the respective period}} \times 365.25$$

Rules for Bleeding Episodes

International Society on Thrombosis
and Hemostasis (ISTH)

“72 Hours Rule”

Bleed Location

(e.g., elbow, knee)

Bleed Type

(traumatic/spontaneous)

Bleed Treatment

(treated/untreated)

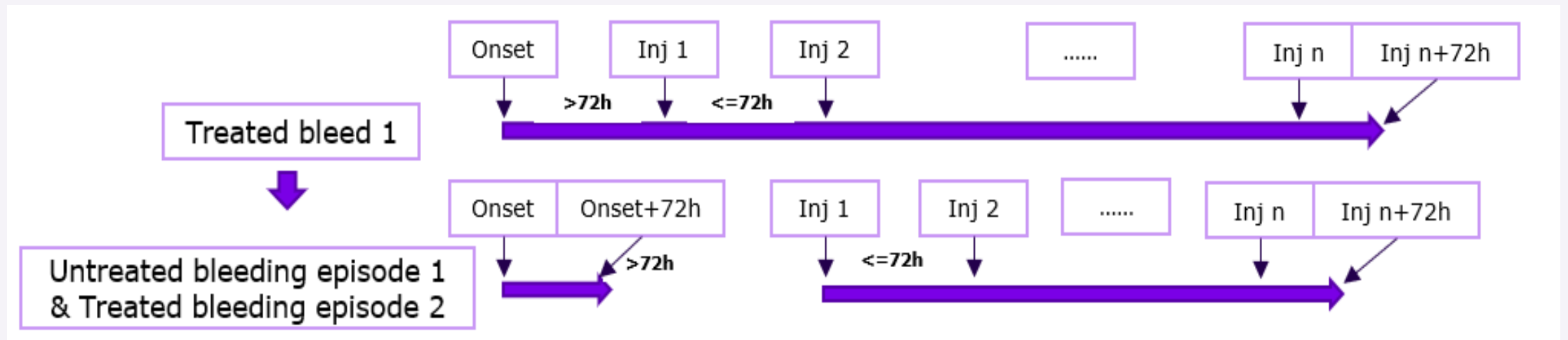
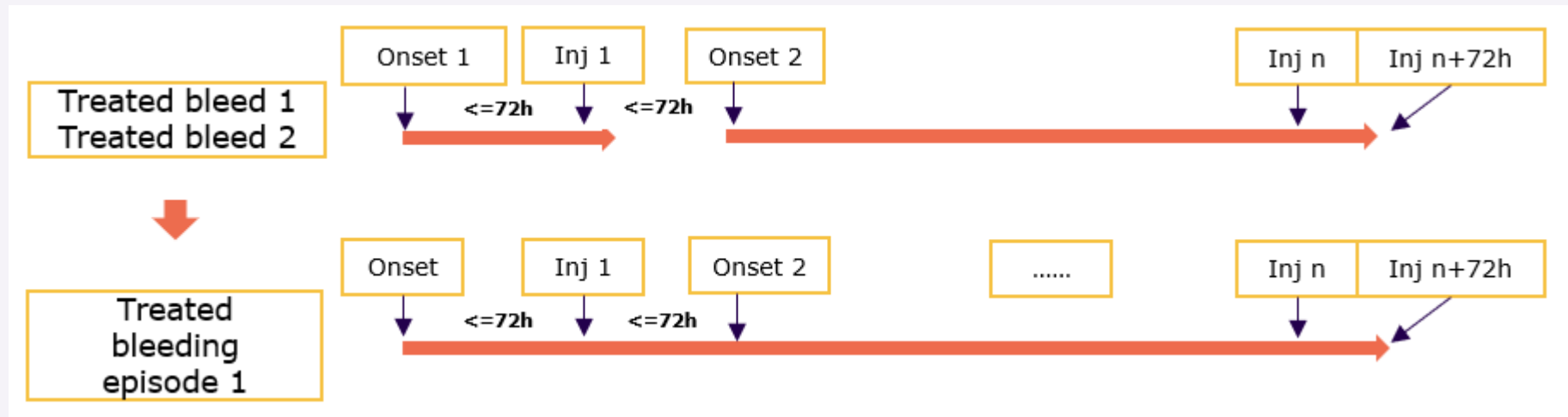
Event Timing

*(within/more than 72
hours)*

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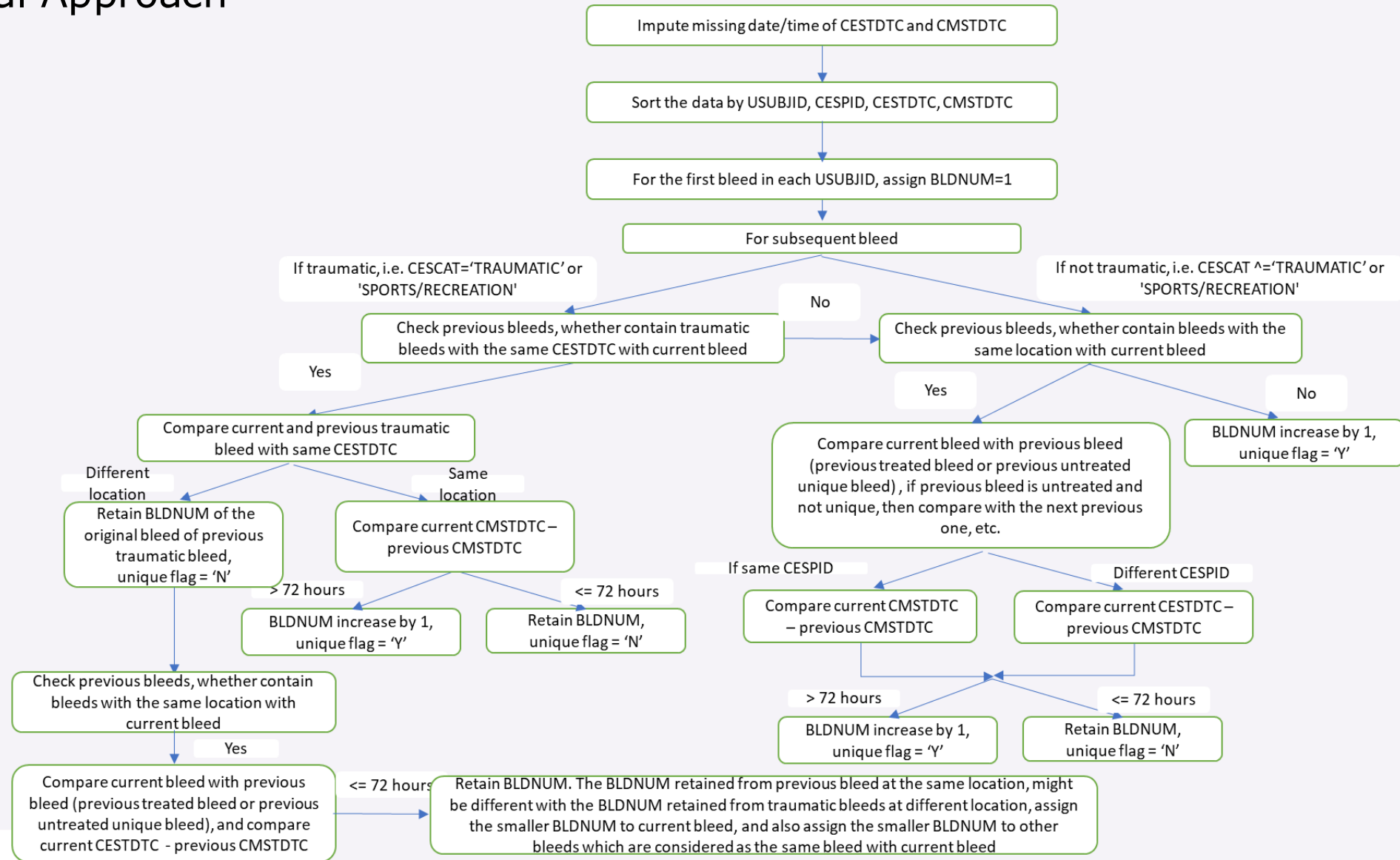
- ① Bleeding or any symptoms of bleeding at the same location that occurs within 72 hours of the last injection used to treat a bleed or within 72 hours after the start of an untreated bleed at that location will be considered a part of the original bleeding event and will count as one bleeding episode towards the annualized bleeding rate (ABR).
- ② Any bleeding symptoms at the same location that begin more than 72 hours from the last injection used to treat a bleed at that location or more than 72 hours after the start of an untreated bleed at that location will constitute a new bleeding event.
- ③ Any bleeding symptom with two consecutive injections started more than 72 hours apart will be split into two separated bleedings, the latter bleeding start date/time will be imputed with the second injection start date/time.
- ④ The first injection more than 72 hours after the bleeding start date/time will be considered as a separate bleeding episode with bleeding start date/time imputed with the injection start date/time. The original bleeding will be considered as an untreated bleeding episode.
- ⑤ Traumatic bleeds that occur in different locations simultaneously (same date/time) in the same participant will be considered as one bleeding episode.
Spontaneous bleeds that occur simultaneously (same date/time) in different locations in the same participant will be considered as separate bleeds.

Examples of Deriving Bleeding Episodes



Derive Bleeding Episodes

Traditional Approach



Challenges of the Traditional Approach

- 1) There are many different bleed scenarios. The programming algorithm could be very long.
- 2) Data issues happened in various unexpected cases, leading to non-robust outcomes.
- 3) The programming hierarchy logic is fixed. When new data came in, we might find the original logic did not cover the new scenario, and we need to revise the whole logic, which is time-consuming.
- 4) The comparison chain depends on the sorting order and can only compare the adjacent records.

Challenges of the Traditional Approach



ASEQ	CESPID	CELOCATION	CESCAT	CESTDTM	CMSTDTM	BLDNUM M	BLDNUM T
1	1	A	SPONTANEOUS	2019-01-01T16:30	2019-01-01T17:30	1	1
2	2	B	TRAUMATIC	2019-01-03T00:00	2019-01-03T00:00	2	2
3	3	C	SPONTANEOUS	2019-01-03T00:00	2019-01-03T00:00	2	3
4	4	C	TRAUMATIC	2019-01-03T00:00	2019-01-04T00:00	2	2
5	4	C	TRAUMATIC	2019-01-03T00:00	2019-01-05T00:00	2	2
6	5	F	SPONTANEOUS	2019-01-06T06:00	2019-01-06T06:30	3	4

- ▲ The comparison chain depends on the sorting order and can only compare the adjacent records.

- 1 Bleeding or any symptoms of bleeding at the same location that occurs within 72 hours of the last injection used to treat a bleed or within 72 hours after the start of an untreated bleed at that location will be considered a part of the original bleeding event and will count as one bleeding episode towards the annualized bleeding rate (ABR).
- 5 Traumatic bleeds that occur in different locations simultaneously (same date/time) in the same participant will be considered as one bleeding episode.

Derive Bleeding Episodes

Matrix Approach

Data
Prep

- Merge treatments (CM) and bleeding events (CE) information to get an all-inclusive dataset

Find the
smallest
bleed
unit

- Per the time criterion of 72 hours, derive collected bleeds to the smallest bleed units (new start/end datetime)

Combine
bleeds

- Apply the matrix approach to combine linkable smallest bleed units to new bleeding episodes

Final
episodes

- Assign final sequential bleeding episode numbers (BLDNUM)

Derive Bleeding Episodes

Matrix Approach

Matrix algorithm (steps)

- 1) Create a matrix saving all the pairwise links (directly or indirectly) between either of two bleeds.
 - => Now we have a matrix, and each element of the matrix represents connection of 2 bleeds (matrix a).
- 2) Then, to calculate power times of the matrix to find out if there is any further connection.
 - *2nd power of matrix => find out connection up to 3 bleeds (matrix a2_2).*
 - *3rd power of matrix => find out connection up to 4 bleeds (matrix a2_3).*
 - *...(n-1) power for n bleeds*
- 3) Eventually, by calculate power of the matrix, we can search connections among all possible combination (matrix a3).
- 4) Extract elements that >0 for each rows to obtain BLDNUM.

Derive Bleeding Episodes

Matrix Approach

Matrix algorithm (example)

a					
1	0	0	0	0	0
0	1	0	1	0	0
0	0	1	1	0	0
0	1	1	1	0	0
0	0	0	0	0	1

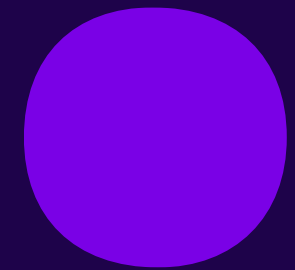
a2_2					
1	0	0	0	0	0
0	2	1	2	0	0
0	1	2	2	0	0
0	2	2	3	0	0
0	0	0	0	0	1

a2_3					
1	0	0	0	0	0
0	4	3	5	0	0
0	3	4	5	0	0
0	5	5	7	0	0
0	0	0	0	0	1

a3					
1	0	0	0	0	0
0	9	8	12	0	0
0	8	9	12	0	0
0	12	12	17	0	0
0	0	0	0	0	1

 cesp	 _BLDNUM	 bdt	 celoc	 onset	 maxmed	 BLDNUM
1	1	Y	A	2019-01-01T16:30:00	2019-01-01T17:30:00	1
2	2	Y	B	2019-01-03T00:00:00	2019-01-03T00:00:00	2
3	3	Y	C	2019-01-03T00:00:00	2019-01-03T00:00:00	2
4	4	Y	C	2019-01-03T00:00:00	2019-01-05T00:00:00	2
5	5	Y	F	2019-01-06T06:00:00	2019-01-06T06:30:00	3

Q & A



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Thank You

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Contact Information

Qianyun (Chivia) Zou
Sanofi, Cambridge, USA
chivia.zou@sanofi.com

Wenruo Hu
Sanofi, Beijing, China
wenruo.Hu@sanofi.com

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Untreated bleed handling

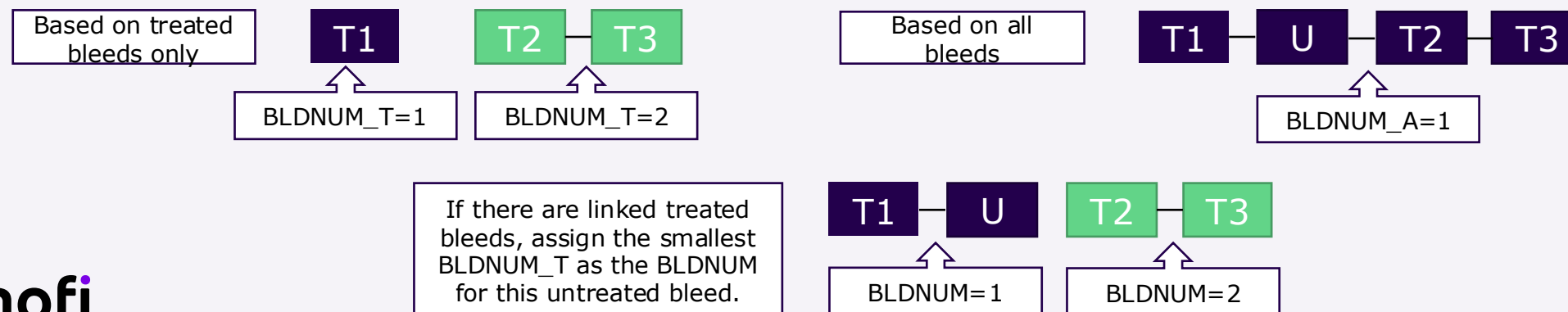
Assumption: Untreated bleed can only link to one treated bleed

We can have scenarios:

- 1) One untreated bleed link to one treated bleed
- 2) One untreated bleed cannot link to any treated bleed
- 3) One untreated bleed link to more then one treated bleed <problematic>**
- 4) Multiple untreated bleeds link together
- 5) More then one untreated bleeds link to one treated bleed

Except for scenario 3, the other scenarios don't have impact on the number of treated bleeds.

- For any untreated bleed that can link to at least one treated bleed, we will artificially link the untreated bleed to the earliest treated bleed.
- For untreated bleed that not link to any treated bleed, we can assign the BLDNUM sequentially.



Derive Bleeding Episodes

Matrix Approach

Step 1: Merge CE and ADCM data together. Create imputed ASTDTM and CMSTD TM.

1. For treated bleed, ASTDTM is bleeding onset date/time, CMSTD TM is BPA/factor administration date/time.
2. For untreated bleed, ASTDTM and CMSTD TM are both bleeding onset date/time.
3. If missing time part, impute "00:00".

Step 2: Check "72h" rule within each bleeding event and split bleeding data into the smallest groups.

1. Compare ASTDTM and CMSTD TM for the first row of each CESPID.
2. Compare adjacent CMSTD TM within each CESPID.

Step 3: Summarize the group of bleeding data to obtain the "start" and "end" datetime.

1. Start = onset date = onsetdtm = min(ASTD TM)
2. End = last medication date = max(CMSTD TM)

Derive Bleeding Episodes

Matrix Approach

Step 4: Use the matrix algorithm to find links among treated bleeds.

- Now we have fixed number of treated bleeding episode.
- The BLDNUM obtained here is used to assign linked untreated bleeds.

Step 5: Repeat the matrix algorithm to find links among all bleeds.

- This step is used to find links between treated bleeds and untreated bleeds. The BLDNUM obtained here is used as search key.

Matrix algorithm (steps)

1) Create a matrix saving all the pairwise links (directly or indirectly) between either of two bleeds.

- => Now we have a matrix, and each element of the matrix represents connection of 2 bleeds (matrix a).

2) Then, to calculate power of the matrix to find out if there is any further connection.

- *2nd power of matrix => find out connection up to 3 bleeds (matrix a2_2).*
- *3rd power of matrix => find out connection up to 4 bleeds (matrix a2_3).*

3) Eventually, by calculate power of the matrix, we can search connections among all possible combination (matrix a3). All >0 elements are connected to each other.

4) Extract elements that >0 for each rows to obtain BLDNUM.

Step 6: Generate final sequential BLDNUM in number for all bleeds.

SAS CODE

```
PROC IML;
/* create shell of n*n matrix filled with 0 */
a=j(n,n,0);
/* update each element of the n*n matrix as 1 if the corresponding 2 bleeds can be linked */
do i = 1 to n;
    do j=1 to n;
        if i=j then a[i,j]=1;
        else if ( i^=j & (celocation[i,1]=celocation[j,1]) & (onsetdtm[i,1] <= onsetdtm[j,1]) &
                ((maxmedtm[i,1] + 72*3600) >= onsetdtm[j,1] ) ) then a[i,j]=1;
        else if ( i^=j & _cescat[i,1] = _cescat[j,1] & _cescat[i,1] = 'TRAUMATIC' &
                celocation[i,1]^=celocation[j,1] & onsetdtm[i,1] = onsetdtm[j,1] ) then a[i,j]=1;
    end;
end;
/* calculate n-1 power of the n*n matrix to find all possible links and convert to diagonal symmetrical matrix */
a2 = 0.5*a + 0.5*t(a);
a3 = a2 ** (n-1);
```