BMJ Open Development of prospective hospital-based venous thromboembolism registry across India: a study protocol

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ABSTRACT

Introduction Indian Council of Medical Research (ICMR), New Delhi has established a nationwide registry ‘Indian Registry for Venous Thromboembolism Disorder (i-RegVed)’ for real-time analytics of sociodemographic profile of patients, disease patterns, management strategies, treatment choices and outcomes of patients with venous thromboembolism (VTE). The purpose is to generate evidence on VTE in order to fill the gaps in the knowledge of the disease across various demographic regions.

Methods and analysis This prospective hospital-based registry will be a continuous data collection process on the occurrence and characteristics of VTE from the 16 hospital sites pan India. This process would include obtaining clinical profiles, risk factors, diagnostic tests, treatment and outcome information of patients collected from medical records through an active method of data abstraction and data capture mechanism guided by an online web-based tool.

Epidemiology and dissemination At centralised programme management unit, the study protocol was approved by the Institutional Ethics Committees (IEC) named ICMR-Central Ethics Committee on Human Research and similarly each of the participating site has obtained the ethical approval by their respective IECs. The results from this study will be disseminated publicly on the study website (https://iregved.icmr.org.in) as well as through scientific meetings and publications.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This registry will record the extensive sociodemographic, epidemiological and clinical information contributing to a better understanding of diseases and current management practices in India.
⇒ The registry will help in the understanding of various epidemiological factors, identifying current practices and gaps, subsequently this will help in devising best practices for venous thromboembolism (VTE) management.
⇒ This registry has been developed as a hospital-based clinical registry, so it will not be possible to perform disease estimates in terms of disease-specific incidence and prevalence.
⇒ The registry will continue to enrol patients on a daily basis, so the sample size of the registry has not been calculated.
⇒ This study will include only confirmed cases of VTE, so sometimes it may miss the misdiagnosed suspected cases of VTE.

INTRODUCTION

Venous thromboembolism (VTE) poses a significant global public health. It is a vascular condition that includes deep vein thrombosis (DVT) and pulmonary embolism (PE) and is initiated by the formation of a thrombus (blood clot) resulting in a hampered flow of blood in the deep vein and pulmonary arteries. Globally, the annual incidence of VTE ranges from 0.75 to 2.69 per 1000 populations.1 In Asian populations, it was observed that in the past few decades, VTE rates have been rising, ranging from 15 to 88 per 10000 hospital admissions which are approximately 15%–20% of the incidence in western regions.2 VTE is under-reported in Asia and epidemiological studies on this under-diagnosed but serious disease are dearth. A comparison of risk profiles and treatment patterns of patients with VTE has revealed that Asian patients have a higher risk of mortality than the rest of the world.3 One of the reasons for the increasing trend could be improvements in the early detection of VTE and subsequent interventions to mitigate the thromboembolism episodes in high-risk patients.4

Indian studies on retrospective hospital-based data from 1996 to 2005 revealed that the incidence of VTE is approximately 22 per 10000 hospital admissions.5 Also, most postoperative patients had lower limb DVT. Being one of the most populous countries, India’s contribution to the global burden of VTE would be very high due to inadequate quality risk assessment tools, lack of documentation, asymptomatic VTE cases, misdiagnosis and improper follow-up of
postoperative patients. Rapid and accurate clinical diagnosis of VTE is also challenging requiring proper patient medical history to identify early risk factors. There is also a need for the appropriate choice of pharmacological and non-pharmacological prophylaxis for patients with VTE to reduce complications. There is an imperative and non-negotiable need for the appropriate choice of pharmacological and non-pharmacological prophylaxis. The registration of VTE is also challenging requiring proper patient information facilitated evidence-based decisions and provide useful measures to reduce major complications. The registry will collect clinical data of patients with VTE from selected hospitals across the country. The overall purpose of the registry is to generate evidence on VTE, improve patient management across different treatment settings and guide policy and health planning. Based on the experiences gained from the study, it is proposed to estimate the burden of the disease, develop risk-assessment strategies, screen patients at risk of developing VTE and develop appropriate thrombo-prophylaxis to reduce complications.

The VTE registry of India inaugurated by the ICMMR is the first in the country. The logo has been provided to the registry to make it unique. The name is an acronym as i-RegVed and it has been from the ancient scriptures of Veda. There are four Vedas among them Rig Veda is the first one and it is the knowledge of verses. Similarly, the VTE registry (i-RegVed) will provide us the information which will further help in better understanding and management of the diseases and make it unique in this modern urbanisation and digitisation era.

**Materials and Methods**

The prospective hospital-based registry will be a continuous data collection process on the occurrence and characteristics of VTE initially for 5 years. Data on the follow-up of patients registered in the study will also be reported. The registry will contain information on the clinical profiles, risk factors, diagnostic tests, treatment pattern and outcome of patients retrieved from the medical records through an active method of data extraction and capture mechanism guided by an online web-based tool. The entire mechanism of VTE registry is exhibited in figure 4.

**Eligible criteria site selection**

The selection of sites was done based on certain criteria such as geographical representation, local population characteristics, VTE caseload, the strength of local sites, the adequate infrastructure of the institution, outreach, patient coverage, availability and engagement of multispeciality experts, the scope of capacity building and so on.

**Identification of the nodal study sites**

The selection of tertiary care hospitals and health institutes participating in the National VTE Registry was through the screening of letter of intent applications floated in the ICMMR web portal. The zone wise distribution of the participant sites is provided in figure 1. Information related to the geographical location, population representation, case load, infrastructure, patient outreach and coverage and engagement of multispeciality staff was obtained from the sites willing to participate. Based on this information, 4–5 sites from the east, west, north and South regions of the country were identified. For each site, a site principal investigator (PI) was identified. The site PI is involved in the management of patients with VTE and would lead the registry in their respective hospitals. The spot map of the participating centre of the national hospital-based registry for VTE disorder (i-RegVed) is exhibited in Figure 2. Each site PI will be supported by co-PIs and co-investigators from various departments like pathology, surgery, obstetrics and public health.

**Characteristics of the VTE registry network and requirement of additional participating centres**

Currently, the registry includes 16 public and private hospitals across India. A dedicated web portal for data entry (https://iregved.icmr.org.in) has been developed by the ICMMR Headquarters, New Delhi with information about the registry for prospective collaborators, publications, breakthrough information, etc. Each participating hospital is supposed to enter the information of the registered patients on this web portal. The details of the web portal can be obtained from the corresponding author on request. The web portal will be monitored and managed by ICMMR—National Institute of Medical Statistics (ICMR-NIMS). The portal would be Secure Sockets Layer certified, ensuring the security of the data at the institutional level. The registry is open to other eligible sites all over India that wish to become a part of this network. Prospective centres are required to contact the coordinator of the registry at ICMMR for collaboration. After reviewing the registration, ICMMR would provide login credentials to the hospital with access control for data entry, data monitoring and data download and report/table generations.

**Patient and public involvement**

The patients/public is involved in the research in two phases: initially, patients will be involved as participants in the study. Afterwards, during the dissemination of the study findings, guidance documents and reports...
of the registry will be provided on the i-RegVed open online source for the information of the public. Additionally, training and capacity-building workshops will be conducted among the staff of the study sites for familiarising them with the components of all the forms in the registry portal. Research questions have been developed by a team of multidisciplinary members. A pilot study was conducted to test the reliability of the question. As this is a protocol, we have given the design of the study. Once the centres will be engaging in the collection of data from participants, ethical consent will be taken from them. The patients will be provided with a participant information sheet and informed consent forms in local languages for inclusivity and understanding. The present study protocol will be followed universally by the medical institutions engaged in the study. Further, data for the study will be collected from the patients. The patients will be discharged but still continuing medication/treatment, follow-up treatment (for postoperative complication), leave against medical advice (LAMA), death or referral to another facility. Medical institutions/study sites involved in i-RegVed will be recruiting the patients for the study based on the inclusion and exclusion criteria defined in the protocol. All the sites will carefully follow the universal protocol for recruiting patients for generating desirable study outcomes. The key findings of research and dissemination of the study report will be provided on the public portal. Also research insights and learnings will be published as a policy document.
Timeline of data collection and enrolment of patients
The registry will collect anonymised real-time data of patients diagnosed with VTE and admitted to the participating hospitals from June 2022 initially for 5 years. The relevant data for the patients with VTE will be extracted on a case record form (CRF) first from the medical records and will be later entered into the web portal in the electronic patient record form by the participating centres. The site PI will be responsible for data entry. Furthermore, the study process of VTE is exhibited in figure 3. Moreover, the entire mechanism of selection of the institute under VTE registry (i-RegVed) is exhibited in figure 4.

Study instruments
The data from medical records will be extracted from the patients with confirmed VTE diagnoses in an online CRF. The CRF is a comprehensive web-based form that includes sociodemographic, epidemiological, clinical presentations, medical and surgical history, laboratory
investigations current diagnoses, treatment details and outcomes in eight sections (table 1).

Selection of patients
Patients will be recruited in the registry based on well-defined exclusion and inclusion criteria.

Inclusion criteria
- Patients of all age groups diagnosed with VTE, ie, acute DVT, PE and/or spontaneous superficial venous thrombosis (SVT), unusual site venous thrombosis and confirmed by contrast venography, ultrasonography, impedance plethysmography or MRI, for suspected DVT; pulmonary angiography, lung scintigraphy or helical CT scans, for suspected PE; ultrasonography for suspected SVT.
- New patients with VTE in all age groups admitted to the hospital or inpatients that develop VTE/PE as a complication in due course of treatment for some other disease.

Exclusion criteria
- Patients having SVT arising out of intravenous line/cannula or a diagnosed case of fat embolism due to any aetiology, including orthopaedic complications. Note: Although, the patients enrolled in a clinical trial or experimental therapy would also be included based on the site local IEC approvals or if they are available for a 3-month follow-up. Informed consent will be obtained according to the requirements of the ethics committee of the participating site.
Outcome
The outcome of the registry to determine the sociodemographic, clinical and epidemiological risk factors that could potentially lead to VTE. The variation in the treatment pattern across the sites and comparison with the international VTE registries is proposed.

Follow-up
The registered patients will be followed up at least twice after discharge. The first follow-up will be on the 30th day and the next one will be on the 90th day after discharge from the hospital. In addition, the hospital staff will do telephonic reminders for the same. The detailed information will be collected on a follow-up form that includes the following:

- Development of any new signs and symptoms or any significant finding during follow-up.
- Any clinical symptoms and laboratory investigations on VTE and associated manifestations (any relapse of symptoms that may occur).
- VTE-related complications that have been diagnosed lately or deterioration of previous illness.
- Comorbidity newly diagnosed, and clinical status of comorbid conditions (under control/further deterioration/any new complication).

Training for data entry, monitoring and quality control
The site PIs and their team will be provided online training for data entry, and quality control measures to ensure the accuracy of the data entered from the study sites. The team at ICMR-NIMS will periodically review the data entered for gaps and discrepancies and provide regular feedback to the VTE registry network hospitals team.
Table 1  Summary of sections covered in digital case record form

<table>
<thead>
<tr>
<th>Sections</th>
<th>Title of section</th>
<th>Brief description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Section 1</td>
<td>Details of hospital/healthcare facility</td>
<td>The details regarding the hospital and healthcare facility provided in this column. The information like the patient identifier, organisational information, facilities, registration details which includes unique ID, date of hospitalisation, department, etc will be recorded.</td>
</tr>
<tr>
<td>Section 2</td>
<td>Patient information</td>
<td>Social and demographic information provided in this column like the date of birth of the patient, age, sex, address, including family details, etc personal information including travel, habits and its frequency.</td>
</tr>
<tr>
<td>Section 3</td>
<td>Detailed medical history</td>
<td>Detail medical history of past and present serious illness will be recorded. History of communicable diseases like HIV, TB, etc. Non-communicable diseases like hypertension, rheumatoid disease, heart disease or failure, stroke, chronic respiratory disease like COPD, etc. The information like a follow-up of patients, registration dates, vital parameters, such as heart rate, pulse rate, temperature, blood pressure, respiration rate, etc, and if any complications then its information will also be recorded.</td>
</tr>
<tr>
<td>Section 4</td>
<td>Clinical examination</td>
<td>During admission, comprehensive clinical examination information will be recorded. The information related to signs and symptoms along with the findings related to general examination and systematic examination will be recorded.</td>
</tr>
<tr>
<td>Section 5</td>
<td>Diagnostic techniques</td>
<td>The comprehensive information will be recorded such as details of biochemical parameters and microbiological parameters. The imaging techniques such as USG, X-ray, CT scan, MRI and Doppler.</td>
</tr>
<tr>
<td>Section 6</td>
<td>VTE details</td>
<td>The information of thrombosis details such as site of thrombosis. Further final diagnosis will be recorded such as DVT, B/L, L/L. The complications observed in thrombosis such as shock, bleeding, sepsis, heart failure kidney injury, pancreatitis, etc will be recorded.</td>
</tr>
<tr>
<td>Section 7</td>
<td>Medications</td>
<td>Comprehensive medication/treatment protocol will be recorded in this section. Details of routes or any surgical procedures will be recorded. The dosage and frequency of various class of the therapeutics will be recorded like corticosteroid, antibiotic, antifungal, non-steroidal, anticoagulants, antiplatelet, thrombolytic agents and other therapeutic agents.</td>
</tr>
<tr>
<td>Section 8</td>
<td>Follow-up</td>
<td>This section covers the outcome in terms of patient discharge from the hospital like cured/referral/LAMA/death. At 30th day and after 90th day of discharge from hospital.</td>
</tr>
</tbody>
</table>

B/L, Bilateral Lower Limb; COPD, Chronic Obstructive Pulmonary Disorder; DVT, deep vein thrombosis; LAMA, leave against medical advice; L/L, Lower Limb; TB, Tuberculosis; USG, UltraSonography.

The recruited study subjects will be given a unique ID. The name and IDs of the study participants will be kept confidential with the site investigators and the personal information of the patients with VTE will not be entered into the CRF or the registry. None of the details of study participants revealing their identity will be used in any reports and publications arising from this study. The site PIs will verify the final entry before entering the data on online web portal.

Data entry and data access will be independently controlled and held behind secure firewalls. Data collected from different study sites will be kept separate, and only specific individuals within a research team will be able to access and edit the data.

Data security

The patient details would be deidentified at the peripheral level, and the identification details would be stored on a separately secured server. In contrast, the deidentified patient details secured by a uniquely generated identifier would be sent to the ICMR server, making the patient’s details anonymised at the ICMR-NIMS level. It will be desirable to have the registry baseline form as part of the patient case sheet so that all relevant data will be collected at the primary interaction. The staff shall update the patient record on time from the patient case records, including follow-up. Wherever feasible and safe, the information will be updated by personal interaction with the patient or her/his close attendant.

Statistical analysis

The burden of VTE and related manifestation will be estimated using standard case definitions and reporting framework. In addition, the pattern of comorbidities/risk factors influencing clinical recovery among patients with VTE may support developing treatment guidelines. Descriptive analysis of the data will be performed by generating means and proportions. Statistical software IBM SPSS V.22.0 will be used for analysis. Further, data analysis will be performed as per the expert committee and the requirements of the state health department. Complex statistical analysis (projections/modelling/forecasting, multivariate analysis, etc) will be done as appropriate.

DISCUSSION

In order to fill the gaps in the current knowledge related to VTE in the Indian scenario, the registry might play a pivotal role. ICMR VTE registry is probably the first of its kind in India and South Asia that prospectively collects data. The information provided by the VTE registry will enable global comparison of the data. Regionally representative data of patients with VTE across various zones of the country will provide information on the treatment patterns and distribution of patients with VTE. The registry will facilitate reinforcing knowledge and the skills of physicians and healthcare staff and evaluate...
the efficiency of dedicated treatment facilities. In due course, the participating centre will be augmented along with that alliance with the international consortium with global experts having experience in mitigating VTE.

Epidemiological studies on Asian demographics reveal that the VTE incidence is increasing among this population. Furthermore, the registry has the potential to establish an understanding of the present status of the VTE, which is yet not unearthed by any researchers of the domain. The registry envisages for filling the void, on screening modalities and prophylaxis protocols for VTE treatment in our country, both in terms of reduction in cost of healthcare and reduction in mortality and morbidity.

During the pandemic, VTE has emerged as an adjuvant to COVID-19, predominantly among the critical patients with existing comorbidities, causing healthcare woes to physicians and patients alike across the globe. This necessitates in-depth research on the pathophysiology that could likely lead to VTE outcomes in patients with COVID-19.

It has been evidenced from RITIE’s VTE registry that 45.08% risk factors are still unknown and other known factors are immobility (23.42%), cancer (22.54%), surgery (10.78%), hormonal use (5.6%), travel (2.54%), pregnancy (0.66%), puerperium (0.52%), etc. The information regarding all known factors will be recorded in the registry.

Hence, the application of information technology for care and research should be linked via several national/local databases relevant to VTE. The registry data will get enhanced and compacted. There is a need to institute a nationwide registry with a standard reporting framework and data capture using electronic information technology for the timely analytics of patterns of disease distribution, patterns of treatment and outcomes of VTE and related manifestations. The registry shall provide information on the disease burden, risk factors and outcomes. This shall contribute to strengthening the state of art, collaborating laboratories across the country, developing uniform diagnostic and treatment guidelines for VTE and associated manifestations, guiding policy and health planning in states and fostering innovative research.

Ethics and dissemination

At centralised programme management unit, the study protocol was approved by the Institutional Ethics Committees (IEC) named ICMR-Central Ethics Committee on Human Research and similarly each of the participating site has obtained the ethical approval by their respective IECs. Before collection of data, to obtain informed consent, a participant information sheet will be shared and explained to each of the patient. For any further inquiry(s), the PI from the respective institute will be the patient’s contact point. Out of 16 sites, 13 sites have obtained IEC and started enrolling patients. The details of IEC’s approval of these sites have been provided in a tabular form in the online supplemental file 1.

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Patient and public involvement Patients and/or the public were involved in the design, conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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