**Overview of HIT-RADIO study**

Heparin-Induced Thrombocytopenia – Retrospective Analysis of Data on Incidence and Outcomes Study (HIT-RADIO) was a retrospective chart review study conducted using a large cohort of patients with a positive heparin PF-4 antibody test. Day 0 was defined as the date the positive test was drawn. The primary objective was to determine the time to occurrence of a composite triple endpoint consisting of death, limb amputation/gangrene, and new thrombosis from the time that the positive heparin PF-4 antibody test was drawn until hospital discharge or day 45, whichever occurred first. Key secondary objectives included:

1. To determine the time to occurrence of radiographically confirmed thromboembolism from the time the positive heparin PF-4 antibody test was drawn until hospital discharge, death, or day 45, whichever occurred first.
2. To determine the time to death from the time that the positive heparin PF-4 antibody test was drawn until hospital discharge or day 45, whichever occurred first.
3. To determine the time to occurrence of limb amputation or limb gangrene from the time that the positive heparin PF-4 antibody test was drawn until hospital discharge, death, or day 45, whichever occurred first.
4. To determine the proportion of subjects with HIT-T and isolated HIT in those with a heparin PF-4 antibody test.
5. To determine the type of heparin exposure prior to the positive heparin PF-4 antibody test.
6. To determine the relationship of the heparin PF-4 antibody titer to the clinical diagnosis, degree of thrombocytopenia, and the primary endpoint.
7. To assess the type of treatment (direct thrombin inhibitor, fondaparinux, warfarin, no treatment) provided to subjects in hospital and at the time of discharge.
8. To determine the time to platelet recovery from the time that the positive heparin PF-4 antibody test was drawn until hospital discharge, death, or day 45, whichever occurred first, among subjects with a decreased platelet count
9. To determine the time to occurrence of major bleeding from the time that the positive heparin PF-4 antibody test was drawn until hospital discharge, death, or day 45, whichever occurred first.
10. To assess the impact of treatments received on the time to occurrence of major bleeding from the time that the positive heparin PF-4 antibody test was drawn until hospital discharge, death, or day 45, whichever occurred first.

Each site's institutional review board (IRB) approved waiver of consent for this retrospective review of data already in the medical record.

Nineteen sites participated in the study. All subjects at these sites with a positive heparin PF-4 antibody test occurring between 1/21/2008 and 9/25/2008 and whose medical record was available for the admission during which the positive heparin PF-4 antibody test was obtained were included in the data abstraction. Relevant data were collected to define whether the subject actually had HIT, and if so what type of HIT; to determine the time to a composite outcome of new thromboembolism, limb amputation/gangrene, or death, and time to each of

those three types of events; time to major bleeding; as well as information on platelet counts, treatment modality, discharge outcome, and discharge medications.

The HIT-RADIO study collected data on 673 patients from 19 sites all in the United States. Sites abstracted the data onto case report forms (CRFs). **Table 1** lists the study case report forms (CRFs) completed for each individual patient. Sites entered data directly into an electronic data management system. Data was encrypted and transmitted through a secure network infrastructure to the TMH Data Coordinating Center at New England Research Institutes (NERI).

**Outline of documentation**

A list of case report forms (CRFs) used for HIT-RADIO study data collection and the associated Question-by-Question (QxQ) instructions are provided in **Table 1**. A list of all public use SAS data sets, and the corresponding codebooks containing summary information for each variable included on the data set, are provided in **Table 2**.

In all four CRFs, parts of the questions are designed to collect multiple responses per patient. For example, one section of form HR03 was designed to collect daily platelet count data, and multiple responses could be data entered for this particular question depending on how many days the subject was followed for the study, and how many of those days had a platelet count performed.

Each such data item is referred to as a 'repeating segment'. The naming convention used for the dataset identified not only the CRF from which it originated but also the information that was obtained (e.g. all daily platelet counts obtained for an individual patient were stored in a dataset named HR03_PLATLT_RS, where HR03 identifies the CRF, PLATLT refers to platelet count and RS identifies it as a repeating segment table). These repeating segment tables can be linked with the main portion of the CRF that contained the information common to the entire CRF (e.g. subject ID). The linking variable between the main portion of the individual CRF and its corresponding repeating segment table(s) is FORMSTAT_ID. (See section **Merging Data Files** below for more detailed information). **Table 3** identifies each CRF that has one or more repeating segment tables.

In addition to the data collected using CRFs, seven analytical datasets were generated using information obtained from one or more CRFs. These datasets were created for use in analyses included in the primary manuscripts. A list of created variables included in each analytical dataset, and explanations as to how the variables were created and coded, are provided in **Tables 4-10**. **Table 4** contains variables related to the creation of event outcome data for each patient; **Table 5, Table 6** and **Table 7** contain variables related to non-heparin anticoagulant medication use, warfarin medication use, and platelet transfusion, respectively, on the days between Day 0 (the date the positive heparin PF-4 antibody test was drawn) and hospital discharge, death, or day 45, whichever occurred first; **Table 8** contains variables related to the admitting service for each patient; **Table 9** contains variables related to the HIT groups and thrombocytopenia (yes/no); and **Table 10** contains variables related to the 4T's score.

Each CRF and each analytic dataset has one or more codebooks provided. The codebook documents contain:

1. Number of observations and number of variables
2. The unit of analysis for the dataset (for example, some data sets have one record per patient, while other datasets have more than one record per patient, such as one record for each transfusion received)
3. Variable names
4. SAS variable labels (for questions taken directly from a CRF the label includes the CRF question number)
5. Codes for categorical variables
6. Summary statistics that include:
    - **for categorical variables:**
        i. number and percent of data values for each coded level of the categorical variable;
    - **for continuous variables:**
        i. number of non-missing and missing data values, mean, standard deviation, median, 25$^{th}$ and 75$^{th}$ percentiles, and the minimum and maximum values
        ii. number and percent of missing data values by missing data types

**Variables modified, collapsed or removed**

1. Master ID variable was replaced by a randomly generated 6 digit number to reduce the likelihood of identifying patients, therefore avoiding potential breach of confidentiality.
2. All date variables were replaced by the number of days from the date that the positive Heparin/PF4 ELISA was drawn. This date was considered as day 0. Dates before that blood draw are indicated by negative numbers, and dates after that blood draw are indicated by positive numbers.
3. All narrative or free text fields were omitted
4. Variables that had small number of subjects in one or more of the categories, that pose a potential risk of patient identification, and were not used in the analyses for the primary manuscript were omitted.
5. Race variable was collapsed to two categories (“White” and “Non-white”).

**Table-1: Data Collection Forms and Question-by-Question (QxQ) Instruction Files.** All case report form (CRF) files and QxQ files are included in the DVD-ROM within a folder “CRFs and QxQ”. The Table includes CRFs pertaining to individual HIT-RADIO patients.

| CRF | CRF Name | Case Report Form files | QxQ files | CRF versions |
|---|---|---|---|---|
| HR01 | Screening and History | HR01 VA.PDF | HR01-QxQ VA.PDF | A |
| HR02 | Data for This Admission | HR02 VA.PDF | HR02-QxQ VA.PDF | A |
| HR03 | Platelet Counts | HR03 VA.PDF | HR03-QxQ VA.PDF | A |
| HR04 | Medications and Interventions | HR04 VA.PDF | HR04-QxQ VA.PDF | A |

**Table-3: CRFs with Repeating Segment Tables.** Each repeating segment data file can be linked with the main CRF data file using the linking variable FORMSTAT_ID.

| CRF | CRF Name | Name of Repeating Segment Table | Questions in Repeating Segment | Description of Repeated segment |
|---|---|---|---|---|
| HR01 | Screening and History | HR01_HEPEXP_RS | B6 | Type of heparin exposure and number of days from positive Heparin/PF4 ELISA to date of exposure |
| | | HR01_CANCER_RS | B7 | Type of cancer and how it was treated |
| HR02 | Data for This Admission | HR02_THRMPR_RS | B12 | Type of thrombosis before the date the positive Heparin/PF4 ELISA was drawn , whether radiographically confirmed, limb, location, side, and number of days from positive Heparin/PF4 ELISA to date of thrombosis |
| | | HR02_THRMAF_RS | B13 | Type of thrombosis on or after the date the positive Heparin/PF4 ELISA was drawn, whether radiographically confirmed, limb, location, side, and number of days from positive Heparin/PF4 ELISA to date of thrombosis |
| | | HR02_CAUSTH_RS | B14 | Other obvious cause of thrombocytopenia and number of days from positive Heparin/PF4 ELISA to date of thrombosis |
| | | HR02_UPCLOT_RS | B15 | Location and side of upper extremity clot found by screening, and number of days from positive Heparin/PF4 ELISA to date clot was found |
| | | HR02_LOCLOT_RS | B16 | Location and side of lower extremity clot found by screening, and number of days from positive Heparin/PF4 ELISA to date clot was found |
| | | HR02_DEVICE_RS | B17 | Type of central venous or arterial access device used, location of device, limb for device, number of days from positive Heparin/PF4 ELISA to insertion date, and number of days from positive Heparin/PF4 ELISA to removal date |
| | | HR02_SURGPR_RS | B18 | Type of surgical procedure and number of days from positive Heparin/PF4 ELISA to date of surgical procedure |
| | | HR02_MEDPRC_RS | B19 | Type of medical procedure and number of days from positive Heparin/PF4 ELISA to date of medical procedure |
| | | HR02_GANGRN_RS | B20 | Limb gangrene, side of gangrene, number of days from positive Heparin/PF4 ELISA to date of gangrene |
| | | HR02_BLEED_RS | B21 | Type of bleeding event, number of days from positive Heparin/PF4 ELISA to date of event, and time of event |
| HR03 | Platelet Counts | HR03_PLATLT_RS | B3 | Daily platelet count value, number of days from positive Heparin/PF4 ELISA to date of daily platelet count, time |

| CRF | CRF Name | Name of Repeating Segment Table | Questions in Repeating Segment | Description of Repeated segment |
|---|---|---|---|---|
| HR04 | Medications and Interventions | HR04_HEPEXP_RS | B1 | Type of heparin exposure, indications for UFH or LMWH, number of days from positive Heparin/PF4 ELISA to start date of exposure, and number of days from positive Heparin/PF4 ELISA to stop date of exposure |
| | | HR04_MEDPF_RS | B2 | Anti-coagulant medication received, number of days from positive Heparin/PF4 ELISA to start date, and number of days from positive Heparin/PF4 ELISA to stop date |
| | | HR04_TRNFSN_RS | B4 | Number of units transfused, type of transfusion, number of days from positive Heparin/PF4 ELISA to date of transfusion |
| | | HR04_AMPUTN_RS | B5 | Type of limb amputation, side, number of days from positive Heparin/PF4 ELISA to date of amputation, and time of amputation |

## Tables 4-10. List of Datasets Containing Created Variables with Description

In addition to variables collected on the HIT-RADIO case report forms, a number of additional variables were created for use in analyses. These variables were created for the 442 HIT-RADIO study subjects that are included in the analysis dataset. To be included in the analysis dataset, the patient must have some heparin exposure during this hospital admission, either on Day 0 or sometime between Day -5 and Day -1 inclusive. Detailed explanations of variable coding, definitions of each created variable, and, in some cases, the purpose of the created variable are included in the following table.

**Table 4: Dataset Name: EVENT_OUTCOMES:** variables are created from combining information from questions on CRF HR02.
The primary outcome for the HIT-RADIO study was time to the composite endpoint (death, limb amputation/gangrene, new thrombosis), and the secondary outcomes included time to death, time to limb amputation/gangrene, time to new thrombosis and time to major bleeding. For use in time-to-event analyses (e.g. Kaplan-Meier plots or Cox regression), the "days" variables are the time to the occurrence of that type of event, or time until the end of the patient's study follow-up time, if the patient did not experience that type of event. Each of these variables has a corresponding variable indicating whether the event was observed to occur or whether the patient was censored.

| Variable Name | Created from | Explanation | Codes |
|---|---|---|---|
| DAYS_FROM_PF4_TO_TRIPEND | HR02: B2, B11, B13, B20, B22 | The time to composite endpoint from the time that the positive heparin PF-4 antibody test was drawn until hospital discharge or day 45, whichever occurred first | Numeric days |
| TRIPEND_CENSORED | HR02: B2, B11, B13, B20, B22 | An indicator variable whether the composite endpoint was observed (at least one of the triple endpoint events was experienced) or censored (no triple endpoint event was observed between the time the positive test was drawn and the end of the patient's study follow-up time) | 0: No<br>1: Yes |
| DAYS_FROM_PF4_TO_DEATH | HR02: B2, B11, B22 | The time to death from the time that the positive heparin PF-4 antibody test was drawn until hospital discharge or day 45, whichever occurred first | Numeric days |
| DEATH_CENSORED | HR02: B2, B11, B22 | An indicator variable whether the patient died | 0: No<br>1: Yes |
| DAYS_FROM_PF4_TO_LIMB | HR02: B2, B11, B20 | The time to occurrence of limb amputation or limb gangrene from the time that the positive heparin PF-4 antibody test was drawn until hospital discharge, death, or day 45, whichever occurred first | Numeric days |
| LIMB_CENSORED | HR02: B2, B11, B20 | An indicator variable whether the patient had limb amputation/gangrene | 0: No<br>1: Yes |

| Variable Name | Created from | Explanation | Codes |
|---|---|---|---|
| DAYS_FROM_PF4_TO_THRMAF | HR02: B2, B11, B13 | The time to occurrence of new thrombosis from the time that the positive heparin PF-4 antibody test was drawn until hospital discharge, death, or day 45, whichever occurred first. | Numeric days |
| THRMAF_CENSORED | HR02: B2, B11, B13 | An indicator variable whether the patient had new thrombosis | 0: No<br>1: Yes |
| DAYS_FROM_PF4_TO_BLEED | HR02: B2, B11, B21 | The time to occurrence of major bleeding from the time that the positive heparin PF-4 antibody test was drawn until hospital discharge, death, or day 45, whichever occurred first. | Numeric days |
| BLEED_CENSORED | HR02: B2, B11, B21 | An indicator variable whether the patient had major bleeding | 0: No<br>1: Yes |

**Table 5: Dataset Name: NONHEPARIN_ANTICOAGULANT:** variables are created from combining information from CRF HR04.
Information was collected on anticoagulant medications received by patients between the time their Heparin/PF4 ELISA was drawn, through hospital discharge, death, or day 45, whichever occurred first. However, for some patients medication data was available after discharge date and therefore included in this dataset. We created 46 variables that indicate whether the patient received non-heparin anticoagulant medication on each day from Day 0 through Day 45.

| Variable Name | Created from | Explanation | Codes |
|---|---|---|---|
| MED_DAY0 – MED_DAY45 | HR04: B2 | Indicator variable whether the patient received non-heparin anticoagulant medication on a given day. The postfix number indicates the date after Day 0. For example, MED_DAY0 means non-heparin anticoagulant medication use on the day Heparin/PF4 ELISA was drawn, MED_DAY1 means non-heparin anticoagulant medication use on the next day after Heparin/PF4 ELISA was drawn, etc If a patient's last day of study follow-up was Day N and the patient had no CRF data indicating that they were on the medication after discharge, then MED_DAYX is missing for all days X after Day N. For example, if a patient was discharged on Day 10, and had no record of medication after Day 10, then MED_DAY11 through MED_DAY45 all have missing values. | 0: No<br>1: Yes<br>*Missing* |

**Table 6: Dataset Name: WARFARIN:** variables are created from combining information from CRF HR04. Information was collected on warfarin use between the time a patient's Heparin/PF4 ELISA was drawn until hospital discharge, death, or day 45, whichever occurred first. However, for some patients warfarin data was available after discharge date and therefore included in this dataset. We created 46 variables that indicate whether the patient received warfarin on each day.

| Variable Name | Created from | Explanation | Codes |
|---|---|---|---|
| WAR_DAY0 – WAR_DAY45 | HR04: B2 | Indicator variable whether the patient received Warfarin on a given day. The postfix number indicates the date after Day 0. For example, WAR_DAY0 means Warfarin use on the day Heparin/PF4 ELISA was drawn, WAR_DAY1 means Warfarin use on the next day after Heparin/PF4 ELISA was drawn, etc. If a patient's last day of study follow-up was Day N and the patient had no CRF data indicating that they were on warfarin after discharge, then WAR_DAYX is missing for all days X after Day N. For example, if a patient was discharged on Day 10, and had no record of warfarin after Day 10, then WAR_DAY11 through WAR_DAY45 all have missing values. | 0: No<br>1: Yes<br>*Missing* |

**Table 7: Dataset Name: PLATELETS_TRANS:** variables are created from combining information from CRF HR04.
Information was collected on platelet transfusions given to the patient from the time their Heparin/PF4 ELISA was drawn until hospital discharge, death, or day 45, whichever occurred first. We created 46 variables that indicate whether the patient received platelet transfusion.

| Variable Name | Created from | Explanation | Codes |
|---|---|---|---|
| PLATES_DAY0 - PLATES_DAY45 | HR04: B4 | Indicator variable whether the patient received platelet transfusion on a given day. The postfix number indicate the date after Day 0. For example, PLATES_DAY0 means platelet transfusion on the day Heparin/PF4 ELISA was drawn, PLATES_DAY 1 means platelet transfusion on the next day after Heparin/PF4 ELISA was drawn, etc. If a patient's last day of study follow-up was Day N, then PLATES_DAYX is missing for all days X after Day N. For example, if a patient was discharged on Day 10, then PLATES_DAY11 through PLATES_DAY45 all have missing values. | 0: No<br>1: Yes<br>*Missing* |

**Table 8: Dataset Name: SERVICES** The admitting service was categorized by physicians on the HIT-RADIO Protocol

| Variable Name | Created from | Explanation | Codes |
|---|---|---|---|
| SERVICE | HR02: B9, B18, and B19 | Protocol Leadership Committee categorization of admitting service, based on the site's answer to HR02 Questions B9, B18, and B19 and their sub-questions. These questions collected data regarding the reason for hospital admission, and what surgical and medical procedures were performed (if any). Each patient's data were reviewed independently by two physicians. If the two physicians did not initially agree on categorization, the PLC discussed the data and achieved consensus. | 1: CT surgery<br>2: Other surgery<br>3: Ortho surgery<br>4: Medicine<br>6: Cannot determine |

**Table 9: Dataset Name: HIT_GROUP:** variables are created from combining information from CRFs HR02, HR03, HR04.

To qualify as a HIT-T patient, the patient must have a thrombosis that meets all the following criteria:

- Thrombosis occurred during this admission.
- Patient known to have heparin exposure during this admission either on the date of the thrombosis or within the 5 days preceding the thrombosis. If this heparin exposure started on the thrombosis date, it must not have been given to treat a thrombotic condition (because it could be that the heparin was started to treat the thrombosis, rather than the thrombosis occurring while the patient was on heparin).
- Thrombosis occurred somewhere between Day -5 and Day 0 inclusive.

If a patient had a thrombosis before the positive test was drawn, but did not have any thrombosis meeting all the above criteria, the patient may be included in the analysis dataset if all other criteria for inclusion are met, and if there is enough information to determine the baseline and nadir platelet counts for assessment regarding thrombocytopenia. However, such a patient will not be included in the HIT-T group. The patient will be included either in the Isolated HIT group or the No-HIT group, depending on the baseline and nadir platelet counts.

| Variable Name | Created from | Explanation | Codes |
|---|---|---|---|
| HIT_GROUP | HR02:B11<br>HR03: B1, B2, B3<br>HR04: B1, B2 | The HIT groups were defined as<br>– HIT-T: positive heparin-PF4 antibody test and a thrombotic event associated with heparin exposure within the preceding 5 days, with or without thrombocytopenia.<br>– Isolated HIT (~HITT & Thrombocytopenia): positive heparin-PF4 antibody test and a nadir platelet count <50% of baseline platelet count associated with heparin exposure in the preceding 5 days, without a thrombotic event.<br>– No HIT (~HITT & ~Thrombocytopenia): positive heparin-PF4 antibody test with heparin exposure in the preceding 5 days, but not meeting criteria for HIT-T or isolated HIT | 1: HITT<br>3: ~HITT & Thrombocytopenia<br>4: ~HITT & ~Thrombocytopenia |
| THROMBOCYTOPENIA | HR03: B1, B2 | Nadir platelet count ≤50% of baseline | 0: No<br>1: Yes |

**Table 10: Dataset Name: FOURTS_SCORE:** 4T's score variables are created from combining information from CRFs HR01, HR02, HR03, HR04 and the created dataset HIT_GROUP (**Table-9**). The 4T's score was calculated based on the available information in the HIT-RADIO dataset and may underestimate the complete 4T's score.

| Variable Name | Created from | Explanation | Codes |
|---|---|---|---|
| THROMBOCYTOPENIA_SCR | HR03: B1, B2 | Calculated using the value of the nadir platelet count and the percent reduction from the peak count to the nadir count. Scores are assigned as follows<br>▪ 2-points: platelet count fall >50% and platelet nadir ≥20<br>▪ 1-point: platelet count fall 30–50% or platelet nadir 10–19<br>▪ 0 point: platelet count fall <30%, or platelet nadir <10 | 0, 1, 2 |
| PLT_FALLTIMING_SCR | HR01: B6<br>HR02: B11, B12<br>HR03: B3<br>HR04: B1 | Calculated using the number of days from the date of the first heparin exposure this hospital admission to the onset date, defined as the earlier of two dates: the date that the patient's platelet count started to fall (if any), as determined by the HIT-RADIO Protocol Leadership Committee from the serial platelet counts collected by the study; or the date of the earliest thrombosis that qualified the patient to be in the HIT-T group (if any). We also took into account the dates of any recent heparin exposures prior this hospital admission. The scores are assigned as follows<br>▪ 2-points: onset between days 5–10 or onset ≤1 day (with heparin exposure between days 5-30 prior to the test draw date)<br>▪ 1-point: onset after day 10 ; or onset ≤1 day (with heparin exposure between days 31-100 prior to the test draw date); or onset between days 2-4 (with heparin exposure between days 0-100 prior to the test draw date)<br>▪ 0-point: onset ≤4 days without recent heparin exposure; or onset between days 0-1 (heparin exposure between days 0-4 prior the test draw date); or neither platelet count fall nor HIT-T qualifying thrombosis; or onset before first heparin exposure this admission | 0, 1, 2 |
| THROMBOSIS_SCR | HIT_GROUP,<br>HR01: B3, B4<br>HR02: B11, B12<br>HR04: B1 | Calculated as 0 for patients with no HIT-T qualifying thrombosis. The scores for HIT-T patients are calculated as follows<br>▪ 2-points: if a patient had at least one HIT-T qualifying thrombosis that the patient had not experienced before.<br>▪ 1-point: if all of a patient's HIT-T qualifying thrombosis were the same type(s) of thrombosis that they had experienced previously (either during this hospital admission but too early to qualify for HIT-T, or prior to this hospitalization),<br>▪ 0 points: all other patients | 0, 1, 2 |
| OTHER_CAUSES_THROMB_SCR | H02: B14 | Calculated using the question regarding whether the patient had any other obvious cause of thrombocytopenia. The scores are assigned as follows<br>▪ 2-points: patients without obvious cause of thrombocytopenia on the date of the test draw<br>▪ 0-point: patients with obvious cause of thrombocytopenia on the date of the test draw | 0, 2 |
| TOTAL_4Ts_SCR | THROMBOCYTOPENIA_SCR<br>PLT_FALLTIMING_SCR<br>THROMBOSIS_SCR<br>OTHER_CAUSES_THROMB_SCR | The sum of all four scores. The minimum and maximum possible values are 0 and 8 respectively. | 0 to 8 |
| TOTAL_4Ts_SCR_Group | THROMBOCYTOPENIA_SCR<br>PLT_FALLTIMING_SCR<br>THROMBOSIS_SCR<br>OTHER_CAUSES_THROMB_SCR | Total 4T's score grouped as low (0-3), intermediate (4-5), or high (6-8). | Low<br>Intermediate<br>High |