



Design and rationale of DISCOVER global registry in type 2 diabetes: Real-world insights of treatment patterns and its relationship with cardiovascular, renal, and metabolic multimorbidities

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ABSTRACT

Aim: The DISCOVER Global Registry (DGR) aims to provide insights into patient attributes and treatment patterns in patients with type 2 diabetes mellitus (T2DM) seen in clinical practice and understand the patterns and impact of treatment strategies on cardio-renal-metabolic multimorbidities. It aims to augment the real-world evidence base created by the DISCOVER study.

Methods: The ongoing study is a global, prospective, open-source, physician-led registry and involves non-interventional data collection through cloud-based electronic case report form platform from participants with T2DM receiving care as part of routine clinical practice. The DGR will collect longitudinal prospective data on the following: (a) patient, healthcare provider, and healthcare system characteristics; (b) treatment patterns and factors influencing therapy changes; (c) disease duration and glycemic control; (d) management of micro and/or macrovascular complications; (e) management of associated risk factors; (f) outcomes (hospitalization/death), (g) quality of care indicators (eye/foot examination); (h) healthcare resource utilization; and (i) patient-reported outcomes.

Conclusion: Establishment of this long-term, scalable, and sustainable global registry offers opportunities to enhance understanding of care gaps, establish quality benchmarks, and understand the role of various treatment strategies in addressing the multifactorial pathophysiology of T2DM and associated comorbidities—potentially enabling transformation of clinical data into actionable insights for improving patient outcomes.

1. Introduction

Diabetes has attained pandemic levels, affecting around 463 million adults (20–79 years), and is estimated to affect 700 million by 2045. The estimated global prevalence of diabetes was 9.3% in 2019, with type 2 diabetes mellitus (T2DM) accounting for over 90% of all forms of diabetes.^{1,2} A global systematic review reported that there were more than

500 million prevalent cases of T2DM in 2018, comparable between high- and low-income countries.³ Global projections from 2018 to 2028 reveal that the prevalence of T2DM will increase in all countries, but the greatest growth will be experienced in lower-income countries.³ Diabetes has substantial economic implications especially in low- and lower-middle-income countries, attributing to an annual average cost (both direct and indirect per person) ranging from USD 29.91 to USD

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237.38; hospitalization being the leading contributor of direct costs followed by drug costs.⁴ Asia is at the epicentre of the diabetes epidemic owing to a phenotype characterised by younger age of onset, predisposition to beta-cell failure, and visceral adiposity, with China and India incurring a considerable burden of the disease.²

Diabetes is innately insidious, and owing to lack of screening facilities in low- and middle-income countries (LMICs), is often diagnosed only once complications develop, namely microvascular (neuropathy, nephropathy, and retinopathy), macrovascular (cardiovascular, peripheral vascular, and cerebrovascular disease), and hemodynamic (heart failure) complications.⁵ Empirical evidence from clinical trials and observational studies have demonstrated that such complications are independently associated with reduced quality of life, an enhanced risk of major adverse cardiovascular events, reduced life expectancy and mortality—highlighting the need for early diagnosis and close monitoring of complications.^{6–11} Additionally, therapeutic inertia, gaps in disease monitoring, lack of effective clinical care delivery models that prioritize prevention through lifestyle measures, and suboptimal drug adherence act as crucial challenges, culminating in a cascade of complications.^{12,13}

With the growing burden of T2DM and its complications globally, the trajectory of care is evolving with a multitude of efficacious and safe therapies that can help reduce the risk. Recently, the landscape of pharmacotherapy for T2DM has changed considerably by emergence of cardio- and nephron-protective glucose-lowering drugs (GLD). The current practice guidelines have mapped a step-wise patient-centered treatment pathway considering comorbidities such as atherosclerotic cardiovascular disease (CVD), heart failure, chronic kidney disease, hypoglycemia, impact on weight, cost, risk of side effects and patient preferences.^{14,15} The guidelines recommend that among patients with T2DM who have established atherosclerotic CVD or indicators of high risk for CVD, established kidney disease (including albuminuria), or heart failure, a sodium–glucose cotransporter 2 inhibitor and/or glucagon-like peptide 1 receptor agonist with demonstrated CVD benefit should be initiated, together with early combination therapy as part of the glucose-lowering regimen independent of glycosylated hemoglobin [HbA1c] or metformin use accounting for patient-specific factors.^{14–16} Although the guidelines have uniformly endorsed these interventions, adoption remains extremely low. Most high-risk patients do not receive optimal quality of care—this is even more exacerbated in LMICs. Lack of effective clinical care delivery models and clinical inertia are key barriers for optimal management. In order to address clinical inertia, understanding and benchmarking quality of care across different geographic regions, especially those with scarce information, is crucial. This can lead to quality improvement initiatives in diabetes care, fostering greater adoption of guideline recommendations and improvement in quality of care and outcomes. In this regard, the DISCOVER Global Registry (DGR) is envisioned as the vehicle to start this process.

DISCOVER, an observational, longitudinal, prospective 3-year study enrolling more than 15,000 participants in 38 countries between 2014 and 2016, was undertaken to provide insights on disease management patterns and associated outcomes in patients with T2DM, initiating a second-line GLD after failure of first-line oral treatment (monotherapy or combination therapy) in routine clinical practice.^{17,18} To augment the knowledge base established by the DISCOVER study and broaden the catchment area, the DGR was initiated, envisaging generation of additional robust, long-term, longitudinal, and large-scale RWE with regard to patient management and quality of care being built on the framework of this rich prior experience. The DGR would allow continued longitudinal data collection per standard of care in the real-world, beyond the 3-year follow-up of the DISCOVER study for countries/sites already included, allow extension of data elements to include key micro and macrovascular complications of T2DM, allow expansion of patient recruitment to developing regions/new sites not included in the DISCOVER study, and allow physicians to increase control over the

management of their patients' population and access data for benchmarking reports through the use of a novel cloud-based electronic case report platform. The goal is to improve patient care and clinical outcomes worldwide by collecting reliable, real-world clinical data on cardiovascular, renal and metabolic diseases. Additionally, it aims to build on the success of DISCOVER study to establish a new long-term, evolving, scalable, and sustainable global registry and strengthen the infrastructure for a contemporary standard clinical management platform.

1.1. Study objectives

The DGR was primarily designed to provide real-world data on patient characteristics, disease management, healthcare utilization, quality of care and outcomes in patients with T2DM and established micro and/or macrovascular disease. Objectives of the registry are described in Table 1.

2. Subjects, material and methods

2.1. Design of DGR

The DGR ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03549754) Identifier: NCT03549754) is an investigator-led, prospective, multinational, observational registry. The registry is an open-source model, relying on voluntary physician and patient participation. The registry involves non interventional data collection from people undergoing clinical assessments and receiving standard medical care as part of routine clinical practice based on the physician's discretion. The engagement with local countries for pilot initiation, mainly aimed for feasibility and infrastructure testing, commenced on November 2017. The patient enrollment started from February 2018 and is ongoing (Fig. 1).

At the first visit, all patients presenting are being assessed for eligibility, consecutively invited to be enrolled in the registry, and thereafter are being followed up per routine clinical care. The data are being uploaded incrementally at each follow-up visit by the physicians, using a cloud-based electronic case report form (e-CRF). Follow-up reflects real-world practice, with clinically indicated visits and no additional mandatory follow-up visits, nor interventions by protocol. Participating clinicians have access to their own patient-level data and can submit requests for data analyses, which can be compared with aggregated national and global data. The pooled anonymized data will be forwarded

Table 1
DISCOVER global registry (DGR): primary and secondary objectives.

Primary	<ul style="list-style-type: none"> To provide real-world data on patient characteristics, disease management, healthcare utilization, quality of care indicators, and outcomes in patients with type 2 diabetes mellitus
Secondary	<ul style="list-style-type: none"> To determine risk factors associated with progression of microvascular and macrovascular complications, patient outcomes (e.g., hospitalization and death), quality of life, and healthcare resource use (HRU) during follow-up, including: <ul style="list-style-type: none"> o patient factors (e.g., age, sex, comorbidities, ethnicity, and socioeconomic status) o disease factors (e.g., duration of diabetes) o treatment factors (e.g., class of glucose-lowering medication) o physician/practice factors (e.g., primary care versus specialists) o regional/geographic factors o general quality of care indicators (e.g., smoking cessation, eye and foot examinations and dietary counselling) To assess the relationship between the complications and comorbidities of type 2 diabetes mellitus and treatment strategies To determine the association between diabetes complications and outcomes (e.g., all-cause and cause-specific hospitalizations, and deaths) To describe HRU (e.g., frequency of emergency department visits, inpatient hospitalizations, and length of inpatient hospital stays) To assess quality of care indicators (e.g., smoking cessation, eye and foot examinations, and dietary counselling)

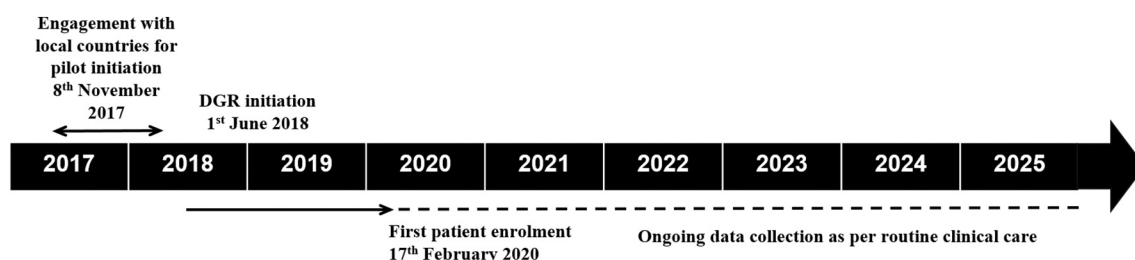


Fig. 1. DISCOVER Global Registry (DGR) Timelines.

to the analytical centers for data analysis.

2.2. Settings and selection of sites

Recruitment into the multinational registry was planned to be phased, starting with a smaller subset of countries in the first phase; however, it quickly expanded by “spread of word” among participating clinicians including a number of additional sites from multiple countries (many of which have little pre-existing real world data available). At the time of the manuscript writing the countries participating in the registry include Argentina, China, Costa Rica, Dominican Republic, Ecuador, Ethiopia, Georgia, Greece, India, Indonesia, Malaysia, Mexico, Peru, Philippines, Russia, Saudi Arabia, Thailand, Ukraine, Qatar, and Singapore. Additional voluntary participation from clinicians in other countries is planned for the next phase of recruitment. The current status of countries participating in the DGR and number of enrolled patients in each country is illustrated in Fig. 2.

2.3. Study population

Eligible patients with T2DM are being invited to participate in the study by their physician. The target population consists of adults (≥ 18 years) with T2DM who have provided written consent to participate in the study. Patients with type 1 diabetes, women who are currently pregnant or nursing, patients having a life-threatening comorbidity with life expectancy below 1 year, or participating in an interventional trial requiring informed consent are being excluded.

2.4. Data collection

2.4.1. Cloud-based electronic data capture

Data is being collected from all eligible patients using a simple, user-friendly, and standardized e-CRF by a web-based data capture system that facilitates accessibility, feasibility, and efficiency of data collection. Data is being saved immediately to a central database, and all e-CRFs are being checked to ensure that they are filled appropriately with available data (because of the inherent possibility of missing data from real-world studies). In-built programmable edits in the e-CRF are facilitating immediate feedback if data is incorrect.

2.4.2. Patient informed consent

The DGR is being conducted in accordance with the Guidelines for Good Pharmacovigilance Practices and Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology (ISPE) and the Declaration of Helsinki, and any applicable national guidelines. Approvals are being obtained from the Institutional review board and ethics committee before commencement of patient enrollment in the registry. An informed consent is being signed by the patient (or the patient's legally authorized representative) before participation in the registry.

2.4.3. Data privacy and security

In order to maintain patient confidentiality, only de-identified data is being entered into the cloud. To achieve this, each patient is being assigned a unique patient identifier upon enrollment, which will be used

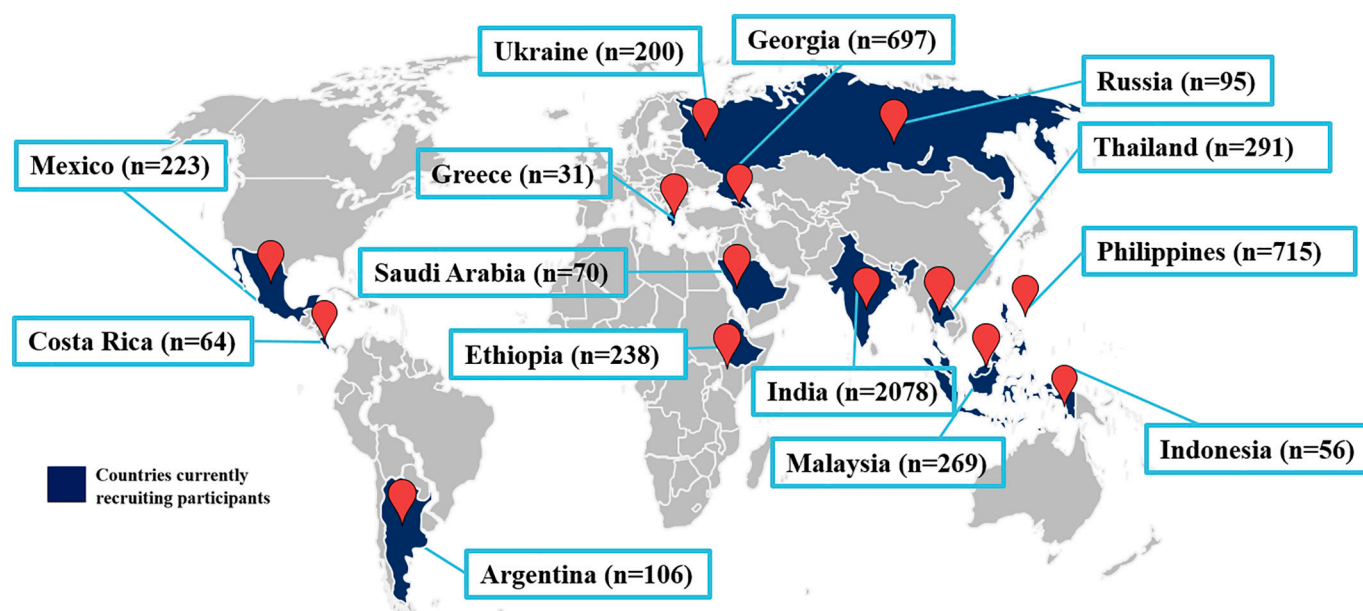


Fig. 2. Current status of countries participating in DISCOVER Global Registry (DGR) and number of enrolled patients in each country (as of 30th November 2019). Countries participating in DISCOVER Global Registry (DGR) are divided into regions according to World Health Organization categories. Enrollment of patients is currently ongoing for other countries.

in place of patient names for the purpose of data analysis and reporting. Protection of patient personal data will be ensured and participant confidentiality will be protected in compliance with the Directive 95/46/EC on the protection of individuals, and Safe Harbor privacy principles, and any other applicable local laws and regulations. An electronic platform for integrated data capture across multiple clinical areas referred to as 'RWE box' has been used in this registry. Security policies of this RWE box are consistent with Good Clinical Practice and Health Insurance Portability and Accountability Act (HIPAA) standards for the protection of any personally identifiable information. The RWE box seeks to protect personal data using appropriate technical and organizational measures. Sensitive information is securely transferred and stored encrypted. Servers with personal information are stored in a controlled environment with limited access and maintain a wide variety of compliance and security programs. The RWE box is hosted on Alibaba Cloud, which undergoes various third-party independent audits on a regular basis, covering compliance controls for its data centers, infrastructure, and operations, including Service Organization Control (SOC) 3 and International Organization for Standardization (ISO) 27001 certification registry.

2.4.4. Data variables

The DGR platform offers a full electronic medical record (eMR) to be flexibly used by the clinicians according to their local needs. However, for the current registry purposes in T2DM, the data domains to be analyzed specifically in the DGR include the following: (a) patient, clinicians, and healthcare system characteristics; (b) treatment patterns and factors influencing changes in therapy; (c) disease duration from date of diagnosis and control (e.g., achievement of HbA1c target and incidence of hypoglycemic events); (d) management of micro and/or macrovascular complications; (e) management of associated risk factors (e.g., hypercholesterolemia and hypertension); (f) outcomes (e.g., all-cause and cause-specific deaths and hospitalizations, including recurrent events), quality of care indicators (e.g., smoking cessation, eye and foot examinations, dietary counselling, and annual monitoring of parameters, such as HbA1c, blood pressure, lipid profile, albuminuria, etc.); (g) healthcare resource utilization (HRU); and (h) patient-reported outcomes.

In addition to sociodemographic characteristics, data regarding family history of T2DM and CVD, health insurance coverage, behavior factors and blood glucose monitoring frequency, vital statistics, concomitant diseases and concomitant medications are being collected

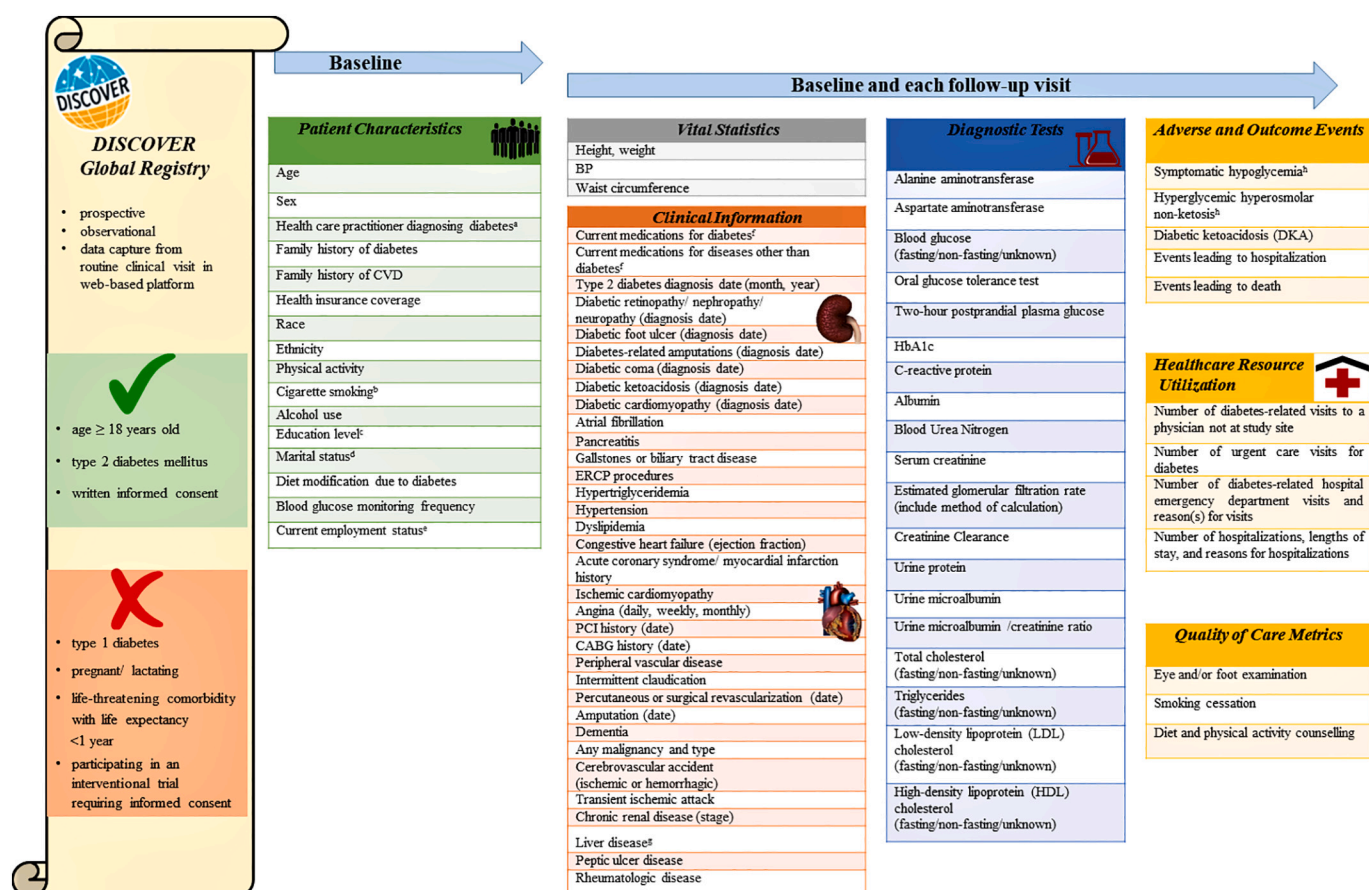


Fig. 3. Data elements captured in the DISCOVER Global Registry (DGR) during baseline and routine clinical follow-up.

BP = blood pressure; ERCP = endoscopic retrograde cholangiopancreatography; PCI = percutaneous coronary intervention; CABG = coronary artery bypass surgery; CVD = cardiovascular disease; HbA1c = glycosylated hemoglobin.

^aHealthcare practitioner diagnosing diabetes: primary care physician/general physician/family medicine/internal medicine, diabetologist/endocrinologist, or other specialist.

^bCigarette smoking: never, former, current; number of pack-years.

^cEducation level: secondary school, secondary school graduate, some university, university graduate, professional or graduate degree.

^dMarital status: single/never married, single/divorced, married, widow/widower.

^eCurrent employment status: employed full-time, employed part-time, work in the house or student, retired, military, unemployed.

^fCurrent medications: medication name, prescription date, dose, number of pills per dose, dosing frequency.

^gLiver disease: mild/moderate/severe.

^hSymptomatic hypoglycemia, hyperglycemic hyperosmolar non-ketosis: number of events since last visit, date and time of each event.

at baseline (Fig. 3).

During each follow-up visit, variables and core metrics (key parameters relevant to the routine clinical practice of diabetes management) are being collected if available. The core metrics include the following: chronic kidney disease, retinopathy, coronary artery disease with details on angina, myocardial infarction, percutaneous coronary intervention and coronary artery bypass grafting, stroke, diabetic foot, amputation, defibrillator use, and heart failure. Other variables such as albuminuria, retinal laser photocoagulation, autonomic neuropathy, peripheral neuropathy, erectile dysfunction, transient ischemic attack, carotid artery stenting, carotid endarterectomy, and peripheral artery disease are also being captured from the diagnosis, medical history, and procedure forms. In addition, available laboratory test results including HbA1c level (per clinician discretion), occurrence and timeframe of minor and major hypoglycemic events, data on HRU such as hospitalizations or emergency department visits, and quality of care metrics are being recorded in specific fields of the e-CRF. The registry is only collecting observational routine clinical data; the follow-up visits, examinations, laboratory tests, or procedures are not being mandated or recommended for this registry. Although patient-reported outcomes are not currently collected, they may be incorporated over time in the registry.

2.5. Data flow and study management

The DGR is a clinician-led registry, guided by a registry Executive Scientific Committee. Data are being prospectively recorded by trained clinician into the cloud-based e-CRF through the RWE box registry system (Fig. 4). This will facilitate visualization of data through a user-friendly dashboard, allow validation of datasets, and will provide the means to perform descriptive analyses for site-specific benchmarking. The e-CRF permits programmable edits to obtain immediate feedback if data are out of range, illogical, or potentially erroneous. Thus, high data

quality standards are being maintained to ensure data accuracy. The site level data will be accessible to the respective clinicians for real-time assessment.

2.6. Sample size and statistical analysis

2.6.1. Sample size

The study is descriptive and no hypothesis is being tested. Being an open-source registry, the countries and physicians are participating on a voluntary basis, and hence, the number of participating countries will govern the sample size. The sample size is potentially estimated to be extensive because of the open-source design of the registry.

2.6.2. Statistical analysis

The statistical analysis plan for DGR is currently being developed.

3. Discussion

DGR is the first global registry for cardiometabolic disease with the capability to serve unmet needs of LMICs having resource limitations for data collection. The DGR will provide comprehensive data for health-care decisions globally including developing countries, which routinely do not collect and analyse available patient data. The registry intends to extend the DISCOVER study and generate long-term and longitudinal follow-up evidence beyond 3 years on real-world management of diabetes, cover a wider geographical area, and provide quality key performance indicators to benchmark and improve quality of care in patients with T2DM. The DGR will be a unique registry for cardiometabolic disease, which spans the disciplines of endocrinology, metabolism, cardiology, nephrology, neurology, vascular with data collected from diseases in primary care and specialist care.

To address the global diabetes crisis, real-world insights into specific

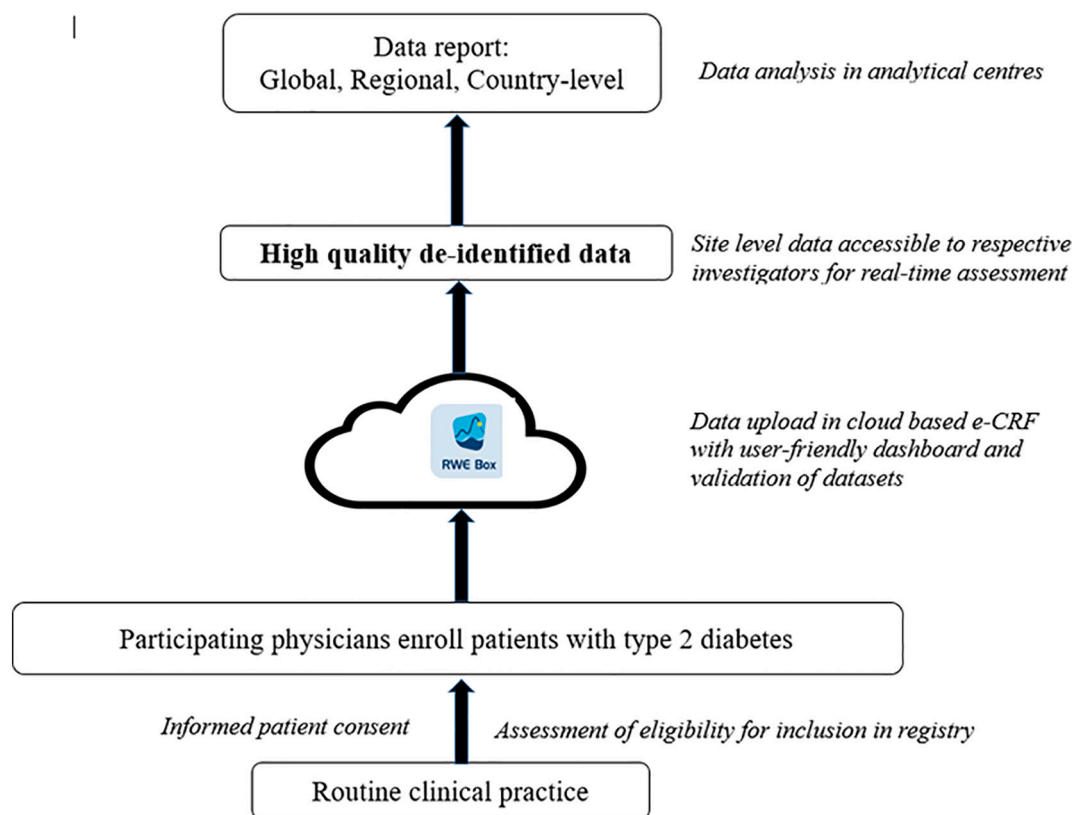


Fig. 4. Data collection and patient flow algorithm in the DISCOVER Global Registry (DGR). e-CRF = electronic case report form; RWE box = real-world evidence box.

patient characteristics, risk factors for progression, and development of complications are urgently needed. Patients with T2DM bear the burden of vascular complications simultaneously affecting several organ systems (the heart, kidneys, brain, eyes, or limbs) across different medical specialties, thus leading to fragmentation of patient records and lack of comprehensive data on individual patients. The DGR is a global prospective registry, encapsulating progressive long-term follow-up of microvascular and macrovascular complications and the resultant therapeutic landscape into one database to overcome this fragmentation. Operationally, the DGR is in line with the Diabetes Collaborative Registry (DCR) led by the American College of Cardiology; however, the DCR collects patient data through an automated system that periodically extracts data elements from electronic health records covering outpatient care.¹⁹ Although there are a number of diabetes registries, most are region-specific, such as those from Sweden, United Kingdom, China, Malaysia, Saudi Arabia, Thailand, Germany, Italy,^{20–27} while others cater to smaller populations from single centres.²⁸ Few registries include specific target population, such as the LMC Diabetes Registry for refractory patients treated by speciality physicians²⁹ and SEARCH registry for youth onset diabetes,^{30,31} whereas some are specific to therapeutic agents like the observational registry of basal insulin treatment (ORBIT) registry focusing on insulin.³²

In the DGR, physicians can view data of their respective sites in real-time, essentially without any “lag time” (i.e., refreshed every 24 h) and in turn can streamline and compare their performance to hospital, regional, national, and global level data and optimize care strategies for mitigating therapeutic inertia. Registry databases provide unique opportunities to monitor data for supporting quality improvement of healthcare services and the delivery of value-based healthcare, as well as provide comparative benchmarking reports facilitating a patient-centred approach.^{33,34} Integrated with other data sources, registries can provide a long-term follow-up data to reflect the natural history of diabetes over time, and support understanding of the temporal trends and emergence of target organ complications.³⁵ The DGR will generate meaningful conclusions for different outcomes based on geographical and genetic variation and can aid inferences about the economic implications. The registry can determine interrelationships between attributes like rapid industrialization, urbanization, and the ensuing lifestyle changes to help understand the phases of epidemiological transition, and identify disease hotspots in the Asia and Pacific regions. The registry may effectively clarify the role of newer strategies in addressing the multifactorial etiology of diabetes and its micro and macrovascular complications by providing long-term comparative effectiveness data. This may further enable the integration of new emerging therapies into clinical practice, and reduce the complexity of the decision-making process for an effective second-line therapy after metformin.

The DGR includes continuous individual level data points, demonstrating variations in practices, complications, and outcomes; thus, facilitating targeted disease management among diabetes patients. Deciphering the barriers to patient resistance and non-compliance may enable a shift in focus from the one-size-fits all approach to more curated and tailored interventions. As diabetes is a progressive disease, the amalgamation of data on clinical characteristics, HRU, and disease monitoring can guide treatment strategies; thus, profoundly impacting patient outcomes.^{36–40} DGR will shed light on determinants of health-related quality of life and patient preferences, and can dictate formulation of comprehensive patient-centric treatment pathways which patients would be likelier to follow for better and holistic management.

Evolving digital technologies like cloud-based patient repositories are crucial tools for efficient, reliable, and effective data capture that can link patient data from all over the world. The web-based platforms can facilitate capture of nuanced data elements such as whether prescriptions were actually filled, complementary or over-the-counter treatments, and outpatient encounters or other care received but not reported to primary treating physicians. These insights into patient experience can enable physicians to recognize early the divergence

between target goals and actual treatment and outcomes, and take corrective actions to enhance quality of care.

Results from the DGR will be generalizable owing to its large sample size and wide geographical reach. This registry was set up to allow countries with limited data collection capabilities to have a data set with enough quality to do research, publish and most of all improve local clinical practice, all based on a database with enough quality. The design and execution of this registry prioritizes the quality of the data as much as possible in the real-world setting, while at the same time being broadly inclusive and representative of many geographies. The prolonged duration of the study will aid deeper understanding of the epidemiological aspects of complications and comorbidities in the advanced stage of progressive diabetes and rationalize therapeutic approaches with newer drugs for second-line therapy and beyond. The end goal of DGR is to create a global initiative to evaluate and improve the quality of care and outcomes in T2DM – foremost through high quality data collection that integrates into the flow of care, and can help create benchmarks. In addition, potential plans for partnership with international and national professional societies can help gain wider perspective and facilitate this endeavour.

However, being a registry, some possible limitations include missing data and loss to follow-up. Selection bias, information bias, and confounding can also stem from the observational design of the registry. The varied geographical distribution and fragmented nature of the healthcare systems may additionally cause dissimilarities in definitions and standards used for data collection with heterogeneous validation. Moreover, medication access and costs may vary widely. However, judicious use of standard definitions and data harmonization is the cornerstone for successful utilization of healthcare data for drafting and implementation of healthcare policies, and will be the cornerstone for the DGR as well.^{41,42}

4. Conclusion

DISCOVER is a multinational prospective registry curated to assimilate real-world data and enhance understanding of care pathways, identify unmet needs and outcomes to improve quality of care, and transform clinical data into actionable insights for patients with T2DM. The registry will provide meaningful information on disease management patterns, quality of life, and associated outcomes in patients with T2DM. With the establishment of this long-term, scalable, and sustainable global registry, long-term data from DGR can enhance understanding of care gaps and potential trade-offs between accessibility, availability, and affordability of health interventions, and thus guide judicious public health resource allocation, leading to better outcomes for T2DM patients all over the world. Leveraging data from the DGR can facilitate benchmarking of clinical practice and address multiple high priority research questions such as pre-trial feasibility analyses or post approval surveillance of new drugs, across geographies. This can address all stakeholders' concerns, which include physicians, payers, and policy makers, and advance healthcare at an individual and population level.

CRediT authorship contribution statement

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article and take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Declaration of competing interest

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